

THE AMERICAN JOURNAL OF MANAGED CARE®

Evidence-Based Oncology™

Medical Homes

Oncology Medical Home: Improved Quality and Cost of Care

Surabhi Dangi-Garimella, PhD

The fragmented nature of the healthcare system in the United States is all too familiar. Lack of coordination between the various providers can impede the quality and efficiency of care, and at the same time elevate the overall cost of treatment. The loser in this process is the patient, who might end up paying more without experiencing improvements in quality.

The patient-centered medical home (PCMH) was developed to mend this disjointed delivery of primary healthcare. When it comes to oncology care, the Oncology Medical Home (OMH) replaces PCMH, although with the same concept that the physician—in this case, an oncologist—performs the role of a coordinator who is in charge of the patient's overall healthcare. Although cancer becomes the focal point, all other comorbidities also need to be addressed.

Why OMH?

The complex and specialized care that is critical for an oncology patient can prove

(continued on page SP419)

Commentary

FDA Oversight of Laboratory Developed Tests Essential for Patient Health and Safety

Rep. Louise M. Slaughter, MPH

On July 31, 2014, the FDA announced a draft guidance for regulating laboratory-developed tests (LDTs), which include many genetic tests, based on the level of risk they carry to a patient. I was pleased to hear of this decision and had, in fact, called on the Obama Administration to do exactly that. These tests play a pivotal role in patient care, and it is critical that they be safe and effective.

Protecting Americans' health and genetic information has been a central mission of mine during my career in Congress. As a microbiologist, I was well aware of the enormous medical potential of the Human Genome Project when it began in 1990. As a member of Congress with years of experience working in health policy, I also understood the potential for abuse this advancement could present. When the era of personalized medicine was just around the corner, I wanted to make sure everyone would have the same opportunity to benefit from this incredible tool without fear of losing their jobs or their healthcare.

In 1995, I introduced the Genetic Information and Nondiscrimination Act (GINA) to protect all Americans from any employment or health insurance discrimination based on their genes. I hoped that for the first time, science and policy would go hand-in-hand and the law's protections would be in place by the time the human genome was sequenced. The latter happened in the year 2000, but GINA was not signed into law by President Bush until 2008, after almost 14 years of advocacy and

Rep. Louise M.
Slaughter, MPH

(continued on page SP419)

Teens in Trials

Cancer Trials Face a Shortage of Teen, Young Adult Enrollees

Surabhi Dangi-Garimella, PhD

A recent report, the result of a collaboration among the National Cancer Institute (NCI), the CDC, and the North American Association of Central Cancer Registries, estimated that 15,780 children and adolescents through age 19 years will be diagnosed with cancer in 2014, of whom 1960 will not survive. That 1 in 285 children will be diagnosed with cancer before they reach 20 years of age is a devastating statistic.¹

According to the National Comprehensive Cancer Network (NCCN), only about 10% of 15- to 19-year-old patients, and 1% to 2% of 20- to 39-year-old patients, enroll in clinical trials (CTs) in the United States. This is in stark contrast to the statistics observed in young children: more than 90% of children <15 years of age diagnosed with cancer participate in CTs.²

This could be the primary reason for the lack of improvement observed in cure rates in adolescent and young adult (AYA) oncology patients (15 to 39 years of age) compared with very young patients.³ AYAs, especially those transitioning into adulthood, are overlooked in cancer CTs, and are increasingly being recognized as a neglected population that should be accounted for by researchers.

Recent Updates on Trial Enrollment

Several studies have examined the deficit of adolescents in trials and identified various factors that influence recruitment patterns. A survey conducted by the NCI revealed that between 1997 and 2003, NCI-sponsored trials recruited only about half of the adolescents as patients <15 years of age, and this was observed to be a global phenomenon.⁴ Several reasons were identified as possible causes of

(continued on page SP420)

Scrutiny of the Growing Incidence of Thyroid Cancer in the US

We examine whether the increased incidence recorded by the CDC is a result of an actual rise in cases or improved detection, as well as the role of proximity to nuclear facilities (SP398).



Also in this issue...

Promise in Treatment for Pancreatic Cancer

Immunotherapy, hailed as a breakthrough in other cancers, is also providing encouraging results in trials of this hard-to-treat cancer (SP401).



Dung T. Le, MD

Familial Genes That Determine Breast Cancer Susceptibility

With rapid advances in bioinformatic tools, recent studies have identified genes, other than the familiar *BRCA1* and *BRCA2*, in hereditary breast cancer. Several of these genes are already included in marketed diagnostic panels (SP416).

Dietary Panel Examines Links to Cancer for the First Time

The Dietary Guidelines Advisory Committee, which makes recommendations that inform US nutrition policy, for the first time examined the evidence tying what Americans eat to the 4 most common cancers, and found the strongest connection to colorectal cancer (SP417).



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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 \$1585 per 3.5-mg vial as of July 2014
- ▼ 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 $\geq 20\%$) 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.



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/m² 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/m² 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/m²/dose administered intravenously twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with previously-treated multiple myeloma (N=1008) and previously-treated mantle cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.

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

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

herpes zoster (11% vs 3%), rash (11% vs 2%), abdominal pain upper (10% vs 6%), and insomnia (10% vs 6%).

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

DRUG INTERACTIONS:

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

USE IN SPECIFIC POPULATIONS:

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

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

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

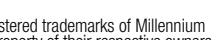
Patients with Renal Impairment: The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing adjustments of VELCADE are not necessary for patients with renal insufficiency. Since dialysis may reduce VELCADE concentrations, VELCADE should be administered after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

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

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

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



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SP396 FROM THE PUBLISHER

SP397 COMMENTARY

Patient-Contributed Tumor Genetics Data: A Pathway to Better Drug Development?

Yair Benita, PhD; Barbara Marino, PhD; Aman Bhandari, PhD; Roni Zeiger, MD; and Sachin H. Jain, MD, MBA

SP398 CLINICAL REPORT

Thyroid Cancer: Increased Incidence or Improved Diagnosis?

Sejal Saraiya, PharmD

A granular look at the CDC thyroid cancer incidence data by county, shows that 13 of the top 18 counties—among 7 states with the highest incidence—are in the contiguous states of New Jersey, New York, and Pennsylvania.

SP401 Immunotherapy Trials Offering Promise in Hard-to-Treat Pancreatic Cancer

Mary K. Caffrey

SP409 Recurrence of Breast Cancer Years After the Initial Tumor

Marj P. Zimmerman, MS, BSPharm; and Stanton R. Mehr

"Breast cancers are made up of a mixture of cells. As a result, the recurrence may not exactly be like the primary tumor and may represent a subset of cells that disseminated. So we sometimes see tumors that were HER2-negative initially show evidence of HER2 at recurrence. The majority of recurrences—about 85%—are same as primary."

—Patricia Ganz, MD

SP414 FDA UPDATE

Surabhi Dangi-Garimella, PhD

AACR Seeks FDA Oversight on LDTs

First PD-1 Inhibitor Approved for Melanoma

Avastin: First in Nearly a Decade for Metastatic Cervical Cancer

SP415 RESEARCH REPORT

Moving Beyond BRCA Mutations in Familial Breast Cancer

Surabhi Dangi-Garimella, PhD

SP418 POLICY

Draft Statement: Evidence Connecting Diet to Colorectal, Breast Cancer Stronger than Links to Lung, Prostate

Mary K. Caffrey



Steven Clinton,
MD, PhD

Clinton presented draft language on the relationships between dietary patterns and 4 major cancers that account for half of the cancer incidence in the United States: lung cancer, prostate cancer in men, breast cancer in women, and colorectal cancer.

SP420 MEDICAL HOMES

Oncology Medical Home: Improved Quality and Cost of Care

Surabhi Dangi-Garimella, PhD

SP420 COMMENTARY

FDA Oversight of Laboratory Developed Tests Essential for Patient Health and Safety

Rep. Louise M. Slaughter, MPH

SP421 TEENS IN TRIALS

Cancer Trials Face a Shortage of Teen, Young Adult Enrollees

Surabhi Dangi-Garimella, PhD



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Welcome to this issue of *Evidence-Based Oncology*, which covers a broad gamut of topics that are creating ripples in oncology care, both clinically and in terms of policy.

The growing field of molecular diagnostics took a major turn this summer when the FDA announced plans to improve guidelines for companion diagnostics and increase oversight for laboratory-developed tests (LDTs). This announcement, which is steeped in a promise of quality, value, and reliability, generated excitement in the field and among members of Congress, including Representative Louise Slaughter, D-NY. In her commentary, which appears on SP420, she emphasizes the need to regulate all laboratory tests, because “an unreliable test could be extremely dangerous: a false positive may lead a woman to have her ovaries removed unnecessarily, and a false negative could be fatal.”

With therapies and drug delivery systems being constantly improved, the discussion of care in cancer today has steered toward quality, value, and accountability. These are the foundations for the Oncology Medical Home (OMH), an initiative by the Community Oncology Alliance (COA). With a medical home for cancer patients, the COA aims to accomplish coordinated care, with the oncologist functioning as the point of care for all of the patient’s healthcare needs. The goal: efficient, patient-centered care that also saves cost. In subsequent issues of EBO, we’ll gain additional insight into the functioning of the OMH.

Another cover article addresses concerns about the dearth of teens in oncology clinical trials. A few recent studies have investigated this situation, and some of the primary causes identified include the overlapping age criteria of trials, cancer type, lack of geographic accessibility to a trial, and inadequate insurance coverage. Gregory Reaman, associate director of the FDA’s Office of Hematology and Oncology Products, told EBO: “The lack of communication between medical oncologists and pediatric oncologists has been an issue. Adult oncologists may not be familiar with some of the diseases that adolescents have, and so the patient may not have access to trials for these cancers, which are usually conducted by pediatric oncologists.” We get a glimpse into the efforts under way to improve recruitment, including some of the provisions of the Affordable Care Act.

In recent years, reports have identified a growing incidence of thyroid cancer, especially among women. The flip side of the argument, though, is whether improved diagnosis is responsible for the statistics. However, evidence provided by the CDC suggests the presence of “hot spots” in the New York–New Jersey–Pennsylvania belt, which correspond with the location of nuclear reactors. We examine some of this evidence to understand the dynamic landscape of the disease.

Please visit www.ajmc.com for additional information on upcoming events, and be sure to join us for our third annual live meeting, Patient-Centered Oncology Care, to be held November 13–14, 2014, in Baltimore, where we will welcome keynote speakers Peter P. Yu, MD, of ASCO, and Burton VanderLaan, MD, of Priority Health. As always, thank you for reading.

Sincerely,

Brian Haug
President, The American Journal of Managed Care

EDITORIAL MISSION

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Patient-Contributed Tumor Genetics Data: A Pathway to Better Drug Development?

Yair Benita, PhD; Barbara Marino, PhD; Aman Bhandari, PhD; Roni Zeiger, MD; and Sachin H. Jain, MD, MBA

As the knowledge of tumor genetics becomes more sophisticated, we continue to further stratify cancer into subtypes. Leukemia, for example, was defined as a single disease in the 1950s, and today it is comprised of more than 70 distinct pathologies. A major treatment challenge is to develop and produce drugs for disease subtypes that are poorly defined clinically. To address these challenges, companion diagnostic devices have been codeveloped and comarketed with drugs. However, developing companion diagnostics has several associated challenges related to cost, access to samples, and clinical trial recruitment. Below, we describe these challenges and report on survey data that suggest a pronounced willingness of patients to share tumor genetics data with pharmaceutical companies to make their contribution to the acceleration of drug development.

The Challenge of Companion Diagnostics

In 2011, the FDA issued a guidance document for the co-development of companion diagnostics,¹ and later in 2012, a draft guidance document on enrichment strategies for clinical trials.² These documents recommend that companion diagnostic assays be analytically and clinically validated prior to phase 3 trials. Effectively, this

recommendation means that diagnostic assays need to be developed as early as phase 1 and be in use for phase 1b and phase 2 trials.

Many challenges exist for the codevelopment of diagnostics,³ and as we pursued the codevelopment of biomarkers for oncology programs at Merck, we assessed the cost of the dual process. The cost of developing a simple clinical assay is at least \$1 million, but can be as high as \$4 million for a complex assay such as the TP53 Amplichip.⁴ It would subsequently cost an additional \$1200 to \$1500 to analyze a single sample.

These costs may appear insignificant in comparison with the high overall costs associated with drug development. However, they pose significant challenges for executing clinical trials, especially for low-prevalence biomarkers. A biomarker with a 10% prevalence would require testing 200 eligible patients with available tumor biopsies to enroll 20 patients. For trials evaluating crizotinib, Pfizer had to assess 20 to 25 eligible lung cancer patients to enroll 1. In practice, the company probably examined more than 1600 patient samples to run the crizotinib trial that finally enrolled 82 patients.⁵ While such an effort can be justified in retrospect, similar efforts for all drugs going into phase 1b or 2 can be difficult to justify, since most drugs fail early in the

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pipeline due to safety or efficacy issues. Thus, biomarker codevelopment leads to a significant increase in the cost of drug development.

The Expected Solution

Molecular diagnostics have grown in sophistication through advancements in clinical next-generation sequencing (NGS). This technology offers the possibility of capturing all genetic alterations in a single assay and may eventually obviate the need for additional genetic diagnostic assays. Leading cancer hospitals already offer their patients exon sequencing of 100 to 300 genes. Companies like Foundation Medicine offer NGS services to patients and have reported delivering clinical results to 3752 patients in 2013. However, the FDA has been cautious about adopting NGS-based biomarkers since there are no accepted standards for data generation, validation, and computational analysis. Hence, pharmaceutical companies are not yet using NGS as a replacement for companion diagnostics.

Alternative Model

To address the challenges and costs associated with developing companion diagnostics, we suggest an alternative model, based on a collaboration between patients and pharmaceutical researchers. Instead of developing clinical-grade assays early in the pipeline, pharmaceutical companies could offer to sponsor the NGS costs of patients who are otherwise eligible for one of their clinical trials. The results—owned by the patient—could be shared with the sponsors in a deidentified form, for research purposes only.

Patients would stand to gain with this approach. The number of trials in which they could likely enroll would no longer be limited by the amount of available tumor sample. In addition, they could receive valuable information that would enable them to make

an informed decision when choosing to participate in a clinical trial. Finally, this approach reduces the out-of-pocket costs for patients. While privacy concerns exist and need to be addressed, results from our survey below suggest they may be significantly outweighed by perceived advantages.

For pharmaceutical companies, this approach might seem expensive since the current NGS cost is in the range of \$5000 to \$6000 per patient. However, given the cost of assay development, it would result in significant cost savings. In addition, knowledge generated from this effort would be extremely valuable—providing molecular information on tumors that do not respond to standards of care—since patients looking for clinical trials represent the unmet need. Finally, additional data would be available for retrospective analysis of clinical trials.

The Patient Perspective

To better understand patients' perspectives on this potential approach, Merck collaborated with Smart Patients, an online community of cancer patients and caregivers. The staffs of Merck and Smart Patients designed a survey that was administered by Smart Patients, and the results were deidentified prior to being shared with Merck.

We first assessed the prevalence of tumor NGS within the existing patient population. Of the 92 cancer patients who answered the survey, 18% (17 patients) had previously had their tumor sequenced. Of these 17 patients, 9 of 13 reported that the results helped them make treatment decisions; 4 did not respond. For 8 of those 13 patients who responded, the results helped in identifying clinical trials in which they could participate. More than 70% of the patients who had not had their tumor sequenced cited lack of awareness about this option. Eight percent of patients did not think sequencing data would be

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useful, while the remaining patients indicated financial or technical reasons.

We then asked patients who had not had NGS done on their tumor if they would be willing to share the results of the sequencing with a pharmaceutical company for research purposes, in exchange for sponsoring the costs of the assay. An overwhelming 63 of 64 patients responded "Yes." Even the majority of patients who had already had NGS responded that they would be willing to share their results. Finally, patients discussed their perception of benefits and concerns with this approach on the Smart Patients conversation platform. Most cited progress in research as the main benefit, while some patients were worried the information might be used against them by insurance

companies to deny future coverage or by pharmaceutical companies to deny participation in clinical trials. These concerns need to be addressed by better educating patients on these issues and by more visible, regulation-driven patient protection.

Conclusion

As genetic testing and study become increasingly important to our understanding of cancer, researchers will need to develop scalable approaches to obtaining genetic information from patient tumors to accelerate and improve drug development. Our data suggest that patients may be willing to contribute data for these purposes if the cost of testing were covered. An important caveat of these results is that the Smart Patients survey population

is biased toward patients who are more engaged and knowledgeable about their own disease. Nonetheless, the opportunity is real. It will be up to pharmaceutical researchers, regulators, patient advocacy organizations, and patients themselves, to collaborate and make the most of it. **EBO**

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Clinical Report

Thyroid Cancer: Increased Incidence or Improved Diagnosis?

Sejal Saraiya, PharmD

Each year approximately 63,000 individuals in the United States will be told that they have thyroid cancer. This places thyroid cancer among the top 10 most common cancers based on incidence in the United States. It will continue to move up that list, being the fastest rising cancer diagnosis in the United States, the most significant reason being increased detection.¹ However, thyroid cancer is not in the spotlight to the same extent as other cancers that are associated with a larger number of fatalities.

The story of thyroid cancer over the past few decades is an interesting one. Several different theories attempt to explain the overall increased incidence of thyroid cancer, as well as why its incidence has been increasing at a relatively faster pace in certain parts of the country.

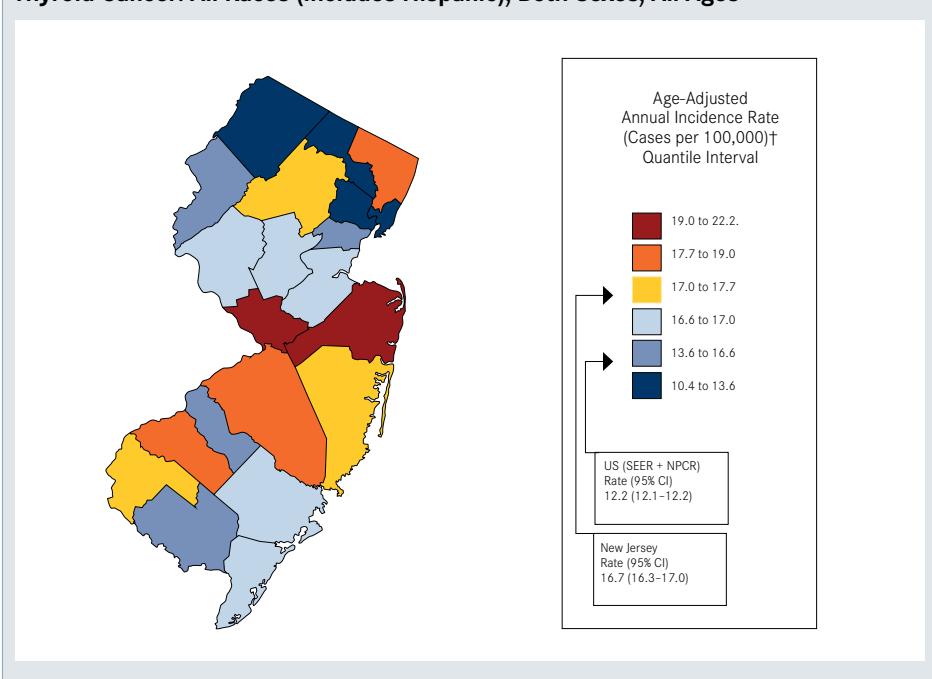
With the number of thyroid cancer diagnoses increasing, healthcare professionals need to have a keen understanding of thyroid cancer and its different subtypes. There are 4 main types of malignant thyroid tumors, a majority of which are differentiated cancers. Papillary thyroid cancer has the highest incidence, with roughly 8 out of 10 thyroid cancers being papillary in nature. These cancers often grow very slowly and normally reside in just 1 lobe of

the thyroid gland, but they can spread to the lymph nodes in the neck. With a high potential for cure, papillary cancers are rarely fatal. The second most common subtype is follicular thyroid cancer, accounting for 10% of thyroid cancer diagnoses. Normally localized to the thyroid, follicular thyroid cancer can metastasize to other organs such as the lungs or bones. Two rare forms of thyroid cancer include medullary thyroid cancer and anaplastic thyroid cancer, which make up 4% and 2% of thyroid cancer diagnoses, respectively.²

Incidence

Evaluation of SEER data between 1973-2002 indicated that thyroid cancer diagnosis rates have been on the rise.³ In the United States, rates increased by 5.4% per year in men and by 6.5% per year in women between 2006 and 2010.¹ While several other developed nations, such as Scotland, France, and Canada, have seen similar increases,⁴⁻⁶ the debate persists: is the increasing incidence in cancer rates real, or is it a consequence of increased diagnostic scrutiny made possible by tools and techniques developed over the past few decades?^{3,7} The argument that the rising incidence is reflective of increased detection, as opposed to an increase in true occurrences, has merit.

Figure 1. Incidence Rates[†] for New Jersey, 2006-2010. Thyroid Cancer: All Races (includes Hispanic), Both Sexes, All Ages



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[†]Incidence rates (cases per 100,000 population per year) are age-adjusted to the 2000 US standard population (19 age groups: <1, 1-4, 5-9,..., 80-84, 85+). Rates calculated using SEER* Stat. Population counts for denominators are based on Census populations as modified by NCI. The 1969-2011 United States Population Data File is used for SEER and NPCR incidence rates.

In fact, thyroid cancer has been a common autopsy finding for over 50 years.⁸ The 2 main diagnostic techniques that have given rise to the increased detection of thyroid cancer prior to autopsy

are ultrasonography and fine-needle aspiration. Both techniques allow for the diagnosis of a much smaller tumor size. A 2006 study found that smaller papillary cancers had the largest in-

crease in incidence among the other types of thyroid cancers. The incidence of thyroid cancer increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002, a statistically significant 2.4-fold increase. During the same period, the rate of papillary cancer increased from 2.7 to 7.7 per 100,000—a 2.9-fold increase. Of the 4 main histologies of thyroid cancer, papillary cancer was the only subtype which had a significant change in the rate of incidence. Since 1988, almost half of the papillary thyroid cancer tumors identified have been 1 cm or less in size, and almost 90% were 2 cm or less.³ These small sizes would prevent the majority of physicians from diagnosing through palpation, leading many to go unnoticed without the newer diagnostic techniques. If the incidence of thyroid cancer were truly increasing, one could expect that the rate of mortality associated with thyroid cancer would also be increasing. However, the mortality from thyroid cancer has remained stable. In both 1975 and 2009, thyroid cancer-specific mortality was approximately 0.5 deaths per 100,000 persons.⁹

Diagnosis Rate

A way to strengthen the argument of “overdiagnosis” in thyroid cancer, meaning the identification of a disease that would not cause symptoms or death to a patient if left undetected, would be to look at how increased access to care influences the diagnosis rate. Upon examining 2 cohorts of patients with differing health insurance access—those 65 years and older, who have near-universal health insurance coverage, and those under 65 years of age, who have varying rates of access—it was observed that those with universal access had higher papillary thyroid cancer rates.⁹ An obvious assumption is that increased age could influence the rate of thyroid cancer development; however, before 1990, the incidence rate of papillary thyroid cancer among people 65 years and older (4 to 6 per 100,000) was only marginally higher than that of patients who were not of Medicare-eligible age (2 to 5 per 100,000). Since the early 1990s, the incidence rates have diverged; in 2009, Medicare patients had an incidence of 18.5 per 100,000 compared with an incidence of 11.6 per 100,000 in the under-65-years-old cohort.⁹ Despite the logic behind the “overdiagnosis” theory and that there is simply an apparent increase in cancer rate, there is still reason to suspect an environmental influence, as there are “hot spots” around the country that have a higher thyroid cancer incidence.⁷

“Hot Spot” Locations, and Proximity to Nuclear Assets

An analysis of data from the CDC, which contains information on state thyroid cancer incidence for 45 states

and the District of Columbia, reveals distinct areas of the country with much higher rates of thyroid cancer than others. Of the 7 states with the highest incidence, 5 are located in the North-

eastern United States. These states, in decreasing order of incidence rate, are Pennsylvania, Massachusetts, New Jersey, Connecticut, and Rhode Island. A more granular look at incidence data



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by county shows that 13 of the top 18 counties are in the contiguous states of New Jersey, New York, and Pennsylvania.⁷ One important characteristic of these counties is there is no other area in the United States with a greater concentration of nuclear reactors. The

high-incidence counties encompass an area within a 90-mile radius that houses 7 nuclear power plants, which contain 16 nuclear reactors. Lehigh County in Pennsylvania is one of the referenced counties within 90 miles of a nuclear reactor. The thyroid can-

cer incidence rate in Lehigh County was 21.4 per 100,000 based on the data extracted from 2001 to 2005. This was significantly higher than the average United States thyroid cancer rate of 8.9 per 100,000 during that same period of time.⁷ As it is well established that exposure to radiation is a risk factor for thyroid cancer, a result of radioactive iodine ($I-131$) being incorporated into the thyroid cells, it is hard to ignore the correlation between proximity to nuclear reactors and a much higher incidence of thyroid cancer.^{7,10}

Standard of Care

It is important to take in the entirety of information regarding the surge in thyroid cancer incidence and what this means for the patient. As previously noted, the mortality rate has not changed in the past 30 years, despite the elevating incidence. If thyroid cancer incidence continues to increase, it may be necessary to determine a more cautious diagnostic approach, focusing more on symptomatic thyroid nodules than just the presence of thyroid cancers, especially for those smaller than 1 cm. This is especially important in that the current standard of care remains the same as it was 2 decades ago and can be fairly invasive for the patient. The evidence-based guidelines released separately by the American Thyroid Association (ATA) and the National Comprehensive Cancer Network for the management of differentiated thyroid cancer both provide a clear recommendation for the use of surgery.^{11,12} Treating with surgery should be individualized to the patient, focusing on the extent of the disease, the patient's age, and the presence of comorbid conditions. The ATA provides an aggressive prophylactic approach, stating that a central neck dissection may be performed in patients with advanced papillary cancer even in the absence of clinical evidence of nodal involvement, and also recommends near-total or total thyroidectomies for all tumors greater than 1 cm.¹¹ Although thyroidectomies are often seen as a low-risk surgery, they can have a major impact on a patient's life, as the patient will be required to take a daily thyroid hormone supplement for the rest of his or her life.² Another medication often used post thyroidectomy in patients with differentiated thyroid cancer is radioactive iodine. It is used as an adjuvant for the ablation of residual thyroid tissue and possible microscopic residual cancer, imaging for possible metastatic disease, and treatment of known residual or metastatic thyroid cancer.¹¹ Other approaches to treating thyroid

Of the 7 states with the highest incidence of thyroid cancer, 5 are located in the Northeastern United States: Pennsylvania, Massachusetts, New Jersey, Connecticut, and Rhode Island.

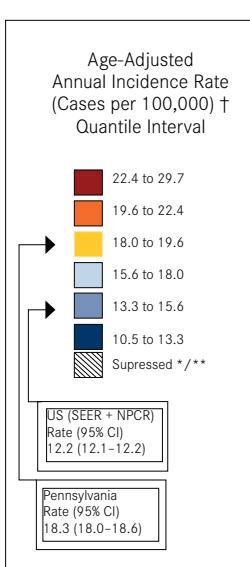
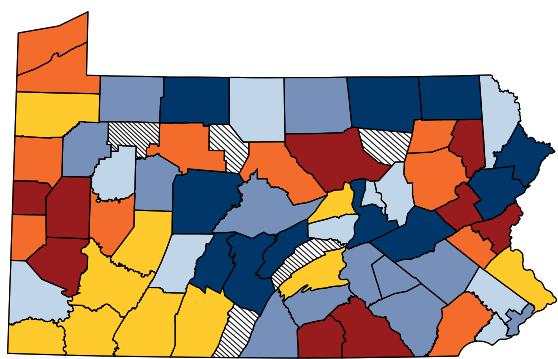
cancer include using external beam radiation and chemotherapy.²

Four medications are currently approved in the United States with a labeled indication for thyroid cancer. In chronological order of FDA approval, these medications are thyrotropin alfa, vandetanib, cabozantinib, and sorafenib.¹³⁻¹⁷ Thyrotropin alfa is a thyroid-stimulating hormone that is used as an adjunct diagnostic tool for serum thyroglobulin testing, and also as an adjunct treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer.¹³ Sorafenib, a kinase inhibitor used to treat kidney and liver cancer, is also indicated for differentiated thyroid carcinoma refractory to radioactive iodine treatment.¹⁶ Two other kinase inhibitors, vandetanib and cabozantinib, are specifically approved for the treatment of progressive, metastatic medullary thyroid cancer.¹⁴⁻¹⁵ Additionally, 1 other medication that was recently evaluated for thyroid cancer in a phase 3 SELECT trial is now under FDA review. The compound—a multi-kinase inhibitor called lenvatinib—was evaluated in $I-131$ -refractory differentiated thyroid cancer,¹⁷ and is now under FDA review.¹⁸

Summary

Driven by increased diagnostic scrutiny and potential environmental factors, rates of thyroid cancer diagnosis continue to climb. As the disease becomes more prevalent, it will be important to study this condition and its potentially causative factors more thoroughly. Treatment for thyroid cancer has not changed very much over the past few decades, and it is still considered a disease that requires surgery. With an increased diagnosis of small tumors, it could not hurt to re-evaluate the treatment algorithm. Questions should be asked regarding what the best possible treatment options are

Figure 2. Incidence Rates[†] for Pennsylvania, 2006-2010. Thyroid Cancer: All Races (includes Hispanic), Both Sexes, All Ages



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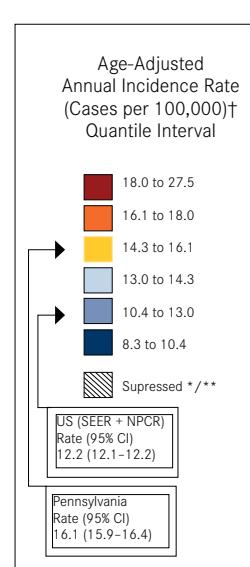
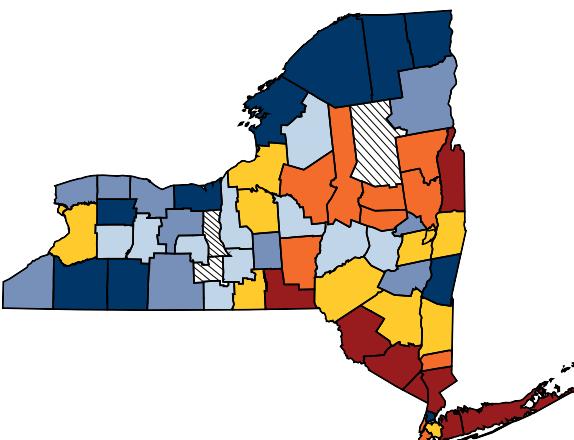
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* Data have been suppressed for states with a population below 50,000 per sex for American Indian/Alaska Native or Asian/Pacific Islanders because of concerns regarding the relatively small size of these populations in some states.

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Figure 3. Incidence Rates[†] for New York, 2006-2010. Thyroid Cancer: All Races (includes Hispanic), Both Sexes, All Ages



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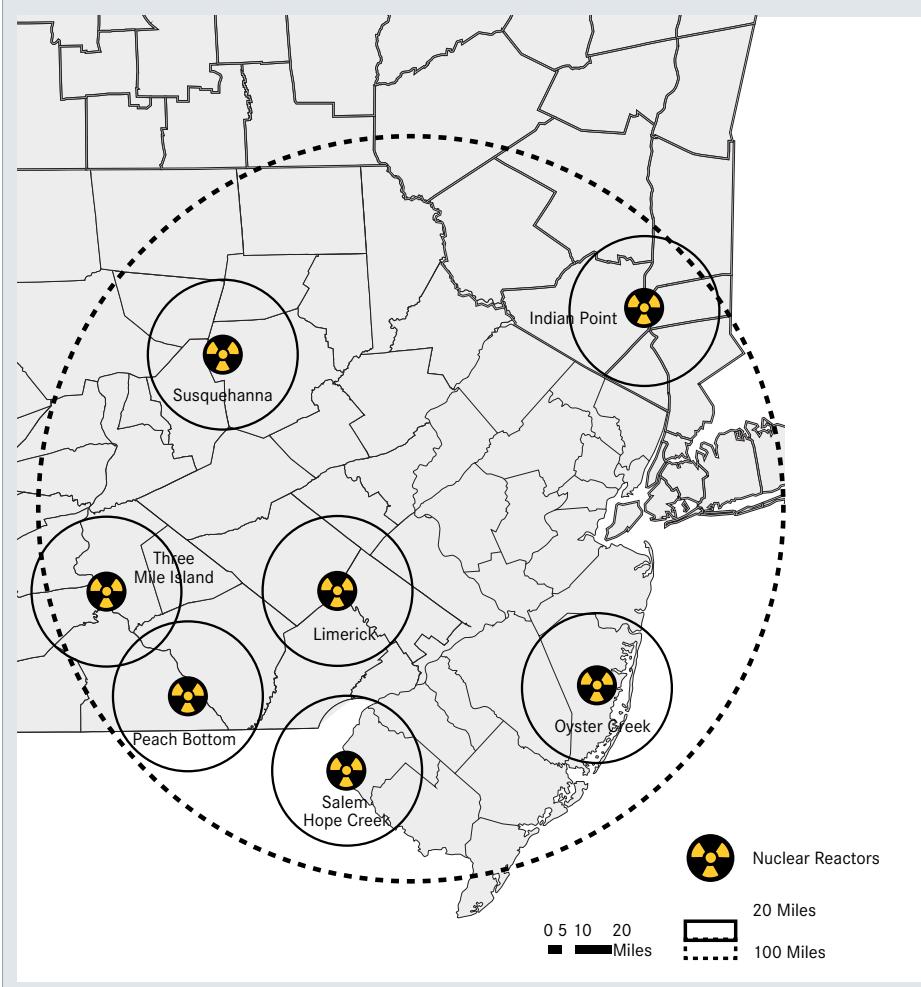
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Figure 4. Nuclear power plants in New Jersey, southern New York State, and eastern Pennsylvania⁷



on an individual basis, and whether or not the potential surgical complications of a thyroidectomy pose more of a health risk over leaving a small papillary thyroid tumor alone. This is very much a chang-

ing disease landscape for many reasons, and care for this condition should adapt accordingly. **EBO**

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Immunotherapy Trials Offering Promise in Hard-to-Treat Pancreatic Cancer

Mary K. Caffrey

Among all cancers, pancreatic cancer stands apart. Everything about the disease makes it hard to diagnose and treat. It often exhibits few symptoms before the cancer has reached late stages. While there are known risk factors, such as smoking, obesity, and some tendency for the cancer to run in families, many who receive the diagnosis have no known risks. So far, there are no biomarkers available that could allow widespread screening of the disease.¹

Once pancreatic cancer is found, the location of the pancreas itself makes removing the tumor difficult and for most patients, impossible. And then there is

the challenge of treatment. In pancreatic ductal adenocarcinoma (PDAC), which accounts for 90% of all cases, tumors are notoriously resistant to chemotherapy; they are characterized by dense stroma with few blood vessels, inhibiting drug delivery.

Taken together, these hurdles leave grim statistics. Estimates from the American Cancer Society put the number of new cases in the United States at 46,420 for 2014, with 39,590 deaths.² While pancreatic cancer accounts for only 3% of all cancer cases, it causes 7% of all cancer deaths,² making it the fourth-leading cause of cancer death in the country. With a 5-year survival rate of 6%, the disease

is "the only one of the top 10 cancer killers with a 5-year survival rate still in the single digits," according to the Pancreatic Cancer Action Network (PanCAN).³

Pancreatic cancer's share in the cancer death toll in the United States has been slowly rising, not only because of improved treatments for other cancers, but also because rising rates of obesity and diabetes appear to be contributing to more cases, according to epidemiologist Ahmedin Jemal, DVM, PhD, vice president for surveillance and health services research for the American Cancer Society.⁴ PanCAN estimates that the number of new cases will grow 55% between 2010 and 2030, and

that pancreatic cancer could become the second-leading cause of cancer death in the United States.³

And yet, there is hope.

Clinical trials across the country are investigating multiple forms of immunotherapy to treat PDAC, often in combinations or in sequence with newer, more powerful forms of chemotherapy.⁵ In some cases, researchers are borrowing lessons learned from the successful use of immunotherapy to treat metastatic melanoma with ipilimumab or castration-resistant prostate cancer with sipuleucel-T.⁶ Researchers say they are learning as much from their successes as their failures, and

while critical phase 3 trials remain, there are signs that longer, better survival may be on the horizon.^{6,7}

What Researchers Are Learning

For some time, researchers have understood that KRAS is a driver of PDAC progression.^{7,8} According to the National Cancer Institute (NCI), KRAS is mutated in approximately 95% of all cases of PDAC, the highest percentage of all solid malignancies.^{1,8} Translating that knowledge into effective treatment has proved exceedingly difficult, as described by Marina Pasca diMagliano, PhD, and Craig D. Logsdon, PhD, in their 2013 review for *Gastroenterology*: “Early attempts to use this molecule as a specific biomarker of the disease, or inhibit its activity as a cancer therapy, failed. This left a situation in which everyone was aware of the association between this important oncogene and pancreatic cancer, but no one knew what to do about it.”⁷

DiMagliano and Logsdon and others report that many assumptions about KRAS and its role in PDAC have been set aside, aided by the use of mouse models, genome sequencing projects, and further exploration into the unique environment of the pancreatic tumor itself. For example, a review this spring in the *British Journal of Cancer* outlines how recent efforts bypass attempts to target KRAS directly and instead direct attention to its signaling networks or downstream effector pathways.⁹

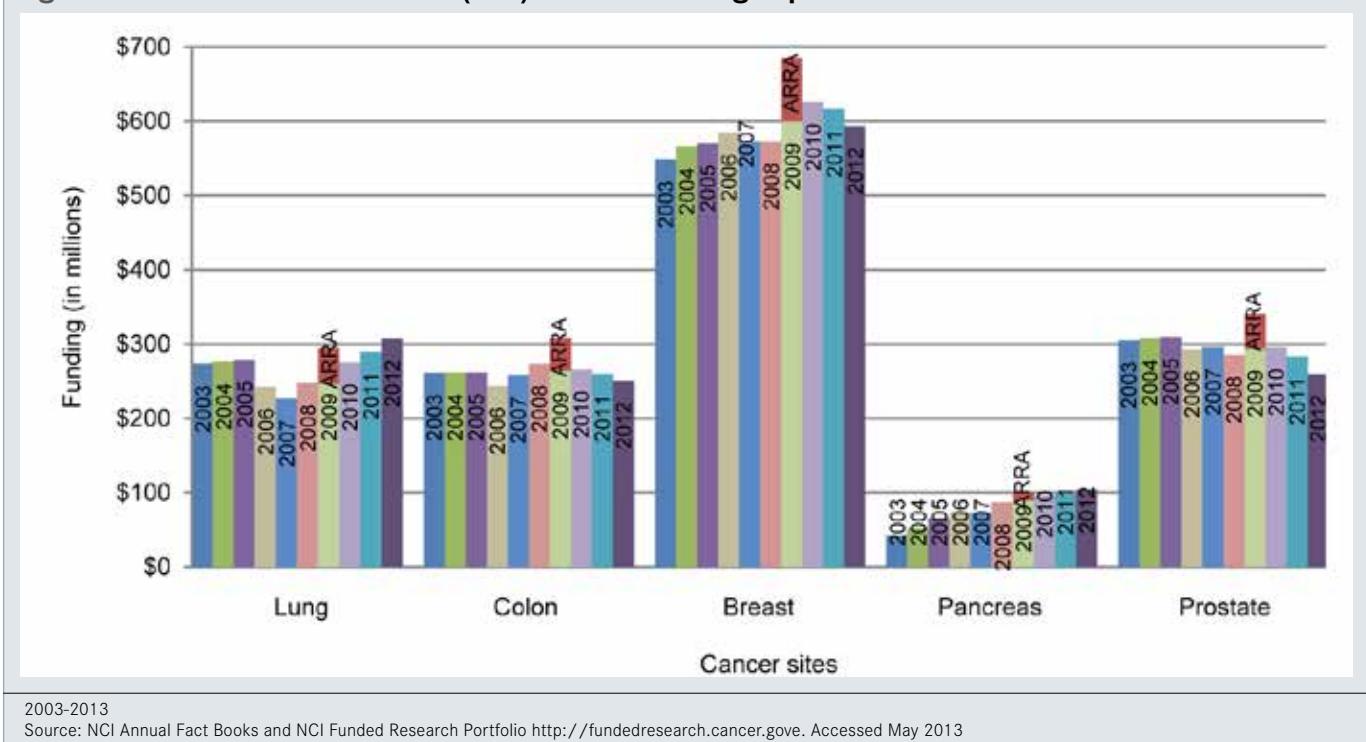
Much important work involves understanding the qualities of the collagen-rich fibrosis around the tumor, which not only acts as a barrier to therapy, but may also be the body’s way of containing cancer cells, according to Hiyadatullah G. Munshi, MD, associate professor of medicine in the Department of Medicine, Division of Hematology/Oncology at Northwestern University Feinberg School of Medicine, in an e-mail to *Evidence-Based Oncology*.

Throughout, clinical trials are informed by an important lesson: when fighting pancreatic cancer, the battle isn’t just against the tumor; it’s against the tumor in a setting hardwired to resist treatment. This makes the central premise of immunotherapy—to train the body to use its own immune system to battle cancer—even more challenging than usual.^{1,6,7,10}

Whole Cell Vaccines

As Jennifer N. Uram, PhD, and Dung T. Le, MD, explain in *Current Problems in Cancer*, treating a difficult disease like pancreatic cancer with whole cell vaccines delivers multiple antigens, avoiding “the difficulty of picking the optimal tumor antigen to target.”⁶ Two such vaccines advancing in clinical trials are algenpantucel-L and GVAX, an acronym for granulocyte-macrophage colony-stimulating factor

Figure. National Cancer Institute (NCI) Annual Funding Top 5 Causes of Death



Source: NCI Annual Fact Books and NCI Funded Research Portfolio <http://fundedresearch.cancer.gov>. Accessed May 2013

(GM-CSF) gene-transfected tumor cell vaccine.¹¹ GVAX is made from irradiated pancreatic cell lines that secrete GM-CSF.¹²

Algenpantucel-L, which is being developed by NewLink Genetics, follows years of work to understand the responses to alpha-gal, a carbohydrate to which humans have a preexisting immunity.¹³ Experiments with mice more than a decade ago yielded the theory that using alpha-gal to trigger an immune response could provide a protective, immune response to cancer.¹⁴ The vaccine uses alpha-gal-modified human cancer cells, which are designed to jump-start the immune system. In effect, when the body attacks the vaccine, the battle against the cancer escalates, too.

The vaccine has been studied in combination with gemcitabine, long the standard chemotherapy for PDAC, in patients with resected cancer. Phase 2 results reported by Hardacre, et al, involved 70 patients who were treated with gemcitabine and 5-fluorouracil-based chemoradiotherapy, as well as algenpantucel-L. The average number of doses was 12, over approximately 8 months. After a median follow-up of 21 months, the 12-month disease-free survival (DFS) was 62%, and the 12-month overall survival (OS) was 86%. The most common adverse events were injection site pain and induration.¹⁴ Reports on the phase 2 trial noted the longer than normal DFS, as well as the presence of antibodies in affected patients that could someday guide future treatment.⁶

A phase 3 trial involving 772 patients, randomized to receive either standard chemotherapy or chemotherapy plus algenpantucel-L, completed enrollment in September 2013 and is ongoing.^{12,15} A separate phase 3 trial for patients with locally

advanced cancer, randomized to receive chemotherapy or chemotherapy plus algenpantucel-L, is currently enrolling.¹⁶

GVAX has been studied as a monotherapy, but its most promising results have involved its use in combination therapy. Work on this vaccine stems from the many efforts to target KRAS directly, and the realization that a different approach was needed. In 2012, researchers found that the KRAS mutation triggers expression of GM-CSF, and that when the molecule comes from tumors it converts immature immune cells into suppressive immune cells. Finding a way to block this activity would allow the immune system to fight the tumor, and it could halt tumor progression.¹⁷

In July 2014, the FDA granted breakthrough status to a combination of GVAX and CRS-207, a live-attenuated *Listeria monocytogenes* (*Lm*), modified to express the protein mesothelin and made safe for human use.^{6,12,18} Le and her colleagues from the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins had presented results with the combination immunotherapy at the February 2014 Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology, where Le said, “This is the first time a randomized study has shown that immunotherapy is effective in pancreatic cancer.”¹⁸

The study involved 90 PDAC patients; all had received some treatment for metastatic disease: 83% had 1 prior treatment and 51% had 2 or more treatments. They were randomized to receive 2 doses of GVAX followed by 4 doses of CRS-207, or 6 doses of GVAX alone, every 3 weeks. (All patients received low-dose cyclophosphamide before GVAX.) Courses could be repeated.

At a median follow-up of 7.8 months, among patients who received at least 1 dose of the vaccine, median OS was 6.1 months for the combination compared with 3.9 months for GVAX alone—a 41% reduction in risk. The greatest reduction in risk was among patients who had all 3 doses, including at least 2 GVAX doses and 1 CRS-207 dose. For this group, median OS was 9.7 months, compared with 4.6 months for GVAX alone, a 47% reduction in risk. Differences were observed in the subgroup of patients who had 2 or more prior chemotherapy regimens. For this group, the combination immunotherapy resulted in a median OS of 5.7 months compared with 3.7 months with GVAX, a 70% reduction. In the group that received at least 3 doses, median OS was 8.3 months compared with 4 months, a 68% reduction in risk.¹⁷ Grade 3/4 side effects were lymphopenia (8.2%), pyrexia (4.9%), fatigue (4.9%), and aspartate aminotransferase increase (4.9%). Local reactions were reported at the administration site for GVAX.¹²

Ipilimumab, in Sequence and in Combinations

As seen elsewhere, trials involving ipilimumab are revealing the value of combination therapy and sequencing immunotherapy after a course of chemotherapy, which can stabilize PDAC and give immunotherapy a better chance of success.⁵ Developments in immunotherapy for pancreatic cancer have been complemented in recent years by new weapons in chemotherapy:

- FOLFIRINOX is a combination of 4 drugs: folic acid (leucovorin), fluorouracil, irinotecan, and oxaliplatin.

When fighting pancreatic cancer, the battle isn't just against the tumor; it's against the tumor in a setting hardwired to resist treatment. This makes the central premise of immunotherapy—to train the body to use its own immune system to battle cancer—even more challenging than usual.

tin. A 2011 study in the *New England Journal of Medicine* reported a median OS of 11.1 months for patients with metastatic cancer taking this combination, compared with 6.8 months with gemcitabine, but noted strong toxicity.¹⁹

- **Abraxane** (nab-paclitaxel) was approved by the FDA in September 2013 to be used with gemcitabine for metastatic pancreatic cancer, after trials showed OS improved by 1.8 months with fewer side effects than occurred with FOLFIRINOX. The chemotherapy combination was shown to delay tumor growth as well, according to the FDA.²⁰

Why ipilimumab for pancreatic cancer? Its blockade of the CTLA-4 inhibitory signal was found effective in depleting regulatory T cells, which suppress anti-tumor immune response in PDAC. A phase 2 trial with ipilimumab as monotherapy (3 mg/kg) did not produce a clinical response. However, 1 patient's brief delayed response to a tumor marker test indicated a small immune response, and suggested that stronger doses or a combination strategy might prove effective.⁶

To test this, Le's group at Johns Hopkins randomized 30 patients with previously treated PDAC in 2 arms. Results were reported in September 2013 in the *Journal of Immunotherapy*. The first arm received ipilimumab alone, but at a higher dose than in the previous study (10 mg/kg); the second arm received ipilimumab (10 mg/kg) plus GVAX. Doses were administered every 3 weeks for 4 total doses, followed by maintenance doses every 12 weeks. In the first arm, 2 patients showed stable disease, but that result was not borne out in CA19-9 testing, which evaluates tumor-

associated antigens. In the second arm, 3 patients had evidence of prolonged stabilization—at 31, 71, and 81 weeks—and 7 patients showed declines in CA19-9 testing. Median OS, 3.6 months compared with 5.7 months, and 1-year OS, 7% compared with 27%, favored the second arm.²¹

Multiple clinical trials involving ipilimumab are now recruiting patients or are under way. Hopkins' Kimmel Comprehensive Center is enrolling patients in another phase 2 trial; patients will be treated first with FOLFINIROX and then with ipilimumab and GVAX. A phase 3 study at Northwestern University will evaluate ipilimumab with gemcitabine in late-stage or recurrent unresectable pancreatic cancer. Pancreatic cancer patients will be included in a broader study evaluating the effectiveness of another combination, ipilimumab and nivolumab, which will enroll patients with different types of cancer.²²

In his e-mail, Northwestern's Munshi said that much work remains before ipilimumab can be approved for widespread use to treat pancreatic cancer, and he doubts it will be approved as a single agent. "In combination with chemotherapy, one has to be careful that there are no untoward toxicities," he said. Approval in combination with a vaccine is a possibility, however.

PANVAC: Injecting the Tumor Directly

The June 2014 American Association of Cancer Research meeting on pancreatic cancer, held in New Orleans, included results from Rutgers Cancer Institute of New Jersey (CINJ) on a phase 1 trial involving PANVAC. This vaccine comes in varieties derived from smallpox and Fowlpox, which are treated with gene additives to stimulate the immune system to attack pancreatic cancer. Edmund Lattime, PhD, CINJ associate director for education and training, and Elizabeth Poplin, MD, co-director of the Cancer Institute's Gastrointestinal/Hepatobiliary Program, and a professor of medicine at Robert Wood Johnson Medical School, were lead investigators.²³

There were 2 phases to the trial. In the first phase, researchers directly injected a live form of the Fowlpox vaccine, which cannot multiply, into tumors for patients who were not candidates for surgery, seeking to shrink tumors without allowing fragments to spread elsewhere. Then patients received a booster, a live but weakened form of smallpox vaccine that can still multiply, injected into the arm. In the second phase, patients received a higher dose of the Fowlpox-derived vaccine into the tumor.²³

Twelve patients began the trial; 2 had rapid progression and were removed, while the remaining 10 received gem-

citabine. Three were found to have distant metastatic disease, with OS ranging from 6 to 22 months. The other 7 patients had OS ranging from 4 to 36 months, and none developed disease that spread beyond the original tumor.

"While the median survival rate for patients without distant metastasis was nearly a year-and-a-half with this treatment, there was 1 patient whose disease remained clinically stable for nearly 3 years," the researchers said in a statement from CINJ. "When you have a disease that only carries a 5-year, 6% survival rate, these findings are very encouraging."²³

What's Next?

Much has happened since Gunturu et al asked, "Are we there yet?" in a January 2013 review article on immunotherapy in pancreatic cancer.¹⁰ The February 2014 report from NCI, "Scientific Framework for Pancreatic Ductal Adenocarcinoma," a call to action required by the Recalcitrant Cancer Research Act of 2012,¹ suggests that while the quest to find effective treatment for pancreatic cancer is no less challenging, a road map is at last emerging. **EBO**

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NEW PHASE 3 DATA

IMBRUVICA® demonstrated single-agent survival in previously treated CLL

INDICATIONS: IMBRUVICA® is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of patients with:

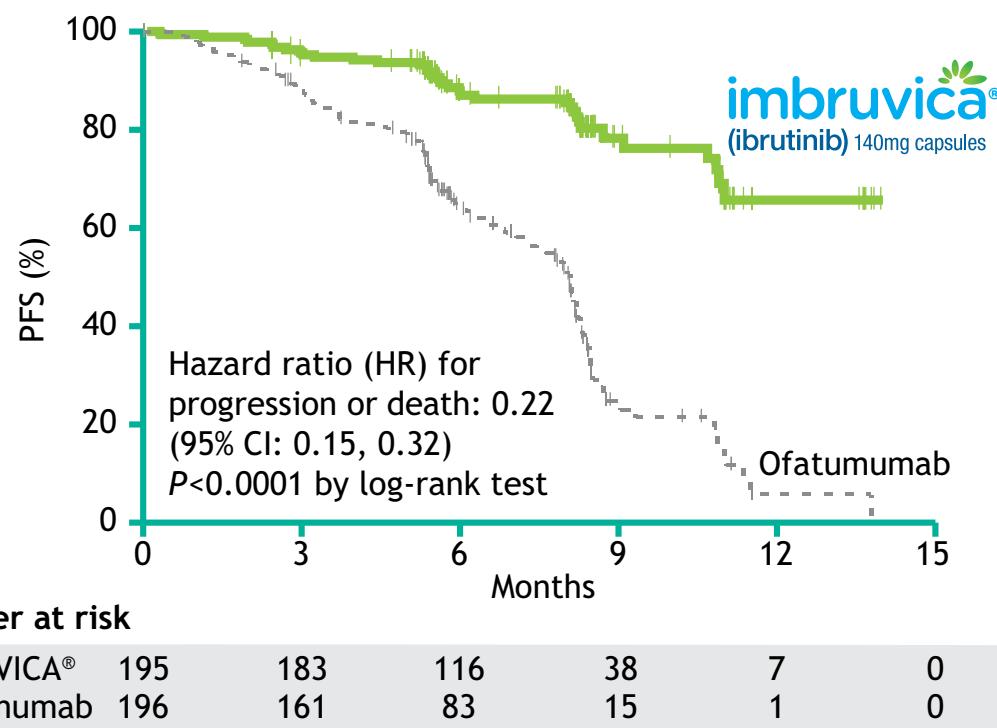
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- CLL with 17p deletion

■ Significantly improved overall survival (OS)—secondary endpoint

- 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA® arm (HR=0.43; 95% CI: 0.24, 0.79)
- Median OS not yet reached in either treatment arm
- 29% of ofatumumab patients crossed over to receive IMBRUVICA® upon progression

■ Significantly extended progression-free survival (PFS)—primary endpoint

78% statistically significant reduction in the risk of death or progression (independent review)



Results from the randomized, multicenter, open-label, Phase 3 RESONATE™ trial of IMBRUVICA® vs ofatumumab in patients with previously treated CLL. Patients (N=391) were randomized 1:1 to receive either IMBRUVICA® 420 mg orally daily until disease progression or unacceptable toxicity or IV ofatumumab at an initial dose of 300 mg, followed 1 week later by a dose of 2000 mg weekly for 7 doses, and then every 4 weeks for 4 additional doses. Fifty-seven patients randomized to ofatumumab crossed over following Independent Review Committee-confirmed progression to receive IMBRUVICA®. Primary endpoint: PFS as assessed by an Independent Review Committee (IRC) according to modified International Workshop on CLL Criteria.

■ Significantly improved PFS in patients with previously treated del 17p CLL

- 75% reduced risk of progression or death (HR=0.25; 95% CI: 0.14, 0.45)
 - Median PFS not reached with IMBRUVICA® vs 5.8 months with ofatumumab

In CLL studies, approximately 5% of patients discontinued due to adverse events

Please review the Important Safety Information on adjacent page.

ORAL, ONCE-DAILY DOSING

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving anti-platelet or anti-coagulant therapies. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and non-fatal infections have occurred with IMBRUVICA®. Twenty-six percent of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 23 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA® treatment and dose modification.

Second Primary Malignancies - Other malignancies (range, 5 to 10%) including carcinomas (range, 1 to 3%) have occurred in

patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 8%).

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA®. 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 a fetus.

ADVERSE REACTIONS

The most common adverse reactions ($\geq 20\%$) in the clinical trials were thrombocytopenia (56%), neutropenia (51%), diarrhea (51%), anemia (37%), fatigue (28%), musculoskeletal pain (28%), upper respiratory tract infection (28%), rash (26%), nausea (25%), and pyrexia (24%). Approximately 5% of patients receiving IMBRUVICA® discontinued treatment due to adverse events. These included infections, subdural hematomas, and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid concomitant administration with strong or moderate inhibitors of CYP3A. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid co-administration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with baseline hepatic impairment.

Please review the Brief Summary of full Prescribing Information on the following page.

To learn more, visit us at
www.IMBRUVICA.com

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)**IMBRUVICA® (ibrutinib) capsules, for oral use**

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Improvements in survival or disease-related symptoms have not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials [see Clinical Studies (14.1) in full Prescribing Information].

Chronic Lymphocytic Leukemia: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy [see Clinical Studies (14.2) in full Prescribing Information].

Chronic Lymphocytic Leukemia with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion [see Clinical Studies (14.2) in full Prescribing Information].

CONTRAINdications

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding [see Clinical Studies (14) in full Prescribing Information].

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Twenty-five percent of patients with MCL and 26% of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE) [See Adverse Reactions]. Monitor patients for fever and infections and evaluate promptly.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 23 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification [see Dosage and Administration (2.3) in full Prescribing Information].

Second Primary Malignancies: Other malignancies (range, 5 to 10%) including carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 8%).

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. 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 a fetus [see Use in Specific Populations].

ADVERSE REACTIONS

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

- Hemorrhage [see Warnings and Precautions]
- Infections [see Warnings and Precautions]
- Cytopenias [see Warnings and Precautions]
- Atrial Fibrillation [see Warnings and Precautions]
- Second Primary Malignancies [see Warnings and Precautions]

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

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

IMBRUVICA® (ibrutinib) capsules

The most commonly occurring adverse reactions ($\geq 20\%$) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions ($\geq 5\%$) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of $\geq 10\%$ are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in $\geq 10\%$ of Patients with MCL (N=111)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administrative site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia: The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included

IMBRUVICA® (ibrutinib) capsules

48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 ($\geq 20\%$) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of $\geq 10\%$ are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in $\geq 10\%$ of Patients with CLL (N=48) in Study 1

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
Infections and infestations	Dyspepsia	13	0
	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infection	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
General disorders and administrative site conditions	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
Skin and subcutaneous tissue disorders	Bruising	54	2
	Rash	27	0
	Petechiae	17	0
Respiratory, thoracic and mediastinal disorders	Cough	19	0
	Oropharyngeal pain	15	0
	Dyspnea	10	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
Nervous system disorders	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
Metabolism and nutrition disorders	Decreased appetite	17	2
Neoplasms benign, malignant, unspecified	Second malignancies*	10*	0
Injury, poisoning and procedural complications	Laceration	10	2
Psychiatric disorders	Anxiety	10	0
	Insomnia	10	0
Vascular disorders	Hypertension	17	8

*One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions

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Study 2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2.

Table 5: Non-Hematologic Adverse Reactions $\geq 10\%$ Reported in Study 2

System Organ Class ADR Term	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Fatigue	28	2	30	2
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

IMBRUVICA® (ibrutinib) capsules**Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2**

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

* Based on laboratory measurements per IWCLL criteria

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

CYP3A Inhibitors: In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of $1445 \pm 869 \text{ ng} \cdot \text{hr}/\text{mL}$ which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity [see Dosage and Administration (2.4) in full Prescribing Information].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in full Prescribing Information].

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction [see Clinical Pharmacology (12.3) in full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category D [see Warnings and Precautions].

Risk Summary: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

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

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) [see Clinical Studies (14.2) in full Prescribing Information].

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Renal Impairment: Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) $> 25 \text{ mL/min}$. There are no data in patients with severe renal impairment (CLcr $< 25 \text{ mL/min}$) or patients on dialysis [see Clinical Pharmacology (12.3) in full Prescribing Information].

Hepatic Impairment: Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) $\geq 3.0 \times$ upper limit of normal (ULN) were excluded from IMBRUVICA clinical trials. There is insufficient data to recommend a dose of IMBRUVICA in patients with baseline hepatic impairment [see Clinical Pharmacology (12.3) in full Prescribing Information].

Females and Males of Reproductive Potential: Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm [see Use in Specific Populations].

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- **Hemorrhage:** Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].
- **Infections:** Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills) suggestive of infection [see Warnings and Precautions].
- **Atrial Fibrillation:** Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see Warnings and Precautions].
- **Second primary malignancies:** Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].
- **Embryo-fetal toxicity:** Advise women of the potential hazard to a fetus and to avoid becoming pregnant [see Warnings and Precautions].
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day [see Dosage and Administration (2.1) in full Prescribing Information].
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose [see Dosage and Administration (2.5) in full Prescribing Information].
- Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

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PRC-00524 07/14

Recurrence of Breast Cancer Years After the Initial Tumor

Marj P. Zimmerman, MS, BSPharm; and Stanton R. Mehr

Tamoxifen was approved by the FDA in 1977 to treat advanced breast cancer. In 1998, the Early Breast Cancer Trialists' Cooperative Group published results showing that tamoxifen was effective in preventing breast cancer recurrence in patients whose tumors were estrogen receptor (ER)-positive or of unknown ER status,¹ which led to an expansion of the drug's indication.² As effective as tamoxifen and other therapies have been, some breast tumors do recur. Despite the considerable scientific data and many successes in treating breast cancer, not much is known about recurrent breast tumors, other than that they can appear in almost any location in the body and at any time after remission is attained—even decades later.

A Cure or a Disease-Free Period?

The incidence of breast cancer has remained relatively stable since 2004.³ Declining incidence during the 1990s was attributed in part to lower utilization for estrogen replacement therapy for the treatment of menopausal symptoms.⁴

Alongside a stable level of breast cancer incidence, breast cancer deaths have dropped 34% since 1990.⁵ Better therapies have led to improved 5-year survival rates, which vary by race (90% for Caucasians and 79% for African Americans) and by stage at the time of diagnosis (Table 1). The relative survival rates at 10 and 15 years are 83% and 78%, respectively, for diagnosis at any stage.³ As a result, the number of breast cancer survivors is accumulating; about 3.1 million Americans are breast cancer survivors, defined as those patients who have completed active treatment.⁶

Despite these encouraging statistics, mortality is still high among patients who are initially diagnosed with advanced-stage breast cancer. For patients who are initially diagnosed with early-stage disease, recurrent breast cancer remains a principal cause of death,⁷ which may occur years afterward: the old philosophy that patients who do not demonstrate tumor recurrence for 5 years are “cured” has been replaced by the more precise observation that they remain “cancer-free.”

The Complexity of Recurrence

Location and Recurrence. Breast cancer survivors may live cancer-free for the remainder of their lives, but several other

outcomes are possible. These include (1) living cancer-free for many years but having a late recurrence, (2) living cancer-free for many years but developing a second cancer, (3) having intermittent periods of treatment for active disease, or (4) living with cancer without any disease-free periods of time.⁶

Up to one-fifth of breast cancer survivors will experience a recurrence.⁸ The rate of recurrence at 10 years has declined since the 1980s and 1990s, when it ranged from 8% to 19%, to 2% to 7% in the past decade, depending on multiple factors. Whether a breast cancer survivor experiences a recurrence can depend on age at initial diagnosis, genetic background, what stage the cancer is at diagnosis, receptor type, histologic and nuclear grade of tumor, and how the original tumor was treated.^{6,8}

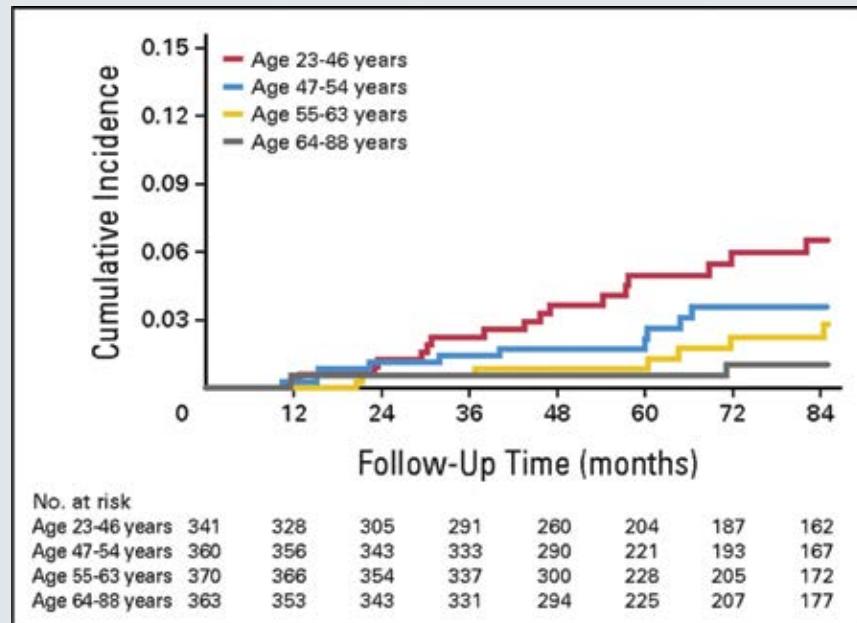
Recurrence, which may not necessarily be the same tumor reappearing, can be 1 of 3 types⁹:

- **Local recurrence.** Cancer recurrence is in the same localized area of the breast (ipsilateral) as the first tumor, or in the mastectomy scar. When breast cancer appears in a different quadrant of the breast from the original tumor or in the other breast (contralateral), it is usually a new tumor.¹⁰
- **Regional recurrence.** The cancer is in nearby lymph nodes (eg, under the arm or around the collarbone).
- **Distant recurrence.** The cancer appears in another part of the body that is some distance from the original site (eg, bone marrow, lungs, liver, brain).

Part of the challenge is determining whether a second appearance of cancer is a recurrence or a new cancer. Regional and distant recurrence likely represent completely new tumors. For example, a recurrence that appears in the liver 10 years after the initial breast tumor is treated with agents appropriate to the tumor location (ie, using hepatic cancer therapies vs breast cancer therapies).

A small study in the mid-1990s found that 36% (N = 18) of the primary tumors that were ER-negative and progesterone receptor (PR)-positive were instead ER-negative and PR-negative in their recurrent form, while tumors that were initially receptor-negative remained so on

Figure. Unadjusted Cumulative Incidence of Local Recurrence by Age Quartile on the Basis of Competing Risks Analysis



Source: Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. *J Clin Oncol.* 2011;29(29):3885-3891.

recurrence. The authors concluded that the loss of ER expression in recurrent breast cancer may be the reason recurrent tumors respond poorly to endocrine therapy.¹¹ This finding suggested a distinct profile of the recurrent tumor. Patricia Ganz, MD, director, Cancer Prevention and Control Research, and director, Patients and Survivors Program Area, of the UCLA Jonsson Comprehensive Cancer Center, told *Evidence-Based Oncology*, “Breast cancers are made up of a mixture of cells. As a result, the recurrence may not be exactly like the primary tumor and may represent a subset of cells that disseminated. So we sometimes see tumors that were HER2 (human epidermal growth factor receptor)-negative initially show evidence of HER2 at recurrence. Likewise, tumors that were ER-positive or -negative may change. The majority of recurrences—about 85%—are same as primary.”

Two-thirds of breast recurrences are identified as being a local recurrence, with the tumor recurring in the same breast in the same place or close to the original tumor; these cases are considered new growth of the old tumor. When there is a local recurrence, it usually occurs within 5 years of the initial breast cancer diagnosis.¹² After initial treatment, approximately 15% of breast can-

cer survivors will develop a second breast malignancy within 10 years,¹³ and about 40% of patients who experience recurrence have a regional recurrence in both the breast tissue or the chest wall, and in the lymph nodes. Fewer than 5% of patients have a recurrence that appears just in the lymph nodes, usually the:

- internal mammary (under the chest wall along the breastbone)
- infraclavicular (just below the collarbone)
- supraclavicular (base of the neck)
- axillary (underarm area) closest to the original tumor site
- axillary on the contralateral side (this is rarely seen)¹⁴

Age and Recurrence. Most women diagnosed with breast cancer are older than 65 years (median age, 61 years). However, one-fifth of those diagnosed are younger than 50 years.⁶ Past studies have shown that patients diagnosed at a younger age have a greater chance of recurrence than those diagnosed at an older age. Even with advances in therapy, younger women are more likely to experience a local recurrence (Figure).¹⁵

Breast Cancer-Receptor Type and Recurrence. Estrogen plays a major role in the development and progression of breast

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PW Oncology Mapped!®

The screenshot shows the homepage of the Patient Assistance NOW Oncology website. At the top, there's a banner for "Patient Assistance NOW ONCOLOGY". Below it, a large orange section features a photo of a woman and a child. Text includes "Are You a US Patient?", "The Program Finder may help you pay for your medicines.", and "Learn More >". Another section titled "Access to Therapies Made Easier" shows a printer and a card labeled "CO-PAY CARD". Text here says "All in one place...co-pay assistance for all Novartis Oncology medications." and "Not eligible for coverage? Other options may be available." with a "Learn More >" button.

The screenshot shows the Novartis Oncology Provider Portal homepage. It features a Novartis logo at the top right. A central image shows two hands reaching towards each other. Text on the page includes "Welcome to Novartis Oncology US", "REGISTER NOW", "Already registered?", "Have questions?", "PRODUCT INFORMATION", "CONTACT US", and "Novartis Oncology shares your commitment to helping patients living...". To the right, a callout box contains the following text:

Convenience and patient access are 1 click away:

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

Novartis Oncology Provider Portal

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- Download forms
- Click on a patient's name to instantly display that patient's information
- Attach a document to a patient's electronic file (as easy as adding an attachment to an e-mail)
- Manage your individual user profile and easily change your contact information

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Patient Assistance NOW Oncology
www.OncologyAccessNow.com

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Recurrent Breast Cancer
(continued from 409)

Table. 5-Year Survival by Stage at Diagnosis

Breast Cancer Stage	5-year Relative Survival
0 (in situ stage)	100%
I (local stage)	100%
II (either local or regional stage depending on lymph node involvement)	93%
III (regional metastasis)	72%
IV (distant metastasis)	22%

HDHP indicates high-deductible health plan; PPO, preferred provider organization.
Source: American Cancer Society. Cancer Treatment & Survivorship Facts & Figures 2014-2015. www.cancer.org/acs/groups/content/@research/documents/document/acspc-042801.pdf. Accessed June 23, 2014.

cancer. Seventy-five percent of breast cancer tumors express ER, and 55% express PR. HER2 also plays an important role in the development and progression of breast cancer. There are 5 molecular breast cancer subtypes, 4 of which are most commonly observed—luminal A, luminal B, HER2 type, and triple negative.^{15,16} Many times, luminal A and luminal B are combined into 1 subtype, estrogen/progesterone-positive.

Patients with hormone receptor-positive tumors have a recurrence rate that is twice as high as those with hormone receptor-negative tumors at 5 years posttreatment.⁸ Women with ER-positive tumors have a greater risk of recurrence in later years than in the first 2 years.^{17,18} Overall, ER-positive tumors are associated with a long-term recurrence rate of 2% per year but are less likely to cause death from breast cancer than other tumor subtypes.¹⁶ Overall, patients with hormone receptor-positive tumors have the best outcomes.

ER-negative tumors mostly recur during the first 5 years, whereas the ER-positive tumors recur later.^{17,18} By 15 years after diagnosis, the risk for recurrence is the same for both receptor types.⁷

Triple-negative breast cancers (TNBC) have a high risk of recurrence, especially for distant recurrences, compared with receptor-positive tumors.⁶ However, patients with TNBC who do not experience a recurrence within 5 years are more likely to remain cancer-free than patients with ER-positive tumors.¹⁶ A study by Miller and colleagues revealed that 15% of locoregional HER2-positive tumors recurred after 5 years, compared with 1% of luminal A tumors.¹⁹

Influence of Treatment Type on Recurrence. Evaluating a patient's risk of breast cancer recurrence is further complicated by another factor: treatment of the initial cancer.¹⁹ The risk of distal recurrence is the same for patients having had a mastectomy or a lumpectomy plus radiation therapy.¹² Patients undergoing lumpectomy plus radiation therapy have an absolute risk reduction of 16% for any re-

currence (locoregional or distant) within 10 years.²⁰ For patients who had a mastectomy, local recurrence will usually be observed 3 to 5 years after the surgery.⁸

When breast-conserving therapy approaches are used to treat early breast cancers, an annual incidence rate of local recurrence of 1.3% to 1.7% has been observed between 2 and 7 years following the initial treatment. The annual recurrence rate drops to 0.4% per year beginning at 10 years after initial treatment.⁷ Recurrence rates are similar for women with ER-positive and ER-negative original tumors when treated with breast conserving surgery or mastectomy.¹⁶ Including radiation therapy for patients with ER-positive tumors lowers their probability of an ipsilateral recurrence, compared with those who have ER-negative tumors. In cases of recurrence, patients with ER-positive tumors present better outcomes than those with ER-negative tumors.¹⁶

For patients with hormone receptor-positive tumors who are treated with endocrine therapy for 5 years after their initial therapy, 20% will have a recurrence by 10 years of completing their treatment, with twice as many having a recurrence during the first 5 years than in the second 5 years.^{8,21} In a study by Cado and associates,¹⁶ in half of the tumors that recurred in patients treated with tamoxifen, recurrence was observed between 6 and 15 years from diagnosis. A study by Davies and associates²¹ showed that continuing tamoxifen for 10 years, rather than 5 years, further reduced the risk for recurrence, especially after 10 years. Adjuvant endocrine therapy for hormone receptor-positive tumors reduces the risk of recurrence by up to half.²¹ The American Society of Clinical Oncology (ASCO) recently updated its guidelines to recommend 10 years of adjuvant endocrine therapy, rather than the 5 years previously recommended, to lower the risk of breast cancer recurrence and contralateral breast cancer.²² More long-term studies will help guide the treatment of patients with hormone receptor-positive

tumors to prevent recurrent breast cancer.

Patients with HER2-positive tumors have a greater chance of local recurrence than patients with ER-positive and HER2-negative tumors after both breast conserving surgery and mastectomy. These patients have a greater chance of a local recurrence than patients with triple-negative tumors; however, after a mastectomy, patients with TNBC seem to have a greater chance of local recurrence.¹⁶

Interestingly, patients with TNBC who have breast-conserving therapy with radiation have a lower risk of a local recurrence than those who have a mastectomy without radiation. These patients also have an increased risk for distal recurrence that peaks around 3 years, and after 8 years, distal recurrences are typically not observed.¹⁶ Even after adjuvant chemotherapy, the risk for recurrence is the greatest in patients with HER2-positive and TNBC tumor subtypes.²³ Ganz added that this aspect has not been well studied. "Registries do not track this information accurately," she said. "There is something called the Metastatic Breast Cancer Alliance, which is a consortium of advocacy groups trying to advocate for more information on this."

Other Considerations. Presence of BRCA1 and BRCA2 gene mutations increase a woman's risk for developing breast cancer. Individuals with these mutations are also at a higher risk for contralateral breast cancer after having been diagnosed and treated for an initial breast tumor compared with those who do not have such mutations (26% vs 3%).⁸

Other factors that appear to influence the risk of recurrence are levels of Ki-67, a cellular marker for cell proliferation, CK 5/6, p53 markers of basal-like tumors, and bcl-2, a proto-oncogene located on chromosome 18. Multiple genes that are potential markers for recurrence are included in the Oncotype DX (21 genes), Mammostrat (5 genes), MammaPrint (70 genes), and PAM50 (50 genes) genomic assays.^{24,25}

Reducing the Risk for Recurrence. Many of the risks for the recurrence of breast cancer cannot be altered. However, lifestyle modifications and monitoring for the recurrence of breast cancer may be strategies that can reduce the risk of recurrence. In fact, key resource recommendations have been developed for appropriate survivorship care²⁶ (see Sidebar).

Trying to Better Understand Breast Cancer Recurrence

Advances in treatment and in understanding the genomics of breast cancer have led to improved 5-year survival in

those patients diagnosed with and treated for breast cancer. However, we do not as yet have a thorough understanding of the patients who have a recurrence of their cancer or who develop another tumor.

According to information from provided by the American Cancer Society to Evidence-Based Oncology, there are no registries that accurately track characteristics of patients and their tumors, and who experiences a recurrence. A better understanding of whether patients at long-term risk for recurrence may redevelop their cancer or develop a new tumor may assist in reducing this risk further, and in optimizing the treatment options available to them.

In the meantime, the concept of a "cure" in patients with breast cancer is more ambiguous than ever: patients in breast cancer survivorship programs with long-term remissions are increasingly being considered to have chronic disease, rather than acute episodic cancers. Ganz commented, "This is pretty common now for patients with HER2-positive disease or hormone receptor-positive disease." The problem is that we really don't know how many people can be addressed in this way. "Exact numbers are not available," she said, "but we're hoping to get a handle on this." **EBO**

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Breast Cancer Survivorship Programs: More Than a Treatment

Patients who have survived the challenges of breast cancer (and its treatment) may find themselves in remission or cancer-free but still experiencing long-term complications, such as lymphedema, fatigue, weakness, osteoporosis, cardiovascular disorders, and cognitive difficulties. The traditional care model for breast cancer survivors focuses on ongoing surveillance to detect recurrence, but does not specifically address their psychological and supportive care needs.¹ Cancer survivorship programs seek to improve coordination of care after the initial treatment of cancer ends.² With the number of cancer survivors on the rise, these programs may have particular value for the growing population of those surviving a bout of breast cancer. These programs emphasize providing surveillance for long-term treatment complications, adhering to clinical guidelines, meeting patients' psychological needs, and providing supportive care services.^{1,3,4} Most major cancer centers in the United States offer these programs. Although the evidence that breast cancer survivorship care programs improve outcomes is limited thus far, patients and providers believe they are of value.^{3,5} Ganz's group in UCLA² published evidence that breast cancer survivors were undergoing unnecessary testing and not getting mammograms when they should, with high variability among individual physicians' patterns of care.

Access to breast cancer survivor care programs is limited. One study found that only 35% of eligible women older than 65 years received a breast cancer survivorship care plan.³ These investigators found that age discrimination may play a role in who receives a survivorship care plan: for each 1-year increase in age, researchers found a 5% decreased probability that the patient would receive a survivorship care plan.³

According to some researchers, employing the Patient-Centered Medical Home or shared-care model, using a multidisciplinary approach, can build improved survivorship programs.⁶ The prospective surveillance program¹ forms the basis for addressing breast cancer survivorship—a sort of rehabilitation of the person from the physical, clinical, and psychological perspective.

The following are but a few examples of breast cancer survivorship programs that embrace the multidisciplinary approach:

- Lynn Sage Breast Cancer Survivorship Program at the Robert Lurie Comprehensive Cancer Center of Northwestern University (http://cancer.northwestern.edu/public/why_northwestern/specialty_programs/programs/womens.cfm)
- UCLA-LIVESTRONG™ Survivorship Center of Excellence at the UCLA Jonsson Comprehensive Cancer Center (<http://www.cancer.ucla.edu/Index.aspx?page=221>)
- Breast Cancer Survivorship Clinic at MD Anderson Cancer Center (<http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-topics/survivorship/follow-up-care/breast.html>)
- The Breast Cancer Survivorship Initiative at the University of Michigan Comprehensive Cancer Center (<http://www.mcancer.org/breast-cancer/survivorship>)

An important requirement of survivorship programs (or good follow-up care in general) is coordination of healthcare personnel. Studies have found gaps in sharing treatment summaries and overall survivorship care plans between medical oncologists and primary care physicians.² Only 20% of the oncologists said they share the full survivorship plan with the primary care physician (PCP), and 50% claim to share a treatment summary only. The percentages of PCPs claiming to receive this information from oncologists are far lower.²

There is activity afoot at the National Committee for Quality Assurance (NCQA) to address the sharing of cancer survivorship program information between PCPs and oncologists. Patricia Barrett, MHSA, NCQA's vice president of product development and policy, told *Evidence-Based Oncology* about a pilot project that is under way to implement and test patient-centered oncology care. Under a contract with the Patient Centered Outcomes Research Institute (PCORI), NCQA is extending the patient-centered medical home model to oncologists. NCQA's accreditation program applies to other specialty specialist groups, called patient-centered specialty practices (PCSPs), which build off the same requirements. How did cancer survivorship programs arise as a measure for oncology specialty practices? Barrett explained, "It came from conversations with cancer survivors and oncologists on our advisory group. It grew out of things that already were in place with regard to transitions from specialty back to primary care. And it clearly is something that is patient centered." In terms of the requirements of cancer survivorship programs for accreditation purposes, "NCQA is not highly specific about the communication includes," said Barrett. "It must consist of a summary of care and an ongoing plan of care from the oncologist to the primary care physician." The PCP will then coordinate the patient's care with other specialists as needed, per the care plan. "Primary care is expected to have that central coordinating role," she stated. **EBO**

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AACR Seeks FDA Oversight on LDTs

Surabhi Dangi-Garimella, PhD

With an increased awareness and use of personalized medicine, the diagnostic test market is thriving. The tests being marketed run the gamut, from companion diagnostics, to lab-developed tests (LDTs), to direct-to-consumer tests. However, the FDA has not been very stringent about validating these products. This can create safety issues, since important treatment decisions are based on the results obtained from these tests.

As reported in a previous issue of *Evidence-Based Oncology*,¹ on July 31, 2014, the FDA announced the issuance of a final guidance for companion diagnostics and a risk-based oversight framework for LDTs. While companion diagnostic tests, which can detect specific gene mutations and help select a treatment regimen, have always been FDA-regu-

lated, LDTs are developed by an individual laboratory and thus far have not fallen under the FDA's jurisdiction.²

The American Association for Cancer Research (AACR), in an effort to hasten the process, issued a policy statement urging the FDA to actively exert its authority to regulate high-risk LDTs that drive physician treatment decisions, including regimens in oncology. According to Charles L. Sawyers, MD, "It is vital that all diagnostic tests used to make high-risk treatment decisions be FDA-approved, so patients and physicians can be assured of the test's safety and accuracy."³ Sawyers, a coauthor of the policy statement, is chair of the Human Oncology and Pathogenesis Program at the Memorial Sloan Kettering Cancer Center in New York and is the immediate past president of AACR.

Affirming the increasing importance of diagnostic tests in various fields of healthcare, the policy statement, published in *Clinical Cancer Research*, states, "Patients and physicians should be able to rely on the test results that are forming the basis of high-risk treatment decisions, whether these tests are developed as an LDT or are kits approved by the FDA. Implementation of a risk-based framework by the FDA that would provide for evaluation of all high-risk molecular diagnostic tests would balance the need for encouraging innovative medical product development with the need for ensuring patient safety."⁴

EBO

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First PD-1 Inhibitor Approved for Melanoma

Surabhi Dangi-Garimella, PhD

The long-awaited PD-1 inhibitor from Merck, pembrolizumab (Keytruda), was granted accelerated approval by the FDA. The approval grants patients with unresectable melanoma, who are non-responsive to other drugs, access to this immunotherapy,¹ which could have a tremendous impact on the prognosis of the 76,100 new cases of melanoma estimated in 2014.²

"Keytruda is the sixth new melanoma treatment approved since 2011, a result of promising advances in melanoma research," said Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "Many of these treatments have different mechanisms of action and bring new options to patients with melanoma."¹

Keytruda is the first immunotherapy molecule in the pipeline—a checkpoint inhibitor—to be approved after ipilimumab (Yervoy; Bristol-Myers Squibb). Ipilimumab, a CTLA-4 inhibitor, has been used in the treatment of metastatic melanoma since 2011.³ Ipilimumab has since been evaluated in other indications, such as non-small cell lung cancer.

Keytruda is the first approved drug

that blocks the PD-1 signaling pathway, which restricts the body's immune system from attacking melanoma cells, and is intended for use following treatment with ipilimumab. For melanoma patients whose tumors express the BRAF V600 mutation, Keytruda is intended for use after treatment with ipilimumab and a BRAF inhibitor.¹

The treatment was granted breakthrough therapy designation following preliminary clinical evidence that showed the drug may offer a substantial improvement over available therapies, which include ipilimumab, peginterferon alfa-2b, vemurafenib, dabrafenib, and trametinib. It also received priority review and orphan product designation. Priority review is granted to drugs that have the potential, at the time the application was submitted, to be a significant improvement in safety or effectiveness in the treatment of a serious condition. Orphan product designation is given to drugs intended to treat rare diseases.¹

The encouraging results with Keytruda resulted in the regimen being evaluated under the FDA's accelerated approval program, which allows earlier patient access to promising new drugs even while confirmatory trials are on-

going, by using surrogate end points. Improved survival or disease-related symptoms with Keytruda have not yet been established.¹

Meanwhile, Bristol-Myers Squibb and Ono Pharmaceutical Company filed a lawsuit against Merck arguing that Keytruda impinges on their patent for a method of harnessing the body's immune system to fight cancer by blocking the PD-1 receptor. The lawsuit was filed on the same day as the market approval of Keytruda. Bristol-Myers Squibb and Ono already have a PD-1 inhibitor, nivolumab (Opdivo), approved in Japan. Nivolumab is expected to be submitted for approval to the FDA by the end of September 2014 for melanoma treatment, and by the end of the year for lung cancer.⁴

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The encouraging results presented by Keytruda granted it a breakthrough therapy designation, along with a priority review and evaluation under the accelerated approval program.

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Avastin: First Molecule in Nearly a Decade for Metastatic Cervical Cancer

Surabhi Dangi-Garimella, PhD

Avastin (bevacizumab), a monoclonal antibody that inhibits the vascular endothelial growth factor and prevents the growth of blood vessels (angiogenesis), has received FDA approval to treat patients with persistent or late-stage cervical cancer.¹ The approval allows administration of bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan in the said population.²

The phase 3 study, conducted in 452 women, met its primary end point of improved overall survival (OS), with a significant 26% reduction in the risk of death when bevacizumab was com-

bined with chemotherapy, compared with chemotherapy alone (median OS: 16.8 months vs 12.9 months; hazard ratio = 0.74; P =.0132). Additionally, inclusion of bevacizumab resulted in a higher rate of tumor shrinkage compared with chemotherapy alone.²

Avastin, approved in 2004 as first-line treatment for patients with metastatic colorectal cancer, was the first angiogenesis inhibitor to be granted FDA authorization.³ Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, said, "Avastin is the first drug approved for

patients with late-stage cervical cancer since the 2006 approval of topotecan with cisplatin. It is also the first biologic agent approved for patients with late-stage cervical cancer and was approved in less than 4 months under the FDA's priority review program."¹

Some of the treatment-related side effects of Avastin include hypertension, thrombosis, and gastrointestinal-vaginal fistulas.² **EBO**

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Research Report

Moving Beyond *BRCA* Mutations in Familial Breast Cancer

Surabhi Dangi-Garimella, PhD

The concept of inherited breast cancer first brings to mind the *BRCA* genes. The 2 genes, *BRCA1* and *BRCA2*, share about 2000 distinct mutations between them, and reports suggest that 1 in 400 to 800 people carry a pathogenic germline mutation in *BRCA1* or *BRCA2*.¹ The phenotype of these mutations: nonfunctional *BRCA1* or *BRCA2* proteins or a complete lack of expression of the proteins. Late last year, the US Preventive Services Task Force provided an update to its 2005 recommendations, which was reported by *Evidence-Based Oncology*,² reaffirming the genetic risk assessment and *BRCA* mutation testing in women susceptible to breast and ovarian cancer, based on family history. The lack of expression, or an inactivating mutation, of a tumor suppressor, increases susceptibility to cancer. Germline mutations in *BRCA1* and *BRCA2* have historically been associated with the development of breast^{3,4} and ovarian cancer,⁵ while recent studies have also identified the role in pancreatic cancer⁶ and colorectal cancer.⁷

However, the *BRCA* genes do not tell the whole tale—while women with

BRCA mutations have an increased risk of breast cancer, mutations in other genes have been identified. These mutations do exist, though they are less prevalent and have a relatively smaller impact on the familial form of the disease. The rapid progress in bioinformatics has given momentum to the evaluation of the genetic profile of a large number of tumor samples, which can identify these rare mutations. One such project, a collaboration between researchers at the Huntsman Cancer Institute at the University of Utah and several other research organizations around the globe, discovered 4 new genes responsible for increased susceptibility to familial breast cancer: *RINT1*, *MRE11A*, *RAD50*, and *NBN*.⁸

Bioinformatics and Personalized Medicine

Targeted/personalized treatment is undoubtedly the future of cancer therapy. Our improved understanding of within-tumor and between-tumor heterogeneity has led to the development of interventions that can be tailored to an individual's specific cancer subtype.

However, the task is daunting—the complex nature of cancer, and the ease with which the tumors adapt, results in resistance phenomena that are at times hard to combat.

With this in mind, the National Cancer Institute (NCI) launched *The Cancer Genome Atlas* (TCGA) in collaboration with the National Human Genome Research Institute (NHGRI).⁹ The pilot, initiated in 2006, was designed to generate an atlas that would map the sea of changes that accompany a specific cancer type. Additionally, the data are accessible to researchers all around the world, which can help them make and validate their own discoveries, as well as fill up the gaps that exist in the current knowledge of a particular cancer type—a concept recently corroborated by researchers at the Broad Institute.¹⁰ In a study published in *Nature* that evaluated nearly 5000 tumor and matching normal tissue samples (many from TCGA), the authors identified nearly all the known cancer genes in the 21 tumor types being evaluated, in addition to 33 novel genes.¹⁰

The New Genes in Familial Breast Cancer

RINT-1

Going back to the recent discovery of genes responsible for breast cancer inheritance, the authors identified 3 as yet undiscovered mutations in *Rad50 Interactor 1* (*RINT-1*). To follow up their findings, they conducted a mutation screen, which distinguished 29 carriers of rare, likely pathogenic variants—23 of these were identified in early-onset breast cancer cases and the remaining 6 were identified in matched controls. In families that had evidence of multiple cases of breast cancer, 4 additional carriers of rare genetic variants were identified. Additionally, *RINT-1* mutations were also found to increase the carrier's susceptibility to Lynch syndrome cancers (inherited cancer of the digestive tract), especially among relatives who had a cancer diagnosis at under 60 years of age.¹¹

RINT1 protein, expressed on the endoplasmic reticulum, the Golgi apparatus, and the centrosomes, has historically been identified as a cell cycle regulator that prevents tumor growth.¹²

Table. Breast Cancer Diagnosis Panels

Test	Company	Genes
High-risk hereditary breast cancer panel	Invitae	<i>BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53</i>
myRisk Hereditary Cancer	Myriad Genetics	<i>BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53, CHEK2, ATM, NBN, BARD1, BRIP1, RAD51C</i> (genes associated with breast cancer risk alone)
BreastNext	Ambry Genetics	<i>BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53, CHEK2, ATM, NBN, BARD1, BRIP1, RAD51C, MRE11A, MUTYH, NF1, RAD50, RAD51D</i>

Disruptions in the expression of this protein were found to cause abnormalities during both the interphase and mitosis, with the mitotic events leading to cell death. Additionally, homozygous deletion of RINT-1 alleles (*RINT-1^{-/-}*) resulted in embryonic lethality in mice, while the animals expressing heterozygous *RINT-1* (*RINT-1^{+/-}*) developed multiple tumors, emphasizing its role as a potential tumor suppressor.¹²

The DNA Repair Proteins: *MRE11A, RAD50, NBN*

Mutations in the *MRE11A-RAD50-Nibrin* (MRN) protein complex, a major player in DNA double-strand break repair, were also found to increase breast cancer susceptibility. Although defects in the MRN complex have previously been shown to predispose individuals to breast cancer,¹³ the exact mechanism of the defect is not clear. In the recent study published in *Breast Cancer Research*, the authors queried if the defect was a result of protein truncation or an expression of a missense protein. Further, they examined whether some of the rare MRN variants are responsible for intermediate-risk breast cancer susceptibility alleles.¹⁴

The results of this study, which evaluated samples from diverse ethnic groups, led the authors to conclude that *MRE11A*, *RAD50*, and *NBN* (*Nbs1*) are indeed intermediate-risk breast cancer susceptibility genes that should be included on cancer susceptibility diagnostic gene panels. Although truncation variants of these proteins were discovered in the patient samples, a significantly higher proportion of missense mutations were identified. However, the authors think that the data are insufficient to establish a clinically actionable classification of individual variants observed in the study.¹⁴

PALB2

The partner and localizer of *BRCA2* (*PALB2*) protein, initially recognized as a *BRCA2* binding partner, was later found

to interact with *BRCA1* as well.^{15,16} Responsible for Fanconi's anemia following a biallelic loss-of-function mutation, the monoallelic loss-of-function mutation of *PALB2* is a risk factor for breast cancer as well as pancreatic cancer.¹⁷ While analyses have provided risk estimates on loss-of-function *PALB2* mutations and familial breast cancer, a recent paper published in the *New England Journal of Medicine* took up the task of obtaining more precise and robust estimates, based on data collected across different locations within the United Kingdom—362 individuals across multiple generations of 154 families, and with different family histories.¹⁸ These individuals, who expressed truncated mutants, splice variants, or deletion mutants of *PALB2*, were 8 to 9 times more likely to develop breast cancer relative to the general population if they were below 40 years of age. Susceptibility reduced, however, with age: those in the 40-to-60-year age group were 6 to 8 times more likely to develop the disease, while those over 60 years of age were 5 times more likely to develop breast cancer.

The authors concluded that loss-of-function mutations in *PALB2* are an important determinant of hereditary breast cancer, although the risk of developing the disease in these individuals could overlap with *BRCA2* mutation carriers.¹⁸

Implications for the Patient

Some of the diagnostic panels that are currently available include some of these genes (Table),^{19,20,21} since they have all been associated with breast cancer. Inventia's "High-risk hereditary breast cancer" panel, for example, is a 7-gene panel that includes

PALB2, along with the *BRCA* genes. Myriad, which has been in the genetic testing marketplace for some time now, has developed the "Myriad myRisk Hereditary Cancer" panel—a 25-gene panel that points to susceptibility of an individual to familial cancers of the breast, ovary, endometrium, prostate, stomach, skin, and pancreas, and colorectal cancer.²² The panel includes *BRCA1*, *BRCA2*, *PALB2*, and *NBN*, among other genes, to identify the risk for familial breast cancer.²³ Myriad also markets the BRACAnalysis test, which evaluates mutations only in the *BRCA*

genes to identify hereditary risk of breast and ovarian cancer.²⁴

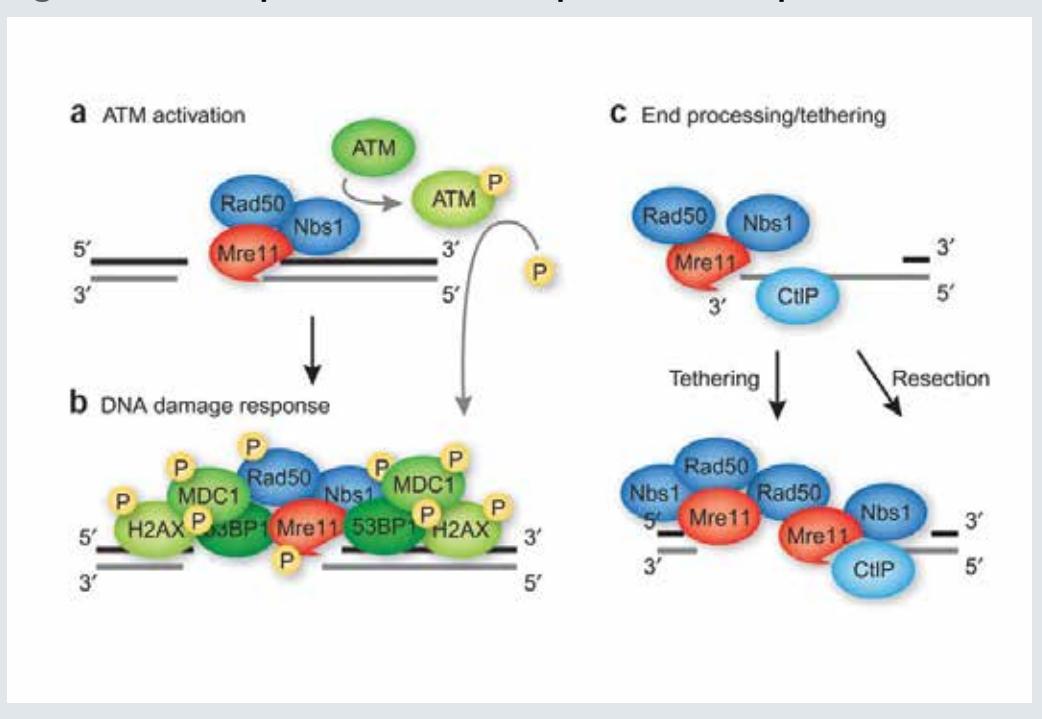
Several health insurance plans cover counseling and testing costs, if individuals decide to go that route. However, to reduce the risk of unnecessary testing, insurance companies like Cigna and Priority Health have mandated pre-testing genetic counseling for hereditary conditions—including breast cancer—from an independent genetic counselor.^{25,26} Additionally, the Affordable Care Act has made provisions for new health plans to provide coverage of physician-recommended counseling and *BRCA*-testing costs.²⁷

The tools are out there—the requirement is raising awareness in the population to appropriately utilize them. Individuals who have had cancer or those who have a known family history of cancer would be ideal candidates

for such testing. However, the process should be aided by a genetic counselor, who can evaluate the person's family tree to determine the need for testing. With newer genes being identified and validated in large and diverse populations, these panels will definitely expand. **EBO**

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Figure. MRN Complex Proteins Participate in DNA Repair

An intricate process with multiple players, the *Mre11*, *Rad50*, and *Nbs1* genes react to DNA damage by sequential interaction with multiple proteins, which together initiate double-strand DNA repair.

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Draft Statement: Evidence Connecting Diet to Colorectal, Breast Cancer Stronger Than Links to Lung, Prostate

Mary K. Caffrey

If you mother told you, "Eat your vegetables," she knew intuitively what science continues to affirm.

The 2015 US Dietary Guidelines Advisory Committee (DGAC), charged with making recommendations to update the nation's policies for healthy eating, held its fourth meeting on July 16 and 17, 2014, in Bethesda, Maryland. During the meeting, a key subcommittee tasked with reviewing recent evidence on how dietary patterns affect health developed draft language on the relationships between what Americans eat and 4 major cancers—breast, colorectal, prostate, and lung—as well as chronic conditions such as type 2 diabetes mellitus (T2DM) and obesity. This is the first time that the DGAC's report will include recommendations on the connections between diet and cancer.^{1,3}

Chaired by Barbara Millen, DrPH, RD, of Millennium Prevention in Westwood, Massachusetts, the 2015 DGAC consists of 15 scientists specializing in nutrition, cancer prevention, public health, and other fields who were appointed in spring 2013 to offer recommendations to the US secretaries of Health and Human Services (HHS) and Agriculture (USDA). As outlined by Congress, the process takes place every 5 years, with management rotating between HHS and USDA.^{2,3}

DGAC's work remains in draft form until the final report goes to the secretaries, who then review it alongside comments from the public—which have been received in-person and online—as well the many “stakeholders,” which include lobbyists for the food industry, some of whom have already appeared before DGAC during the public comment sessions.³

The final policy is released as *Dietary Guidelines for Americans*, a document that affects everything from the composition of school lunches, to the makeup of meals fed to the military, to the allotments that go into the Supplemental Nutrition Assistance Program. Fall-out from the guidelines sometimes stirs controversy. The work of the 2015 DGAC continues as the National School Boards Association and other groups lobby Congress for relief from the Healthy Hunger-Free Kids Act of 2010, which revamped the rules governing what school districts

receiving federal funds can serve in school lunches.^{4,5}

In prior remarks and in her opening address to the committee on July 16, Millen discussed the committee's assignment of examining how the improvements to the American diet can reduce chronic disease. The committee, she said, “is charged with providing technical assistance on how food, nutrition, and physical activity can do 2 things: promote the health of the US population and help reduce the burden of chronic disease and other lifestyle-related problems, and also develop recommendations and best methods and practices, at the individual and population level.”¹

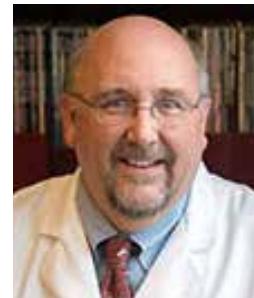
Millen said the emphasis on “dietary patterns” allows for several things: a review of how Americans eat now, a review of the evidence of what dietary patterns are associated with chronic disease and with cancers, and an analysis of “what works,” which will provide practical recommendations for healthcare and public health officials.

The first day of the July meeting featured presentations from Frank Hu, MD, PhD, MPH, of the Harvard School of Public Health, and Steven Clinton, MD, PhD, of the Ohio State University. Hu presented draft language on the relationship between dietary patterns and CVD, body weight/obesity, and T2DM, while Clinton presented language on the relationships between

dietary patterns and 4 major cancers that account for half of the cancer incidence in the United States: lung cancer, prostate cancer in men, breast cancer in women, and colorectal cancer.

As Hu and Clinton outlined, and as committee members noted, there was a high degree of consistency across the evidence base when examining what dietary patterns were connected with lower or higher incidence of chronic disease and with cancer. Among the 4 major cancers, evidence showed the strongest links between dietary patterns and colorectal cancer, and moderate evidence involving dietary patterns and postmenopausal breast cancer.

More illuminating, however, was the high level of consistency in the draft recommendations, whether they involved major cancers or chronic diseases. (For



Steven Clinton, MD, PhD

Table. DGAC Draft Conclusions, Dietary Patterns, and Selected Cancers¹

Colorectal Cancer

Moderate evidence suggests an inverse association between risk of colorectal cancer and dietary patterns that are:

- high in fruits, vegetables, legumes, whole grains, lean meats/seafood, low-fat dairy
- moderate in alcohol, and
- low in red or processed meats, saturated fats, and sodas/sweets.

In contrast, greater colorectal cancer risk is associated with diets that are:

- high in red/processed meats, French fries/potatoes, and sources of sugars (ie, sodas, sweets, and dessert foods).

Breast Cancer

Moderate evidence suggests that dietary patterns,

- rich in fruits, vegetables, and whole grains
- low in some animal products and refined carbohydrates,

are associated with reduced risk of postmenopausal breast cancer.

The data regarding this dietary pattern and premenopausal breast cancer risk points in the same direction, but the evidence is limited due to fewer studies.

DGAC indicates Dietary Guidelines Advisory Committee.

draft conclusions in colorectal and breast cancer, see the Table.) In summary, the committee draft conclusions find links between better health outcomes and:

- A diet high in fruits, vegetables, and whole grains
- A diet with regular amounts of fish, legumes, and low-fat dairy. Alcohol can be consumed in moderation
- A diet low in sugar-sweetened beverages, red and processed meats, refined grains, and saturated fats

there is some evidence that dietary patterns similar to those that affect breast cancer outcomes are in play, but it is very limited. And regarding lung cancer, Clinton said, additional research is needed to understand the interplay between diet and tobacco use, including the age when tobacco use starts and the type of tobacco involved.

More research is also needed, Clinton said, to understand the role of dietary patterns in premenopausal breast cancer. **EBO**

The consensus in the draft statements emerged from a rigorous process for all 4 major cancers and for the chronic diseases. Clinton said the literature review for dietary patterns and cancer covered the period from January 2000 through 2014, taking in a total of 82 articles: 25 involving breast cancer, 22 involving colorectal cancer, 4 on lung cancer, and 7 on prostate cancer.

At the outset, Clinton explained the limitations involved in the committee's review. “Despite the expanding number of available studies regarding dietary patterns and cancer risk, the portfolio of quality studies remains modest and employs a wide methodology in study design, dietary pattern assessment, and statistical approaches,” he said.

Indeed, the committee was unable to draw any conclusions about links between dietary patterns and prostate cancer, due to the disease's complex epidemiology and a variety of other factors. In lung cancer,

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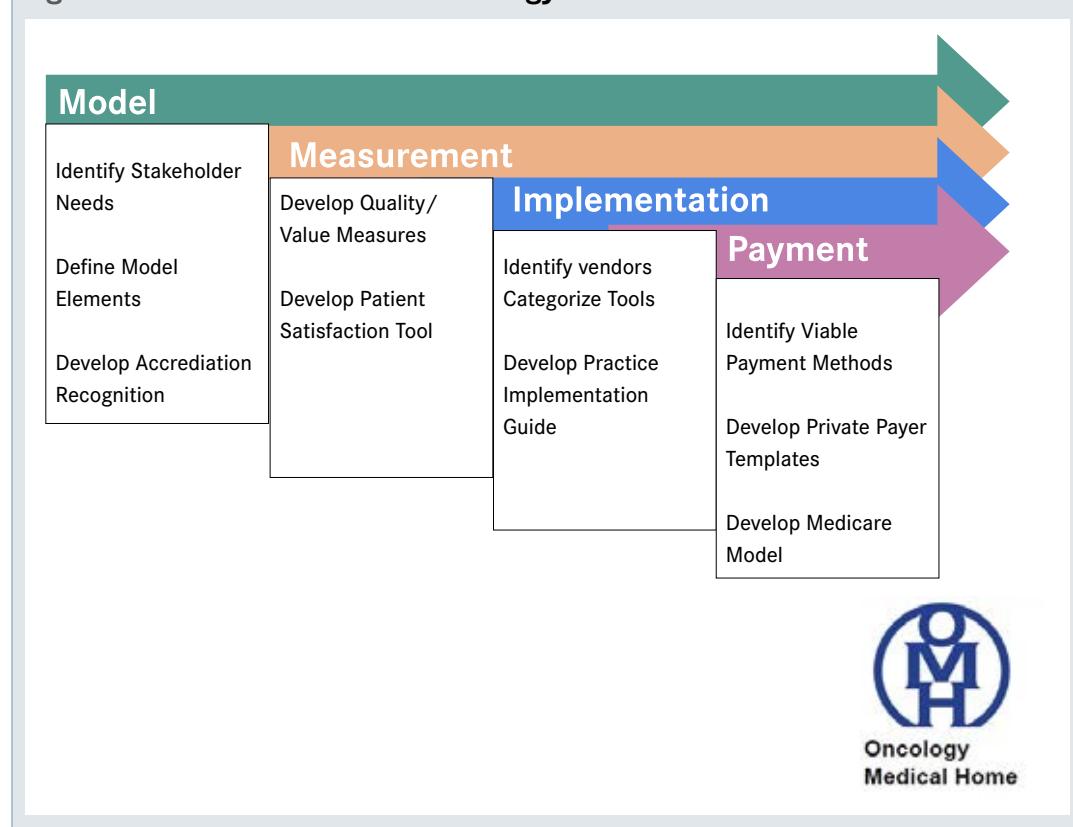
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Oncology Medical Home: Improved Quality and Cost of Care
(continued from cover)

Figure. Functional Model of the Oncology Medical Home



overwhelming for a primary care physician, especially with respect to symptom management (pain, nausea/vomiting, neuropathy, blood count, etc).¹ With the oncologist's clinic filling in as the medical home, the treatment and care process can be optimized to improve quality and efficiency, while minimizing adverse effects. Chemotherapy, in some patients, can lead to severe side effects that are quite difficult to manage and might require additional hospitalization, which can affect treatment outcomes and increase expenditure.¹

The following are key traits foreseen for an OMH:

- Coordinated, patient-centered care
- Evidence-based treatment plans with the aim of quality outcomes
- Accessible, efficient, and affordable care
- Care that is continuously improved by measuring against quality standards.¹

COA's OMH Initiative

Community Oncology Alliance wants to model OMH with care coordination, quality, and cost as their mantra. OMH could function on different reimbursement models that would place the patient front and center. COA's emphasis is on creating an accountable care model balanced with appropriate reimbursement, to ensure patient access to quality care that is also cost efficient.

With this objective, COA's OMH brings together oncologists, payers, insurance administrators, cancer care advocates, patient advocates, nursing representatives, and pharmacists to steer the initiative toward its goals.² To convert a clinical practice into a medical home, COA has laid down certain standards:

- Defining core quality and value measures for performance, including patient satisfaction surveys
- Developing a benchmark capability so providers can compare perfor-

mance with peers

- Develop tools and services that would help a clinic transition to an OMH
- Establish a platform of information exchange for practices to improve outcomes
- Develop different payment models with private payers as well as with Medicare to make OMH a viable oncology model.¹

A very important aspect of OMH is gaining accreditation. In collaboration with the Commission on Cancer (CoC), COA has developed an accreditation program—with input from cancer care stakeholders—in the following domains:

- Patient engagement
- Expanded access
- Evidence-based care
- Comprehensive team-based care
- Continuous quality improvement.³

Additionally, several payment-reform initiatives have been undertaken, under the guidance of both oncologists and practice administrators, to explore fee-for-service, shared savings, and bundled or episodic payment models. These initiatives involve COA's collaboration with the American Society of Clinical Oncology, Medicare, PriorityHealth, Aetna, and UnitedHealthcare, among others. COA will also be hosting a Payer Exchange Summit in Washington, DC, in October to exchange information on payment reform in oncology.⁴

OMH promises a radical change in oncology care that is—most importantly—patient-centric. As these models are implemented, and their performance analyzed across practices, we could expect a change for the better in cancer care. **EBO**

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The Community Oncology Alliance's emphasis is on creating an accountable care model balanced with appropriate reimbursement, to ensure patient access to quality care that is also cost efficient.

FDA Oversight of Laboratory Developed Tests Essential for Patient Health and Safety
(continued from cover)

education among my colleagues.

The dream of personalized medicine is now becoming a reality. Doctors can order genetic tests to determine disease risk or treatment options with a turn-around time unheard of when GINA became law. Doctors can now prescribe specifically tailored therapies based on

the genetic status of a cancerous tumor. For example, 80% of patients with non-small cell lung cancer with a mutation in their EGFR gene can benefit from a drug that targets this specific mutation. However, only one-fifth of patients with this type of cancer have the EGFR mutation, so it is imperative that doctors use

genetic testing to identify those patients who will respond to the drug and not waste time—and the \$12,000 that each treatment costs—giving it to those who cannot benefit from therapy. With the genetic test, doctors can target an incredibly effective drug to those patients from whom they expect the best response.

Commentary

The drug in this example was found to be safe and effective in an extensive review process required for FDA approval. However, some genetic tests, like this one to assess the EGFR mutation, are considered LDTs and have not been subject to FDA review. Without the FDA's review process, how can we be sure of the

reliability of these genetic test results?

Originally, LDTs were used to measure routine physical data such as cholesterol levels or white blood cell counts, and they were often designed, manufactured, and used in a single laboratory, such as a particular hospital. As such, while the FDA maintained the statutory authority to regulate these tests, it chose not to, due to the tests' simple nature and limited use. Since the completion of the Human Genome Project, however, LDTs have become much more sophisticated, and the repercussions of a false result can now be dangerous. The regulatory framework, however, has remained the same, with no assurance that the tests are reliable, safe, and effective.

The Clinical Laboratory Improvement Amendments (CLIA) directs CMS to oversee laboratory safety and ensure that LDTs are conducted in laboratories that meet clinical quality standards for personnel and laboratory practices. CLIA does not, and is not, authorized to ensure that laboratories performing LDTs produce evidence of effectiveness, nor does it require the reporting of post market adverse events. This means that under the current regulatory framework, patients and their doctors have no guarantee that the tests upon which they base important medical decisions are valid, reliable, safe, or effective. The FDA's recent action would change all of this, providing clarity and security for patients.

This situation is not hypothetical.

In June 2008, one of the largest clinical laboratory companies, LabCorp, began marketing OvaSure, an LDT designed to detect early-stage ovarian cancer by measuring the levels of 6 proteins in a blood sample. This kind of test is extremely valuable to patients with a risk of ovarian cancer. Removing the ovaries from an early-stage ovarian cancer patient, before the cancer has had the opportunity to spread, could save her life. Ninety percent of patients who catch the disease in the early stage are still alive 5 years later, but only 30% are likely to survive for 5 years if the cancer is caught late. Unfortunately, the vast majority of ovarian cancer cases are caught late.

While the need for an early diagnostic test is critical, an unreliable test could be extremely dangerous: a false positive may lead a woman to have her ovaries removed unnecessarily, and a false negative could be fatal. With only CLIA oversight, LabCorp was not required to prove that the 6 proteins the test detected could accurately predict disease. OvaSure was rushed to market before this crucial validation step and was later found to have an unfortunately high false positive rate. Many healthy women had unnecessary surgery to remove their ovaries, thinking they had ovarian cancer, only to discover after their surgery that they did not. In October 2008, just 4 months after its introduction, the FDA stopped the sale of OvaSure in the interest of public safety—they used a technicality to pull the prod-

uct, given the lack of a published framework for oversight of LDTs. Because the research underpinning OvaSure had been performed at Yale University, and not at LabCorp, OvaSure qualified as a medical device rather than an LDT. Had the DA been able to review this product through its currently proposed regulatory framework for LDTs, the test would never have made it to market in the first place.

LabCorp's OvaSure is not the only complex screening test the FDA has stepped in to regulate, which demonstrates the need for a new metric to guide oversight. FDA's recent proposal allows for proactive identification of riskier tests, eliminating the risk to patients of LDTs that are only regulated after they hit the market. This risk-based approach also puts all diagnostic test makers on equal footing, with each company required to prove its tests' effectiveness, regardless of how the test was produced. When laboratories provide doctors with data that directly impact patient diagnosis and treatment, doctors should have confidence that these tests are valid and the results reliable.

The FDA's newly announced framework for oversight provides for greater patient protection. Regulation by the FDA will ensure that LDTs are safe and effective, adverse events are properly reported, unsafe devices can be removed from the market, and patients are protected by informed consent procedures

LDTs have become much more sophisticated, and the repercussions of a false result can now be dangerous.

prior to their use of any investigational devices.

Now that genetic information is used regularly to guide treatment decisions, from cancers to cardiovascular disease, FDA is correct to take these steps to ensure that doctors are receiving test results that are accurate, safe, and effective. GINA empowered Americans to look into our own genes without fear of losing our healthcare or getting fired. This decision by the FDA will further empower patients to trust the results they receive, so that they and their doctors can make important, and lifesaving, healthcare decisions. **EBO**

Rep Louise M. Slaughter (D-NY) has been a member of the House of Representatives since 1986. As chair of the House Rules Committee from 2007 to 2010, she helped guide the Affordable Care Act to passage.

Cancer Trials Face a Shortage of Teen, Young Adult Enrollees (continued from cover)

this phenomenon: overlapping age criteria, cancer type, and geographic accessibility.

"With pediatric clinical trials, patient enrollment decreases with age—a 17-year-old is less likely to be enrolled than a 2-year-old," said Karen Albritton, MD, medical director, Adolescent and Young Adult Program, Cook Children's Hematology and Oncology Center, in conversation with Evidence Based Oncology. Albritton pointed out that not just age, but the site of care—pediatric institution versus an adult institution—determines participation in trials. "The AYA patient, who could be seen at either site, is more likely to be enrolled at a pediatric institution, where the culture prioritizes clinical trial availability and enrollment."

Evaluation of data from a Surveil-

lance, Epidemiology, and End Results Program, which examined CT enrollment and time to treatment among 1358 AYA cancer patients, showed that only 14% of patients in the 15- to 39-year age group had enrolled in a CT, with certain cancer type-specific trends observed—patients with acute lymphoblastic leukemia (ALL) and sarcoma demonstrated the highest participation. While the reason for non-enrollment for more than 60% of patients was not documented, 16% of patients noted that no CT was open for registration. The report indicated that unin-

sured older patients (35 to 39 years), and those treated by nonpediatric oncologists, were the least likely to participate in trials. When the authors evaluated

the time to treatment from diagnosis, especially in the older AYA population, they discovered that efficient referral mechanisms to tertiary care facilities—such as comprehensive cancer centers or children's hospitals that offer specialized cancer treatment or trial participation—could prove extremely important for achieving earlier access to care. The study's conclusion was that improved access to



Gregory Reaman, MD

Teens in Trials

trials for this age group could result in better survival outcomes.⁵

Several studies have indicated that AYA patients have better outcomes when treated with pediatric-based protocols than when treated with protocols for adults (18 years and older).⁵ On this premise, a multicenter trial sponsored by the NCI is evaluating a pediatric chemotherapy regimen administered by adult hematologists/oncologists in AYA patients (16 to 39 years of age) with acute ALL.⁶

According to Albritton, the medical oncology community should be engaged in the design of clinical trials for AYAs to ensure the feasibility of enrollment and compliance of AYAs treated in the medical oncology community. "All the stakeholders—the patient, the primary care provider, and the oncologist—need

“The lack of communication between medical oncologists and pediatric oncologists has been an issue.”

—Gregory Reaman, MD

Associate Director,
Office of Hematology and Oncology Products,
FDA

to be educated about and advocates for the importance of clinical trials in this age group. Patients should be aware and ask if the hospital has AYA-appropriate care, including AYA clinical trials,” said Albritton.

Barriers to Treatment

In the year 2012, the CDC’s Division of Cancer Prevention and Control convened a working group to understand and address the barriers and challenges that discourage the participation of adolescents in CTs. The participants included research scientists across the spectrum of care (pediatric and adult oncology, health informatics, behavioral science, CTs) working at clinical, academic, and government institutions as well as nonprofit organizations. Together, they identified 5 major barriers to AYA recruitment in trials:

- low referral rates of adolescent patients with cancer to pediatric cancer centers
- limited availability of CTs for certain cancers
- physician-related barriers that limit CT accrual
- institutional barriers that impede collaboration between pediatric and adult oncologists on CTs
- unique psychological needs of adolescent patients with cancer.⁷

The working group posited that the adolescent population has some unique issues associated with the transition to adulthood that can significantly impact recruitment into trials. Addressing these matters would therefore require a coordinated effort from the various stakeholders in this domain.

Age restrictions prove a major barrier to the recruitment of AYAs. Some pediatric hospitals do not enroll young adults older than 18 years while others have an upper age restriction of 21 years. Some pediatric centers will

enroll older patients only if the tumor is deemed to be of pediatric origin or if there is an open treatment protocol. Unfamiliarity of the family practice physician, who refers the young patient for treatment, with pediatric oncology programs can also influence choice of treatment site.⁸

“Age restrictions are not usually a barrier in adult hospitals; however, some pediatric hospitals do have an upper age limit. Some may have an upper age limit of 18 years, while others may enroll young adults up to 29 years of age,” Albritton informed EBO. “However, federal regulations necessitate appropriate credentials for the institute and staff, which could influence the ability of a hospital to admit (and then offer age-appropriate CTs to) AYAs,” she said.

“The place of care does make a difference,” agreed Eric Tai, MD, MS, medical officer with the Comprehensive Cancer Control Branch, Division of Cancer Prevention and Control, CDC. Speaking with Evidence-Based Oncology, Tai said, “Pediatric and adult cancer trials usually have age restrictions; so a 20-year-old patient will be considered an adult and may lose out on participating in a pediatric trial, and an 18-year-old may not be able to participate in an adult trial. What we need is more collaboration and dialogue between medical oncologists and pediatric oncologists,” so the patient stands at an advantage.

“The lack of communication between medical oncologists and pediatric oncologists has been an issue,” acknowledged Gregory Reaman, associate director, Office of Hematology and Oncology Products, FDA, in a conversation with Evidence-Based Oncology. “Specific efforts over the past decade by the NCI and the Cooperative Groups, the American Society of Clinical Oncology, and the American Association for Cancer Research have drawn attention to AYAs as an under-researched population that falls in between pediatric and adult specialists. Adult oncologists may not be familiar with some of the diseases that adolescents have, and so the patient may not have access to trials for these cancers which are usually conducted by pediatric oncologists.”

The Children’s Oncology Group (COG), an NCI-supported CT organization with global research partnerships, conducts CTs exclusively for childhood and adolescent cancers for an improved understanding of the underlying disease bi-

ology and to evaluate new treatments, supportive care, and survivorship.⁹ COG, in order to maintain impeccable research standards, has stringent regulations in place for its member institutions that have also proved a hindrance for recruiting younger patients, especially AYAs. For example, COG members need to have a pediatric intensive care unit—not an easy requirement to fulfill for hospitals that primarily treat adult patients. COG requires that the radiation oncologist who renders treatment be a COG member, even if the site (which needs to be approved by the Quality Assurance Review Center) is a non-COG treatment site.⁸

However, according to Reaman—who is past chairman of COG—the organization has amended age eligibility requirements on studies to accommodate adolescents as well as young adults, especially for studies in leukemia and in soft tissue and bone sarcomas.

One solution, recommended by 2 leading pediatric oncologists in the field, is to increase referrals to centers that have higher rates of enrollment of AYAs, such as pediatric cancer centers, AYA oncology programs, and NCI-designated cancer centers. They suggest that the centralization of services to institutes with high rates of accrual can improve the current dismal outcomes in AYAs with cancer.¹⁰ Additionally, pediatric treatment centers should be encouraged to be more flexible on their age restrictions for enrollment, based on resources and outcomes.

Albritton and Tai both emphasized the use of NCI’s Central Institutional Review Board (CIRB), versus using separate IRBs at the individual pediatric and adult institutions may alleviate some of the barriers to opening clinical trials. According to Albritton, the study should ideally be formulated by medical and pediatric oncologists together, considering even subtle differences in approach between an adult oncology treatment model and a pediatric treatment model. “An example would be the starting criteria for initiating a round of chemotherapy—a pediatric oncologist might be more comfortable starting at a lower white

blood count level than a medical oncologist. So successful implementation of a common IRB protocol would require improved collaboration and communication between the medical and pediatric oncologists. “Additionally, barriers to physically getting the patients and enrolling them at each site need to be overcome. Once the trial sites are open, ensuring that they are presented to the patient is also important,” she said.

Added Reaman, “NCI’s CIRB is a testament to improving recruitment. There is an adult and pediatric CIRB and a memorandum should be issued to improve understanding between them.”

What Are the Steps Being Implemented?

As a relatively new discipline, says Tai, research being conducted and resources made available to study the AYA population are a bit lagging. However, he believes identifying this population is important to determine the involvement of specific institutions as well as to pinpoint funding sources.

NCCN, in collaboration with the NCCN Foundation, the LIVESTRONG Foundation, and Critical Mass, released specific guidelines with the aim of providing support and counseling to AYAs with cancer. In addition to basic information on cancer as a disease, treatment options, and more, the NCCN provides information on websites and support groups (eg, www.stupidcancer.org) as well as suggestions to cope with the stress of transitioning back to a “normal” life with friends and peers.¹¹

The LIVESTRONG Foundation’s website emphasizes the importance of social and emotional support for teenagers, who may have developed adult-onset cancers and may have a specific need for social and emotional support different from what’s needed by younger children with cancer. The website underscores the fact that teenagers, transitioning into adulthood, could develop cancers usually found in adults—and they could receive medical treatment that is similar to an adult’s, complemented by age-appropriate social and emotional support.¹²

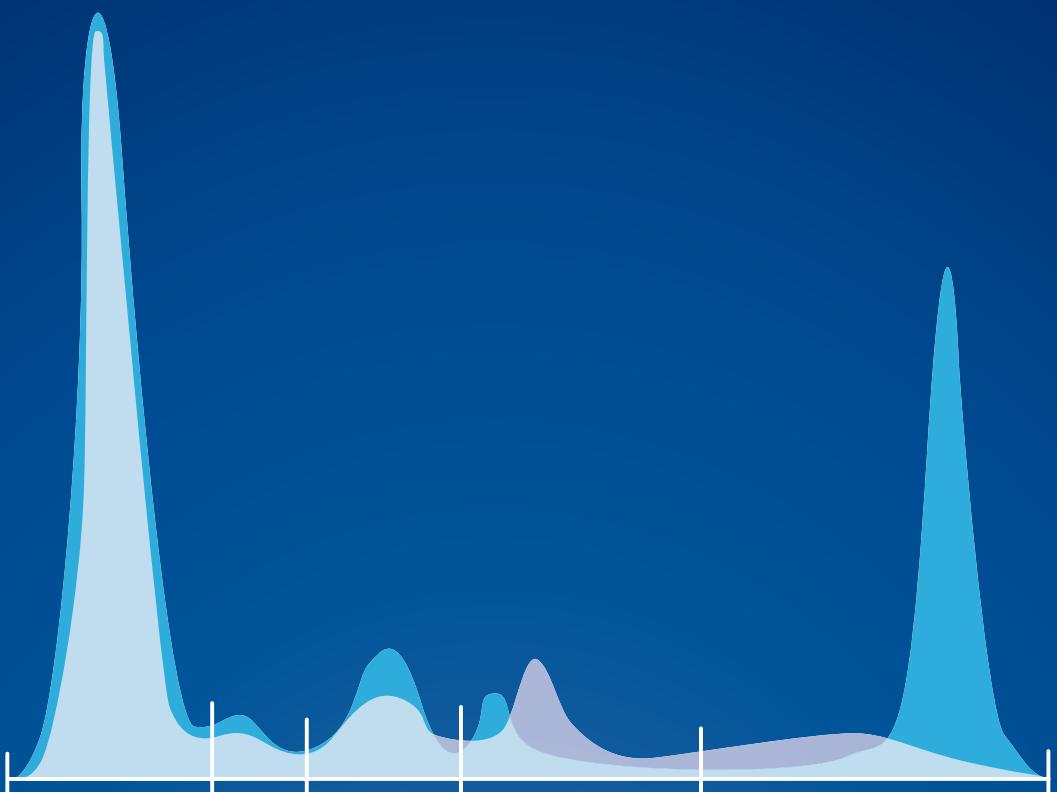
The Knight Cancer Institute at the Oregon Health and Science University has a specific AYA oncology program to support the treatment of patients in this cohort, one of a few in the United States. In collaboration with the Lance



Karen Albritton, MD



Eric Tai, MD, MS



MULTIPLE MYELOMA **NEVER GIVES UP. BUT NEITHER DO WE.**

There is no cure for multiple myeloma. That's why we've dedicated ourselves to three guiding principles: a relentless commitment to scientific advances, a persistent focus on patient needs, and a progressive approach to collaboration.

Celgene has put these beliefs into practice for more than 15 years. And we're not done yet.



Cancer Trials Face a Shortage of Teen, Young Adult Enrollees

(continued from 422)

Armstrong Foundation, the AYA team—which includes pediatric oncologists, a psychosocial researcher, and a social worker—provides specific services tailored to young cancer patients, including fertility preservation and connecting with support groups.¹³

Cancer Centers at the University of Chicago (for 15- to 30-year-olds)¹⁴ and at Northwestern University (15- to 39-year-olds)¹⁵ have programs in place specifically for the AYA population.

Reaman added that publications, monographs, and journals focused on AYAs with cancer have evolved to draw attention to this underserved patient population. Additionally, "Training programs have developed mechanisms to cross-train both pediatric and medical oncologists. Some medical oncologists are taking the initiative to train in pediatric cancers," he said, to enhance their abilities to treat those patients.

As for the FDA's role in improving the situation for AYAs, Reaman informed Evidence-Based Oncology that although the FDA does not necessarily have jurisdiction over patient recruitment, the FDA is committed to facilitating pediatric cancer drug development and has recently taken the position that AYAs may be eligible to participate in certain adult trials. "So we are in the process of developing a pediatric oncology product development guidance that states that in certain diseases—such as melanoma, Hodgkin lymphoma, sarcoma—where the age at presentation overlaps (both adult and pediatric populations), the trial could enroll patients down to the age of 12 years if there is reasonable evidence of the prospect for direct clinical benefit from preclinical and early clinical data."

AYAs and the ACA

Some of the health insurance barriers, especially among younger adults with

childhood cancer who may have been denied coverage due to preexisting conditions, will now be eased thanks to the stipulations of the Affordable Care Act (ACA). Specific provisions within the Act ease follow-up care for some of the adult survivors:

1. No denial or cancellation of insurance coverage due to preexisting condition or development of a new condition.
2. Mandatory coverage allowed up to age 26 years on parents' private insurance plan.
3. States can decide to raise the Medicaid minimum eligibility to 133% of federal poverty level.
4. Insurance companies can no longer set annual or lifetime coverage limits for medical services.
5. Each state will have a marketplace to purchase health insurance, with subsidies for qualifying individuals.¹⁶

Reaman emphasized that the ACA provides "a major opportunity to improve enrollment because one of the barriers to enrollment is the fact that many of the young adults are uninsured. There are frequently added costs associated with CTs, some of which are covered by third-party carriers, which makes it difficult or impossible to enroll in CTs." He added that for most pediatric cancers, the aim is "cure." So side effects and toxicities in the long term, following cancer therapy, can impact the quality of life of the patient. Reaman emphasized that long-term survivorship coverage is, therefore, extremely important among the AYAs.

Albritton agreed that the ACA, although in its early stages, might prove a tremendous boost for the AYA population, "The 18-25 year old AYA population has traditionally been the most uninsured and underinsured age group, limiting their access to treatment options and perhaps even making some hospital administrations hesitant to invest in programs to attract more of this age group. Hopefully more AYAs will be covered because of the ACA and have equal access." **EBO**

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FDA Has Teens on Its Radar

Prevention is better than cure—and when it comes to cancer, the FDA has complemented its role as a drug development regulator by implementing steps to help prevent the disease. Specifically with teenagers in mind, the FDA initiated an advertising campaign earlier this year to try to dissuade teenagers from smoking.¹ An infographic developed by the regulatory authority provides the statistics on teenage smoking, along with the number of deaths caused by cigarette smoking, and encourages parents to speak to their children about the health consequences of the habit. The FDA simultaneously launched a public education campaign on "The Real Cost" of smoking, targeting youth 12 to 17 years of age who are exposed to or are experimenting with smoking.²

Another area that the FDA is working to regulate, with prevention in mind, is tanning salons. Despite the grim statistics on the heightened risk of melanoma with indoor tanning (a 59% increased risk at first visit, which increases with successive visits),³ 13% of high school students reported using tanning beds during a survey conducted in 2011.⁴ Considering all of these factors, the FDA decided to alter its regulation of sun lamp products and UV lamps for use in sun lamp products. The improved oversight mandates the inclusion of a blackbox warning on the sun lamps stating that they should not be used on people under the age of 18 years. Additionally, the FDA now requires all associated user instructions and promotional materials to include certain warnings and contraindications to regulate exposure.⁵ **EBO**

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Each year
70,000
young adults &
adolescents
are diagnosed with
**CHILDHOOD
CANCER**



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 $\geq 10,000 \times 10^6/L$ 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 $> 100,000 \times 10^6/L$) 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_{0-24}) 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.

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Manufactured by:
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Vilnius, Lithuania
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North Wales, PA 19454

Product of Israel

GRX-40188 January 2014

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

Take a bite out of G-CSF acquisition costs*

**GRANIX™ is another option in short-acting
G-CSF therapy**

**GRANIX™ is an option for hospitals and
payers to consider when determining
health system budgets**

- » FDA approved through the rigorous BLA[†] process
- » Teva's short-acting G-CSF was first introduced in Europe in 2008 and is available in 42 countries^{‡1}
- » **GRANIX J Code: J 1446-Injection, tbo-filgrastim,
5 micrograms, effective January 1, 2014**

[†]Biologics License Application.

[‡]As of February 2014.



*Based on wholesale acquisition cost (WAC) of all short-acting G-CSF products as of November 11, 2013. WAC represents published catalogue or list prices and may not represent actual transactional prices. Please contact your supplier for actual prices.

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 brief summary of Full Prescribing Information on adjacent page.

For more information, visit GRANIXhcp.com.

Reference: 1. Data on file. Teva Pharmaceuticals: Filgrastim MA Approvals Worldwide. February 2014.