Bridging the gap between payer and provider perspectives

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Evidence-Based Oncology

Quality Care

QOPI, the ASCO Initiative, Improves Compliance and Promotes Quality of Patient Care

Surabhi Dangi-Garimella, PhD

Following a pilot launch in 2002, the Quality Oncology Practice Initiative (QOPI) was opened up to all members of the American Society for Clinical Oncology (ASCO) in 2006 with the objective that ASCO be the international leader in ensuring high-quality cancer care.[1,2] The ball was set rolling by the final report, (*Ensuring Quality Cancer Care*), submitted by the National Cancer Policy Board (NCPB) created by the Institute of Medicine (IOM), with the chair of the NCPB, Joseph Simone, MD, proposing the concept of QOPI.[2,3] With more than 973 registered oncology practices across the United States involved in the program as of November 2010,[4] QOPI is designed to measure care provided in outpatient oncology practices against evidence-based and expert consensus care recommendations.


Joseph Simone, MD

Substandard healthcare provided by oncology practices and centers can result in avoidable morbidities and mortalities and accumulate unnecessary healthcare costs. In 2010, Don

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Drug Pipeline

Targeted Programmed Cell Death in Lung Cancer Treatment

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

Despite new and improved therapies, lung cancer remains the second most common type of cancer in men and women (not including skin cancer), and is the leading cause of cancer-related death for both men and women (**Table 1**).[1] The 5-year survival rate for all stages is 16.3%, which is lower than many other types of cancer. Most patients are not diagnosed in the early stages of the disease, so more than half the patients die within 1 year of being diagnosed.[2] In 2010, an estimated $12.1 billion was spent on treating lung cancer.[3] However, research is ongoing to uncover and better understand potential treatments for lung cancer.

Recently, immunotherapeutic approaches involving the body's T-cell immune system were effectively implemented in lung cancer therapy. T-cell activity is regulated by a balance of costimulatory and inhibitory signals, known as checkpoints. The body's self-regulation through these checkpoints enables it to respond to infections and prevent tumor progression, as well as to prevent autoimmune-type responses.[4]

Ipilimumab, which has been approved for use in patients with advanced melanoma, is known to have antitumor activity mediated via T cells.[5] Knowing that T-cell function is suppressed in lung cancer, researchers explored the effectiveness of ipilimumab for treating lung cancer. Early trials have indicated that this immune checkpoint inhibitor, administered in combination with chemotherapy, can improve progression-free survival (PFS) in patients with advanced lung cancer.[6]

Another key checkpoint pathway that is mediated via T cells is the programmed death-1 (PD-1) pathway. Together with its ligands PD-L1 and PD-L2, the PD-1 receptor, a doorway through which T cells either recognize and attack tumor cells normally or

(continued on page SP155)

Policy

50th Anniversary Report: Even More Known About Smoking, Cancer Connections

OSH Director: We Must Get Cancer Patients to Quit

Mary K. Caffrey

If you thought the link between cigarette smoking and cancer was old news, you would be wrong.

To be sure, it's been 50 years since the announcement from US Surgeon General Luther L. Terry, MD, that smoking causes lung cancer in men and probably in women.[1] Terry's action unleashed the public health crusade against cigarettes; since 1964, adult smoking rates have fallen from 43% to 18%.[2]

But a report issued on the milestone of Terry's bold step, in a White House ceremony held on January 17, 2014,[3] pores through the most recent data and makes several new findings about smoking and cancer, including:

- Female smokers face a greater risk of lung cancer than ever.[4]
- Cigarettes are linked to multiple other cancers; scientists can say with certainty that smoking causes colorectal cancer. While the report stops short of saying that smoking causes breast cancer, it states, "The evidence is sufficient to identify mechanisms by which cigarette smoking may cause breast cancer[3] (see **Figure 1**).
- Falling rates of squamous cell cancer of the lung, accompanied by the relative rise of adenocarcinoma of the lung among smokers, are most certainly due to changes in the design of cigarettes themselves.[3,5] The consequences have been deadly, and US cigarettes may be the deadliest of all.[3,6]

An important lesson of the anniversary report, officially titled, *The Health*

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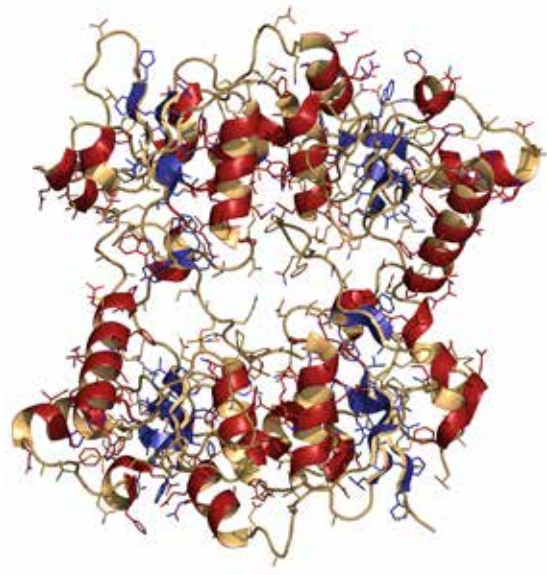

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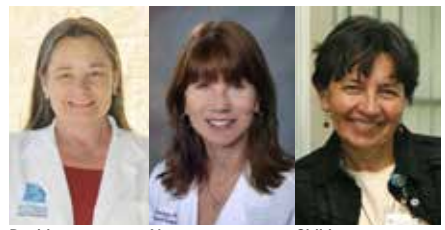
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From the Publisher

THE AMERICAN JOURNAL OF MANAGED CARE

The realm of cancer care is very dynamic, and the information overload generated by the vast amount of research, both basic and clinical, can cause delays in policy changes. This edition of *Evidence-Based Oncology* features 2 articles on the important role that policy recommendations play in delivering quality care: A discussion of the US Preventive Services Task Force's updated recommendations on BRCA testing, and the role that the Quality Oncology Practice Initiative, or QOPI, will have in placing the American Society of Clinical Oncology (ASCO) at the center of ensuring high standards as the Affordable Care Act gains its foothold in medicine.

In December of last year, the USPSTF made recommendations that women with a familial history of breast, ovarian, tubal, or peritoneal cancers should undergo screening and only those with a positive screening result should be tested for *BRCA1/2* mutations, after genetic counseling. Women that lack a family history are specifically advised not to undergo screening. However, the guidelines are riddled in loopholes, according to Ellen T. Matloff, MS, director of cancer genetic counseling at Yale Cancer Center. Matloff points out several areas where the task force could go further, making this an ongoing process. Our discussion of QOPI provides an insight into the evolution of ASCO's initiative to improve and standardize the quality of cancer care patients receive, both in oncology practices and at outpatient cancer clinics. Joseph Simone, MD, the driving force behind QOPI, tells *EBO*: "One of (QOPI's) major successes has been engaging a wide array of oncologists from across the country. I believe it was because it was built by and for them." The QOPI certification program, QCP, is a step further to ensure a high standard of care for cancer patients. Health care plans, such as Blue Cross Blue Shield of Michigan, are providing financial incentives for QOPI participation, as they expect that adherence would have a positive impact on the quality of life of patients, reduce off-label drug use, and reduce healthcare costs. The ultimate aim of this program is not the elimination of substandard practices, but rather, to continually raise the bar for care, so that cancer patients experience good care no matter where it occurs.

Our discussion of QOPI provides an insight into the evolution of ASCO's initiative to improve and standardize the quality of cancer care patients receive, both in oncology practices and at outpatient cancer clinics....The ultimate aim of this program is...to continually raise the bar for care...

This issue also provides an update on the current status of immunotherapy in the treatment of lung cancer, with a focus on PD-1 inhibitors, which target the programmed death-1 pathway via T-cells. Early combination trials of ipilimumab with chemotherapy improved progression-free survival in patients with advanced lung cancer. Several other PD-1 and PD-L1 inhibitors are exhibiting promising results in various stages of clinical development. The issue also includes the second half of our peer exchange on the emerging importance of immunotherapy in cancer care, with the panelists discussing recent additions to the pipeline, success of combination therapies, resource allocation, and payer approaches.

As always, thank you for reading and look for updates on www.ajmc.com.

Brian Haug
Publisher

EDITORIAL MISSION

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

Part Two Immunotherapy in Cancer Care: Understanding the Impact of Shifting Treatment Paradigms in the Managed Care Setting

The previous issue of *Evidence-Based Oncology* (EBO) featured the first part of a condensed edition of a peer exchange on the future of immunotherapy in cancer care, which was convened by *The American Journal of Managed Care*. This edition of *EBO* features the rest of that exchange. Immunotherapy, according to the American Cancer Society, is treatment that uses the immune system to ward-off diseases such as cancer by either boosting the body's immune system in general or by training the immune system to attack some specific cancer cells, and may be used alone or in combination with other chemotherapy regimens. Panelists discussed the positive and negative aspects of using immunotherapy, traditional chemotherapy, and combination regimens. They addressed the importance of promoting both patient and provider understanding of immunotherapy. Finally, panelists discussed the cost associated with immunotherapy in cancer care.

The discussion was moderated by **Peter Salgo, MD,** a professor of medicine and anesthesiology at Columbia University and an associate director of surgical intensive care at NewYork-Presbyterian Hospital, New York City. The panelists included:

- Jeffrey Weber, MD, PhD, senior member of the H. Lee Moffitt Cancer Center and director, Donald A. Adam Comprehensive Melanoma Research Center, Tampa, Florida
- Michael A. Kolodziej, MD, national medical director, Oncology Solutions, Aetna
- Daniel J. George, MD, Duke Cancer Institute.

Peter Salgo, MD, continued the discussion by asking the panelists to comment on the excitement surrounding the use of novel cancer therapies such as immunotherapy. Dr Salgo asked whether the thought process for funding the associated costs of the new treatments would be similar to traditional treatments.

Michael A. Kolodziej, MD, warned that excitement is tempered by a need to wait for evidence. Immunotherapy, he said, is not treated differently from other therapies from an insurance standpoint.

Michael A. Kolodziej, MD: I'm not an immunotherapist, so I'm waiting to see the results. I mean, I still remember when the IL-2 paper was published and we were going to cure renal cell cancer with IL-2. So I'm waiting to see what the results are. Do we distinguish? No, I don't think so… We're interested in what it's going to mean to our members. Are our members going to get better?

Daniel George, MD: I think skepticism is healthy. We still give IL-2 in limited circumstances, but we're frustrated by the limitations of the therapy. What we're excited about are the advances which seem to be moving us faster beyond those limitations….This is the opportunity to move those therapies that are doing some remarkable things, granted maybe not in everybody, but in a subset of patients with advanced metastatic disease, to earlier settings.


Peter Salgo, MD

However, we have to meet a bar, and we have to pass the standards set by both skeptics and our regulatory agency. We owe that to all the future patients out there that those bars are met. However, what we are frustrated by is when we have met those bars and when people are still skeptical because this doesn't fit the paradigm of traditional chemotherapy and shrink the cancer 20%, and therefore, I know it's working in those circumstances.

Dr Salgo asked for comment about the fact that, compared to traditional chemotherapy, immunotherapy is subtle and quite well-tolerated.

Jeffrey Weber, MD, PhD: The effects depend on the situation. You might see tumor responses with PD-1 or PD-1 plus ipilimumab that are almost as impressive as you would see with chemotherapy or targeted drugs. You can see responses that happen rapidly and steeply. So we're in a different realm, and as we expand the repertoire of drugs available to us, you're going to find that we will be able to overcome the skepticism.

Dr Salgo nudged the panelists to discuss the safety profile of immunotherapies. Traditional chemotherapies shrink the tumor burden but are associated with a lot of side effects. On the other hand, immunotherapy has a good safety reputation.

Dr George: A cancer patient wants to live as long as possible, and he wants the quality of life, with not much concern for reduced tumor burden or slow progression. We have patients with a tumor burden that have a fantastic quality of life and they're going along just fine. As long as that quality of life is going along and we're not seeing any detriment in terms of either the disease progression or their cumulative toxicities, we're achieving their goals. So, to me, tumor regression is probably the least valuable of all the surrogates that we tend to use in our practice….

Dr Salgo continued the discussion by commenting that although it made sense that living with a tumor burden may not affect survival and well-being, he had never heard an oncologist endorse the concept.

Dr George: Well, let me qualify this that I'm a prostate cancer doctor. For the longest time, we've had bone scans that don't meet RECIST (Response Evaluation Criteria in Solid Tumors) criteria. They don't even represent the cancer, they represent a reaction around the cancer, the calcium deposition around the cancer. And we've had (PSA) prostate specific antigen as a biomarker. We really haven't had measures of tumor burden, and it's actually been the biggest hindrance to drug development in prostate cancer over the last 30 years, and we've just finally gotten over that in the last 10 years. So, I'm probably a little bit of a different oncologist than maybe what you've heard before.

> ***"Immunotherapy is something that is just ridiculously interesting and ridiculously exciting."***
>
> **—Peter Salgo, MD**
> Columbia University

Dr Weber: Although, to be honest, reduction of tumor burden is usually not regarded as an end in and of itself; it is a surrogate or a substitute for the greater variable, which is obviously survival and progression-free survival. …

On the other hand, there are plenty of patients who present a significant decrease in morbidity and improvement in their symptoms and increased quality of life when they get some tumor reduction. So it can be a desirable endpoint, and the FDA (US Food and Drug Administration) does recognize, in single arm studies, that tumor reduction is an acceptable end point. They much prefer the ultimate end point, as they'll always tell you when you meet them, of survival in a well-controlled, well-conducted randomized trial. So I agree with Dr George in principle; response is not the ultimate end point but it can be a useful end point.

Dr Salgo continued the discussion by asking how payments are made; questions such as is it a single payer, is there a committee that decides, is it practice-driven? He also asked the panelists to discuss the influence of the 12-month review by the Centers for Medicare & Medicaid Services (CMS) on

Provenge and other immunotherapies on managed care.

Dr Kolodziej: The situation varies by payer. We have an evidence shop that adjudicates the evidence. We do pay attention to bodies like the NCCN (National Comprehensive Cancer Network) as we make our determination. It's interesting because that particular committee is actually firewalled off from the coverage policy committee and the pay committee. So the evidence shop is all about evidence, but they do respect what other people say….As for the CMS review, I wasn't at Aetna then, but I don't think the review had much influence. CMS had already decided they were going to pay for it, and then they opened the national coverage decisions. Additionally, the FDA had approved the drug and there was already a coverage policy in place. I don't think that it didn't make people feel that they got it right.

Jeffrey Weber, MD, PhD

Dr Kolodziej pointed to the example of bevacizumab in breast cancer treatment. The FDA withdrew approval, but CMS still pays for it and NCCN still recommends it.

Dr Salgo continued the discussion on decisions made on the cost of treatment. One treatment may cost $100,000, while another may cost less initially but must be taken over several years, with possible hospital admissions and treatment for side effects…. He asked whether the actual cost of treatment had been estimated for Provenge, ipilimumab, tumor-infiltrating lymphocytes (TIL) for melanoma, transduced T-cell therapy, and other high-attention agents.

Dr Weber: Well, they're going to be very different with TIL, which is essentially a 1-time treatment. The approved regimen for ipilimumab is 4 doses over 12 weeks. Maybe you'll get reinduced somewhere in the future but usually not. Some targeted drugs are taken every day forever until you progress, and if the *BRAF/MEK* combination has a 2-year median survival, that means half the patients will be on for a year or more. So that could get even more expensive because if it's $100,000 a year and you're on for 3 years, now it's $300,000.

Dr Kolodziej: Leave cost out of this for a second, okay? How many drugs are available for renal cell cancer? Six?

Dr George: Seven.

Dr Kolodziej: Seven oral agents? I suspect, and I did a lot of genitourinary medicine when I was in practice, if you start with drug A and then give drug B, that may be different than starting with drug B and then giving drug A. However, if you talk to people who do renal cell, they will come to you and say, I intend to use every drug, every single one, as long as the patient can tolerate it…. Now, is that the right thing to do? I don't know. In some cases it's futile. But we actually don't know the answer to that question.

Dr Weber: It's a testable question. All the more reason why Aetna should be supporting that kind of research.

Dr Kolodziei: It is a testable question. The data that are required to do that is, it may sound simple, but it's not so simple. So this is the heart of comparative effectiveness. And we will come to a point where those questions are going to get answered.

Dr Kolodziej said comorbidities make such answers complex, and costs may be spread in many places. But he agreed with Dr George that the real questions are: how much does it cost to take care of a patient with cancer, and what is the timeline? Patients who respond live longer and live better. Dr George said these questions affect how patients are selected for clinical trials.

Dr Salgo then specifically asked Dr Weber to explain some of the factors that would determine a product's cost versus benefit.

Dr Weber: Well, the cost is obviously set by the pharmaceutical company; as Dr Kolodziei said, the process is ambiguous. Although, my gut, by the way, is it's whatever the market will bear, and we do live in a capitalist economy. The FDA explores this extensively because they're always thinking risk-benefit. That's the charge of the FDA and the Code of Federal Regulations….However, we think about this as oncologists. Can I take an 85-year-old and give him ipilimumab if he's got Crohn's disease? Well, that's probably not going to happen. So I have to always make the assessment, as all of us do as physicians, of will a patient be able to tolerate a drug, does the drug have more than marginal benefit, and what's the likelihood it's going to prolong survival with a decent quality of life?

Dr Salgo then asked the panelists to define meaningful improvement. What is reasonable improvement if the length and quality of life is weighed against the cost of treatment?

Dr Weber: Well, I think most people in the business would say, as a rule of thumb, if you have a prolongation in survival with a hazard ratio of 0.75, meaning you have a one-third increment in survival over the control group, that's probably meaningful. However, if that increment is weeks or a month, forget it. If that increment is months added to a baseline of a year, then yes. If someone said we'd like you to do this, you'd live a year with the control, 15 months with the drug, which is a 25% or a 30% increase, I'd say, that's reasonable.

It's marginal benefit, and Americans are willing to pay a certain amount of money in general per year of quality-adjusted life gained. And that turns out to be $50 to 150,000. If I told you, as the consumer, that, well, we're going to give you this therapy to prolong your life by 6 months but it's going to cost $500,000 and there were a couple of hundred thousand of you in a survey, you'd probably give it thumbs down.

> ***"If nobody wants to buy your product, it doesn't matter how much you charge, you're not going to make any money."***
>
> **—Jeffrey Weber, MD, PhD**
> Director
> Donald A. Adam Comprehensive Melanoma Research Center

Dr Salgo asked whether the government or the provider is obligated to honor the patient's decision to follow up on an expensive treatment. Where do you draw the line?

Dr Weber: It's not clear to me whether I am obligated to honor that as a physician.

Dr Kolodziej: So Aetna doesn't draw the line and neither does the government, because there has not been political appetite in this country for doing that. In the UK there's an organization called NICE (National Institute for Health and Care Excellence) that sets a threshold for what constitutes reasonable. We do not do that in this country, and I don't know if we will. But the NICE experience has led to alternative approaches to paying for expensive therapy. (In some cases, payment is not made until a therapy is proved effective.)

Could I envision this in the United States? Maybe, but there's other ways that people have talked about it, such as value-based insurance or referenced pricing. Let's say the federal government says, all right, we pay $12,000 for this. Anything that you want that costs more than $12,000, it's on your nickel. With value-based insurance, if it's curative therapy, you pay nothing. If it's therapy that has little benefit, you pay most of it. People have a hard time with those constructs. There's a lot of emotion tied up into it.

Dr Kolodziej said Aetna is not doing this, but there is a lot of discussion about the concept.

Dr Salgo asked Dr Kolodziej about why the provider might reject the upfront one-time cost of immunotherapy, which has proved successful, when traditional therapies keep incurring cost due to extended regimens. Dr Salgo also asked whether risk is being shifted from the payer to the provider and consumer.

Dr Kolodziej: The answer is that that is speculative and actually that work hasn't really been done….What we know is that some patients have durable responses. About 10% of patients have durable responses. So you got 90% who got treated with a very expensive drug and are going out to more expensive therapy. It's not simply, oh, well, it's clearly worth it because 10% of people are (responding).

I'm not shifting risk anywhere. I'm just telling you the options that are out there. Remember, *you're* the payer. I'm not the payer. We're not spending Aetna's dollars. When the government pays, they are spending taxpayers' dollars. It's very important to remember that because, ultimately, it's a societal decision…

Dr Salgo asked who drives decisions on treatment: the patient, the provider, or the payer? How are options presented?

Dr Weber: I don't believe that everyone will be in a position to make that decision; this is a societal decision. Our country and most other countries will

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THE AMERICAN JOURNAL OF MANAGED CARE

ACO and Emerging Healthcare Delivery Coalition

Background

As ACOs and other emerging delivery and payment models evolve and move away from traditional fee-for-service system models towards cost-effective and value-based care, the need to understand how these models will evolve is critical to building long term strategic solutions. The mission of the coalition is to bring a diverse group of key stakeholders together, including ACO providers, payers, IDNs, specialty pharmacy and pharmaceutical manufacturers to work collaboratively to build solutions and improve the quality and overall outcomes of patient care.

Coalition Goals

- Gather insights of current "real-world" best practices and strategies for care management interventions
- Gather insights of current ACO physician challenges and best practices in executing successful ACOs, as well as new healthcare delivery models, including the impact of incentive structures for ACO providers–implementation strategies and measurement
- Identify operational lessons and best practices, including key components of transitions-of-care programs; patient and physician engagement; quality measures; formulary decisions; and protocol development.
- Translate key findings into actionable solutions for key stakeholders

Key Stakeholders

- ACO Providers
- Payers
- Integrated Delivery Networks
- Specialty Pharmacy
- Pharmaceutical Manufacturers

Deliverables

- **Participation in two live working group sessions with coalition members:**
  - Free registration for live interactive meeting with Industry leaders across ACOs, payers, IDNs, specialty pharmacy and pharmaceutical manufacturers
  - Opportunity for exclusive breakout sessions with coalition members
- **Two virtual meetings with coalition members - free registration**
- **Ongoing collaboration opportunities with coalition members:**
  - Monthly executive interchanges with thought leaders (includes Q&A)
  - Active participation and proprietary questions in pulse surveys
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  - The *American Journal of Managed Care*
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  - **ACO and Emerging Healthcare Delivery Coalition** newsletter
- **Expedited peer review for submissions to AJAC**
- **Additional Resources:**
  - Development of training modules: live, on-line, etc
  - Development of patient education
  - Access to ACO portal resource center within AJMC.com

AJMC's **ACO and Emerging Healthcare Delivery Coalition** is the premier managed care alliance for ACOs, payers, IDNs, specialty pharmacy and pharmaceutical companies. This coalition provides the platform for diverse stakeholders to collaborate and interact regarding the current and evolving healthcare delivery models–to build strategies and solutions, in addition to developing enduring materials to ensure continuous engagement and innovation for all alliance members.

(continued from SP132)

need to make decisions on where you put the resources, and I think those decisions are going to be made for us. I don't think, as an oncologist, in 10 years, I'll get to choose to treat someone with a drug that cost $300,000 that will prolong life, on average, by 2 to 3 months. I'll be in a position where I can spend a fair bit of money, but I have to have a high degree of assurance that I'm going to benefit the patient at a modest cost, in terms of toxicity.

Dr George: This is going to have to fall back on the provider, because the variability here is the tumor. There's incredible heterogeneity. There's no way our patients are going to have the wherewithal to make a value decision about their cancer, and their life, and their cost without the information that we have. And so I think we're going to have to be, as providers, part of that decision process. But let me just say that I think the problem that I see happening is that there are already situations where this is coming to fruition, with capitations or other things. And, as a society, we really haven't addressed this...

Dr Kolodziej: There is no reason that an oncologist should be uncomfortable talking about the cost of care with their patient. Let's face it, in the current system, as imperfect as it is, medical bankruptcies are skyrocketing. So, we're not doing our job right if we're not telling patients what they should expect in terms of cost...

Dr Salgo then initiated discussion on the use of combination regimens and how the combinations, including immunotherapy, are impacting resource allocations. Panelists were asked whether an evidence-based method exists for determining this cost-benefit ratio for the various possible combinations.

Dr George: I would think of combinations with immunotherapy differently than the way we thought about combinations with traditional therapies, or just chemotherapies or targeted treatments. Getting back to what Dr Weber alluded to, whether it's a single dose or there's a series of dosing that happens, a treatment effect subsequently emerges. So you could think of combinations with ipilimumab as happening after the ipilimumab is done, whether it's radiation, or chemotherapy, or other strategies. The same is true with Provenge.

I'm not sure we necessarily have to think of combinations in the same context as what we thought of before. Now, there are targeted therapies that don't work that way. They work as long as the drug is on and when the drug is off, they stop working; so the combinations have to be synchronous. Immunotherapy is not that paradigm. So we should think about this, not in terms of upfront cost, but as the cost over the life span of that patient, and all the subsequent therapies, as being a combination.

> ***"Some people might look at healthcare reform and grappling with quality and value as a hardship. It's an opportunity."***
>
> **—Michael A. Kolodziej, MD**
> National Medical Director, Oncology Solutions
> Aetna

Dr Weber: (We're hearing about) the first simultaneous combination of PD-1 and (ipilimumab);...It has a pretty high response rate between 40% and 50%, and a 50% dose-limiting toxicity; but those patients will live long. The combination is already being developed in phase III studies, with durable responses and survival being the endpoints, and those endpoints will probably show that there is a benefit to doing some combination of immunologic therapies.

The question is: if ipilimumab is $140,000 a year for the wholesale price, can we imagine the cost of PD-1? What if it's an equal cost? PD-1 is administered every other week for multiple weeks. What if it's $300,000 a year? Can we afford that? That's a tough one.


Michael A. Kolodziej, MD

Dr Salgo continued the discussion by asking Dr Kolodziej to provide examples of cost effectiveness or quality-of-life data that would aid in these decisions on coverage and reimbursement. Additionally, he asked if money was the major driving force in the decision-making process and whether the benefit of therapies was underestimated.

Dr Kolodziej: As we discussed before, that has typically not been the process, partly because it's politically unpalatable. In addition to poor quality of data, it is a difficult pill to swallow.

If a medicine invented tomorrow could cure cancer, people would get it. We would, as a society, decide it was worth it irrespective of what the price is. The elephant in the room is why do things cost so much money. We've heard the excuse that drug development is expensive and maybe that's right. It's not my area of expertise. Are we going to get at the ultimate cost of developing a drug? What a fair price is? Is the government going to step in?

Dr Weber: Part of it's because so many drugs fail.

Dr Kolodziej: We will see. I don't know where the truth lies, but I don't think it's an accident that everything costs $10,000 a month now. You said it yourself. It's what the market will bear.

Dr George: When you talk to drug companies and ask, "How do you set the price? Why do you set the price so high?" They'll come back and say, "We have to." Like Dr Kolodziej says, it's not his money. He's really just being a steward. They're stewards of their shareholders, and their shareholders will come back and sue them if they don't price that drug at what it maximally could be priced at. That's the capitalist society that we have.

Dr Weber: It's a very simple solution in the capitalist system: if nobody wants to buy your product, it doesn't matter how much you charge—you're not going to make any money. But if you drop the price and people start to buy it, then you might start to make some money.

Dr Kolodziej: But we're going to see a very interesting thought experiment play out over the next 18 months with TKIs (tyrosine kinase inhibitors) and CML (chronic myelogenous leukemia). Recently there was an article in *Blood* where the CML researchers went out there and said, these drugs are really, really expensive. We're not sure why they cost so much more money. The new ones cost more and have small incremental benefit.

So what's the thought experiment? Imatinib goes generic in a year, which means that we're going to have drugs like dasatinib or nilotinib that cost from $8000 to $10,000 a month and we're going to have imatinib. And I don't know what it's going to cost. Let's just argue $1000 a month or $500 a month. So should we step? Should we require people get imatinib first? Is there a reason not to do that? Now we have this scurrying going on about trying to define a value proposition for the newer TKIs. Yes, they have a better depth of response and a better molecular profile. The question though is if you start with imatinib, is there any risk to the patient of doing a step?

Dr Salgo furthered the case for immunotherapy by sharing beneficial data on Provenge. This therapy for prostate cancer resulted in fewer hospitalizations (1.2% versus greater than 26%), fewer discontinuations, and fewer deaths than AEs (adverse events) with docetaxel in prostate cancer. These data suggest that Provenge could save money compared to traditional therapy, and it is only administered once.

Dr Kolodziej: People don't get either/or. Talk about disingenuous. People know that there's a lot more toxicity with chemotherapy. People who fail Provenge get chemotherapy later. It's not the right question.

Dr Salgo: But take it the other way around. People who do well on Provenge don't, and then it may be much more than cost-effective. Dr Weber?

Dr Weber: The benefit to Provenge is the same way they get docetaxel. The clinical trial that was done, these were clinical trial patients in the United States, and only 50% of them got docetaxel chemotherapy when that was really the only other approved therapy at the time for advanced prostate cancer. So I would just push back on Dr Kolodziej a little bit.

I'm not sure that everybody is going to get every therapy with prostate cancer or even kidney cancer. If you look at our registry on kidney cancer, 20% of patients have third-line therapy. So there's a drop-off with each of these, and some of that is disease progression and death, and in some cases patients don't want any more therapy. Considering the heterogeneity in this field, moving some of these therapies, particularly immunotherapies that have demonstrated the greatest value in the long-term survivors, to me makes the most sense. If you're going to use those treatments, use them in a setting where they have the potential for that patient to live long enough to really get a more absolute benefit, whether it's due to sequential other therapies or not.

Dr Salgo then asked Dr Weber's opinion on the impact of the ACA (Affordable Care Act) on the coverage for cancer in terms of immunotherapies.

Dr Weber: Obamacare consists primarily of expanding the equivalent of Medicaid to a larger chunk of the uninsured population, which is a good thing. This country has a huge proportion of uninsured folks; I'm sure we have the highest share in the industrialized world. That means patients who did not have insurance in the past will now be able to come to Moffitt, which has some modest proportion of charity care, but most everybody we see has some insurance. It means we'll be able to see more patients, get them on better treatments, get them on trials, which is a plus. There will also be some reasonable guidelines, as there are for can you use ipilimumab, can you put them on a trial? So I don't have a problem with that.

Dr Salgo: What about ACOs (accountable care organizations), organizational models such as that; are they feasible for oncology reimbursement?

Dr Kolodziej: I would agree with Dr Weber. I think the thing that we're going to see most immediately is the health insurance exchanges and the expansion of Medicaid, which will provide a large number of patients, who previously had no health insurance, some health insurance.

Dr Salgo: The number is 40 million or so.

Dr Kolodziej: The truth of the matter is that we actually don't really know how cancer patients are going to be taken off within that construct. Because the benefits design is a very basic benefits design. It's better than nothing, but I think the question is, so how do you take care of cancer in that universe? I assure you they would pay premiums in the health information exchanges for several years for how much it costs for 1 cycle, 1 treatment of Provenge. So I think its unclear how cancer care is going to happen in that world. Now, that's the immediate change. The long-term change of course is going from fee-for-service, paying for transactions to paying for value. When I was in practice, I thought, "There's no way that ACO is going to happen," and you know what, now I think they're going to happen.

Dr Salgo pointed out that he did not agree with this. Since a part of the drug cost includes research and development, if the drug manufacturing cost alone is covered, then it might just freeze the system.

Dr Kolodziej: We talked about the possibility that up to 30% might be waste. I've always thought of that as the pool of money to pay for innovation. That's my own perspective, not Aetna's, but I've always thought that's a lot of money…

So the challenge is "Who's going to be the ACOs?" There are integrated delivery systems like the Mayo Clinic and Geisinger. There are numerous hospitals that aspire to transform themselves to be ACOs. There are a lot of reasons why it's hospital systems, but let's just accept the fact that hospital systems are the predominant player in this area. They've got to really change the way they're thinking about care. Keeping beds full is no longer your primary driving force…If we can execute that change, that's where the money comes from.

> ***"We should think about (immunotherapy), not in terms of up-front cost but cost over the life span of the patient."***
> **—Daniel George, MD**
> Duke Cancer Institute

Dr Salgo then specifically asked Dr George and Dr Weber how they thought the ACA would particularly impact immunotherapy. In their opinion, would it help or hurt the implementation of immunotherapy and research and development?

Dr George: This is a dynamic area. This is a phased healthcare reform and, as pointed out by Dr Kolodziej and Dr Weber, the first phase is greater access to patient care. Now, these are expensive therapies and to what extent the basic plan, or the Medicaid plan, covers an expensive therapy remains to be seen. But I'm encouraged because patients who are most likely to benefit most from immunotherapy are going to be more likely to have some insurance to allow us to treat them. The societal benefit is that we treat the right patients with the right drugs, and avoid waste. So the patients that have some coverage now they can get that, and we'll be able to increase that enrichment strategy.

Dr Salgo: Is the way to carve out your 30% waste that you could put it going forward, is that going to be at the cost of small practices versus large practices, large practices that achieve economies of scale?

Dr Weber: I'm not in private practice, so it's not something I've thought extensively about, but I don't see that point. I think that if you're practicing value medicine, you should be able to survive in a small group or a large group.


Daniel J. George, MD

Dr Salgo asked whether the days in which the doctor could treat a patient, unmindful of the associated cost, were numbered.

Dr Kolodziej: I think so, and we need to get comfortable with the idea that…As a healthcare consumer, I appreciate that we're getting to a record-and-verify point in healthcare. Doctors who do a good job are thinking of ways to continue to do a good job going forward, while those who don't want to be told what to do, well, you know what? Sorry.

Dr Weber: Data talks. To paraphrase an old radio commercial from New York when I was growing up, data talks and nobody walks.

Dr George: Just so we don't lose sight. Cost is really not the equation. We're talking about *value*, which is quality over cost. What I don't want to see happen (are limits) on practitioners who do a good job and actually keep a patient alive longer. By selecting the right therapy for the right patient, they actually get a really good treatment response that's going to cost more inevitably. And so, to some extent, you're penalized for doing a quality job. I think we have to recognize in the end that it's not the lowest cost that wins here.

Dr Salgo: Although, if you listen to the debate in Congress, that's often what you hear.

Dr George: That's what I worry about.

Dr Kolodziej then asked the other members on the panel their definition of quality.

Dr Salgo: It's amorphous, isn't it?

Dr Weber: Quality-adjusted years of life prolonged would be a reasonable parameter.

Dr George: Life prolonged. The problem is on an individual basis; how do you know you prolong that life? On an individual basis, we can use prognostic models and nomograms. It's an imperfect science.

Dr Salgo pointed out that the focus is always on the length and quality of life, disregarding aspects like physician interaction with the family to discuss outcomes and options.

Dr Kolodziej: So the answer is, if you look at some of the proposals for quality metrics, and some of them are outcomes like quality adjusted life years and some of them are process measures. Patient satisfaction is typically included in that. I think that the time has long passed where we need to be more transparent about our outcomes. We need to be more transparent about what people think of us. We all remember that cardiothoracic surgery was such a big deal, and reporting the outcomes of cardiothoracic surgery was such a big deal. And now it's held up as the model for transparency, and fairness, and shared decision-making, consumerism. But people would not be comfortable with that in oncology.

Dr Salgo then raised a chicken-or-egg argument. Of the 12 cancer drugs approved by the FDA in 2012, 11 cost more than $100,000 a year, either coincidentally or maybe these are just expensive technologies to develop. The technology cannot be developed unless someone pays for it, and unless you got the $100,000 for a therapy that does seem to work, we wouldn't have it. How would this argument fit in the model?

Dr Weber: Well, the companies will only develop the drugs if they can make money selling them. But if the companies are convinced that, at the end of the day, they'll be able to sell the drug for a profit, whatever that may be, they will continue to develop new and innovative drugs that will benefit patients.

Dr Salgo asked panelists for their final thoughts.

Dr Weber: Immunotherapy has arrived. It's only going to get better, and the best is yet to come. Americans will anguish about change; but as for the future of being a physician, I don't think that much will change. I think there will still be a place for the great physician who has an intuitive grasp of what the best treatment for a patient is. I don't see how we're going to be hurt by being

more data-driven. As a research oncologist, like Dr George, we're certainly more data-driven than most, but a lot of what we do is not data-driven. I think the society, the patients, the insurers, will be better off when the practice of oncology, which we pursue, is done in a more rigorous and data-driven way. I don't have any problems with that at all.

Dr George: I agree with Dr Weber and I'm very excited about the future of immunotherapy as well. I'm a little bit concerned that there is an educational lag, both for patients and for some providers, so there's still a learning curve there like with any new modality. However, with immunotherapy branching into numerous fields and not simply a niche of oncology, we're going to overcome that pretty quickly.

I look forward to being able to be smarter about how we use our immunotherapies like with all our other therapies in precision medicine, helping identify the right patients. However, the oncologist will always play a role in making individual decisions on patients, and we can't lose sight of that. We have to have mechanisms to do that. I think the future is bright for oncology and immunotherapy, in particular.

Dr Kolodziej: As both an oncologist and as a person who works for a payer, but largely as an oncologist, we are living in a golden age. So much of work that has been done for a long time is coming now to fruition. We're understanding personalized therapy. We're understanding immunology. It is tremendously exciting. Some people might look at healthcare reform and grappling with quality and value as a hardship. It's an opportunity. It's an opportunity for oncology, for the pharmaceutical industry, for the entire healthcare enterprise, to redefine itself. And, at the end of the day, we'll have enhanced benefit for our members or our patients, we'll have more transparency, and it will be driven by data.

Dr Salgo: I agree, this is a remarkable time. I have never seen so much excitement, so much real progress on the part of oncologists before. This is a magical time. Immunotherapy is something that is just ridiculously interesting and ridiculously exciting. It is heading us where we need to go and based on my experience in medicine and based on my experience with the folks I've met here, we're going to get there. **EBO**

Molecular Diagnostics

A New Concept to Broaden Access to Molecular Testing

Mary K. Caffrey

During a 2013 discussion on treating non-small cell lung cancer, a group of oncologists from academic medical centers were asked what share of cancer patients have access to molecular testing.

The answers varied: One said he guessed 40% to 50%, another said "a large minority." Anne S. Tsao, MD, director of the mesothelioma program at MD Anderson Cancer Center, University of Texas, said surveys put the share at about 25%, in contrast with National Comprehensive Cancer Network guidelines that suggest "all of them" should be tested.[1]

Why the gap? Mark A. Socinski, MD, director of the lung cancer section at the University of Pittsburgh, said that while things are changing, "At the community level there are a number of barriers" to molecular testing. In community practices, Socinski said, there's not a pathology department to handle testing, so it's all on a busy oncologist to get testing done—and reimbursement may be a challenge.

Within a month of that discussion, 2 entrepreneurs in McLean, Virginia, set out to address barriers to molecular testing at the community level, and in turn help take both oncologists and their patients to the next step in personalized medicine: not just using a molecular test to match the drug to the patient, but to ensure that the right combination of genetic or proteomic tests has been performed, so that the oncologist has best information available to guide treatment.

Perthera, which is short for Personalized Cancer Therapy, seeks to find its niche by helping what it calls "the busy oncologist" facilitate all phases of molecular testing: collecting tumor samples, deciding what tests would be helpful, getting them ordered, and creating a report for the oncologist. If an ideal therapy for the patient's cancer is not approved, Perthera will try to connect the patient with a clinical trial.

Michael Pishvaian, MD, PhD

"We provide an interpretive service," said Michael Pishvaian, MD, PhD, chief medical officer, and an assistant professor in hematology and oncology at Lombardi Comprehensive Cancer Center, Georgetown University. "We don't want to get in the way of the testing companies; in fact, we scour for the best testing companies."

A scientific distinction of Perthera is that it does not limit recommendations to genomic testing but also includes proteomics, or testing of proteins, which is the expertise of company cofounder and Chief Scientist Emanuel F. Petricoin, PhD[2] (**see related story, page SP149**).

But it's the aspect of Perthera's service that would appear most helpful to community oncology—handling all reimbursement—that presents a conundrum for patients. While part of Perthera's appeal is that it helps patients negotiate with insurers, its own services—all that legwork that would otherwise be absorbed by the community oncologist—are not yet covered by insurance. At the moment, fees are $5800, according to Dave Anderson, a spokesman for the company.

That amount may seem high, but it pales compared with the out-of-pocket cost of many of today's cancer therapies, particularly those for patients suffering later-stage or difficult-to-treat cancers. In an interview, Pishivaian said Perthera was steadily serving patients it met through local oncologists, most of whom were also willing to grant Perthera consent for their tissue to be stored in the company's biobank for future research. Pishivaian said Perthera plans to publish on the effectiveness of its approach once the company has results from 50 to 100 patients of specific disease types.

Perthera's approach, of offloading both the headaches and financial risk of molecular diagnostic testing from community oncologists, comes as testing companies are at odds over reimbursement from the Centers for Medicare and Medicaid (CMS). With most new cancer diagnoses occurring in persons above age 50 years,[3] what Medicare is willing to pay in areas of cancer care can define who gets access.

At a time when the US Food and Drug Administration (FDA) is defining both the importance of molecular testing and the agency's role in regulating it,[4] CMS is moving in a direction that both the nation's testing companies and pathologists say could limit access to molecular diagnostic tests. CMS and testing companies are at odds after a tumultuous 2013, which ended with CMS' rule change that it will annually review testing codes based on advancing technology, and adjust reimbursement accordingly. The process will start this summer and take effect in 2015.[5] **EBO**

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USPSTF Recommends *BRCA* Testing in Women Based on Familial History

Surabhi Dangi-Garimella, PhD

In late December of 2013, the US Preventive Services Task Force (USPSTF) provided an update to its 2005 recommendations, reaffirming the genetic risk assessment and breast cancer susceptibility gene (BRCA) mutation testing in women susceptible to breast and ovarian cancers in women, the most common and ninth-most common cancers in US women, respectively.

The task force recommends that women whose family members have been diagnosed with breast, ovarian, tubal, or peritoneal cancers be screened to identify a family history that may be associated with an increased risk of potentially harmful mutations in *BRCA1* or *BRCA2*, the well-identified breast cancer susceptibility genes. Women with positive screening results are advised to undergo genetic testing, but only following genetic counseling. Further, women who lack a family history of an increased risk for *BRCA* mutations are specifically advised against genetic counseling or BRCA testing (**Figure**).[1] In an e-mail response, Virginia Moyer, MD, MPH, chair of the USPSTF, informed *Evidence-Based Oncology* that the Task Force is currently in the process of updating the 2009 recommendation of biennial screening mammography for women aged 50 to 74 years.

Virginia Moyer, MD

Etiology of the *BRCA*-Associated Disease

BRCA1 and *BRCA2* are tumor-suppressor genes that were discovered in 1994 and 1995, respectively. Germline mutations in these genes predispose to ovarian and breast cancer, while somatic mutations have also been found to result in numerous cancers.[2] The proteins translated from these 2 genes lack structural homology, but are actively associated with DNA repair; so functionally defective BRCA1 and BRCA2 would result in faulty DNA repair mechanisms.[3] Individuals with germline mutations in *BRCA1* or *BRCA2* genes have been shown to have an increased susceptibility to certain cancers: 45% to 65% of females with the mutation may develop breast cancer while 11% to 39% may develop ovarian cancer.[4] An increased susceptibility to pancreatic adenocarcinoma[5] has also been identified in individuals carrying either of the mutations, while *BRCA1* mutation carriers in the United States, Canada, or Europe, below the age of 50 years, were recently shown to carry an increased risk of early-onset colorectal cancer.[6] The association between *BRCA1* mutation and the risk of colorectal cancer holds significant importance in terms of the current USPSTF recommendations for the cancer. The current guidelines recommend testing beginning at age 50 years and up to age 75 years for the general population, but those with an increased risk are advised to undergo early and more frequent testing. However, based on the results of this study, women with *BRCA1* mutation should initiate screening for colorectal cancer at age 40 years.[6,7]

Counseling for Cancer Survivors

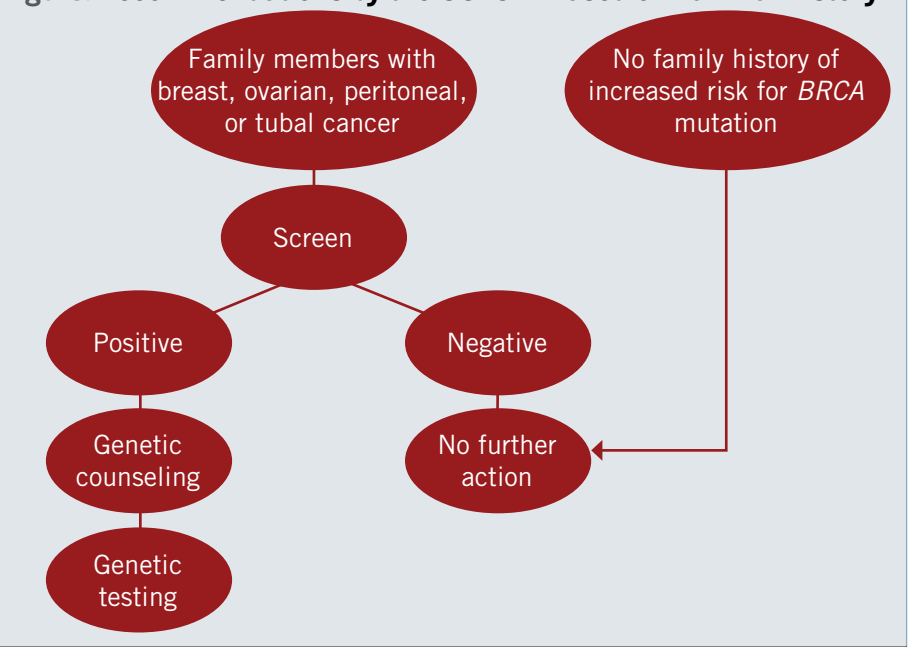
The current task force recommendations are aimed at women previously undiagnosed with breast or ovarian cancer, but with a familial history. Ellen Matloff, MS, director of cancer genetic counseling at Yale Cancer Center, strongly believes that "these prevention guide-lines *should include* patients, *male and female*, who are cancer survivors and would like to prevent the development of a future primary cancer." Working in collaboration with the nonprofit organization Facing Our Risk of Cancer Empowered (FORCE), Matloff raised concerns and made suggestions to the USPSTF regarding the reach of the current guidelines.[8]

However, the task force responded that recommendations for cancer survivors, although important, would encompass *disease management*, which falls outside of the scope of their current recommendations and are aimed at preventive services in the general population with no symptoms of disease.[8]

BRCA Mutations in Men, and Risk of Cancer

Numerous studies have documented an increased risk of cancer among men with *BRCA1/2* mutations. A study conducted among male breast cancer patients in Canada found a strong association between familial history (at least 1 first- or second-degree relative with breast cancer), *BRCA2* mutation (2 of 14 patients) and a previous history of other cancers prior to the breast cancer diagnosis,[9] while another study in Ashkenazi men found an increased risk of prostate cancer in *BRCA2* mutation carriers.[10] A recent study recognized poor overall survival in *BRCA2* mutation–carrying prostate cancer patients with multiple breast cancer relatives.[11] Says Matloff, "The guidelines stress throughout that women should have genetic counseling and testing. Unfortunately, this perpetuates a pervasive and dangerous myth in the patient, lay, and medical communities that a family history of breast and ovarian cancer somehow applies only to women…Statements like this gloss over the critical fact that a male who is a *BRCA* carrier may have daughters, granddaughters, and other female relatives at risk who can be helped by identifying the *BRCA* mutation in the family. We should not discriminate against males and should offer them the genetic counseling and testing services available to women." However, according to Moyer, USPSTF currently has no recommendations on counseling and testing for men with *BRCA* mutations as there has yet to be a thorough examination of the available evidence.

Figure. Recommendations by the USPSTF Based on Familial History



USPSTF indicates US Preventive Services Task Force.

Physician Awareness and Involvement

With an upsurge in the research and awareness on hereditary cancer risks (approximately 5%-10% of cancers are hereditary in nature), family physicians are paying increased attention to family history and referring high-risk patients to genetic counseling and testing. Early detection and intervention can lead to preventive measures—such as prophylactic mastectomy; awareness of this procedure increased due to the so-called "Angelina effect"[12] after actress Angelina Jolie announced last spring she had both breasts removed due to the presence of a *BRCA* mutation and the loss of several close relatives from breast cancer. Another preventive measure is oophorectomy—removal of the ovaries. Both procedures improve patient outcomes (incidence of breast cancer reduced by 95% and ovarian cancer by 84%).[10] However, research studies point to the failure of primary care physicians and OB/GYNs to provide genetic counseling or refer testing in high-risk patients. A major fraction of the family physicians and OB/GYNs who did order *BRCA* testing were inconsistent in recognizing high-risk and low-risk patients; some failed to accurately stratify women as high versus average risk for *BRCA* mutations, and a few failed at following the standard of care guidelines which demand an evaluation of a 3-generation pedigree for risk assessment. Altogether, these reports point to an increased burden on individual practitioners, and warrant a multidisciplinary collaborative approach (by partnering with academicians) to improve patient care.[13]

The American Society of Clinical Oncology (ASCO) recently updated its

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Table. PARP Trials for BRCA1/2 Mutations

Cancer Type	Drug	Company/Institute	Phase
Advanced solid tumors (ovarian, peritoneal, breast)	BMN 673	NCI	Recruiting for 3
Ovarian	KU-0059436 (AZD2281)	AstraZeneca and KuDOS Pharma	2
Breast and ovarian	AZ2281 and carboplatin	NCI	Recruting for 1
Triple-negative breast cancer	Rucaparib and cisplatin	Hoosier Oncology Group, Clovis Oncology Group	
Metastatic breast cancer	Veliparib (ABT-888) and temozolomide	Dana Farber, Beth Israel	2
Relapsed ovarian cancer	Veliparb (ABT-888)	Vejle hospital, AbbVie	Recruiting for 1 and 2
Pancreatic	Rucaparib	Clovis Oncology	Will recruit for 2
Newly diagnosed stage II/III/IV ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer	Veliparib (ABT-888), paclitaxel, Carboplatin, and Bevacizumab	NCI	3

BRCA indicates breast cancer susceptibility gene. Source: www.clinicaltrials.gov.

guidelines for hereditary risk assessment to improve oncology care and the quality of care by providing greater access to genetic counseling and testing services.[14] The recommendations are aimed at helping oncologists gain information on a patient's family history to enable a preliminary risk assessment, by examining factors such as early onset of cancer, multiple relatives with cancer on the same side of the family, and multiple primary tumors in the same individual in the same organ. Preventive interventions in such individuals are expected to prove beneficial for the patient as well as his or her relatives. The ASCO guidelines mirror the importance placed on counseling by the USPSTF suggestions; they recommend pre- and post test counseling for the patient, and an open communication channel that provides detailed information to the patient to familiarize him or her with the process and the implications of testing for both the patient and his or her relatives. The update directs clinicians to use electronic data tools to alleviate some of the physician workload.[14]

However, when contacted for comment, Virginia Kaklamani, MD, DSc, director of translational breast cancer research and codirector of the cancer genetics program at Northwestern University, said in an e-mail response that most providers and insurance carriers use the National Comprehensive Cancer Network guidelines to determine if a patient needs counseling or testing.

Need for Board-Certified Counselors

The current recommendations have stressed the need for genetic counseling in women found to be at an increased risk of *BRCA* mutation. A study conducted at the Yale Cancer Center, with Matloff as the senior author, highlighted the negative outcomes of cancer genetic testing without a qualified counselor on board and identified the following patterns: wrong genetic test ordered, misinterpreted test results, and inadequate genetic counseling. The study recommended education programs for healthcare providers in addition to an increased collaboration between the providers and genetic counselors.[15] Matloff emphasized the importance of board-certified counselors: "Without accurate ordering, interpretation and appropriate recommendations, these data are meaningless or harmful to the patient and the entire family."

A panel discussion convened last year by *The American Journal of Managed Care* brought together genetic counselors, the chief medical officer of the American Cancer Society (ACS), and the national medical officer from Cigna.[16] On the heels of the Myriad Genetics case (that previously held patents for *BRCA1* and *BRCA2* genes, a decision overruled by the US Supreme Court) and the aftereffects of Jolie's announcement, the panel members discussed the need for promoting awareness on the implications of testing, and also the increasingly important role played by genetic counselors in ordering the right tests and the accurate interpretation of results. The panel emphasized that the providers (both physicians and nurses) who consult with patients have limited genetic knowledge and that there is a rising need for board-certified genetic counselors. The consensus reached by the panel corroborates the current USPSTF recommendations.

Current Treatment Options

The ACS projected 232,340 new cases of invasive breast cancer among women in the Unites States in 2013, with 39,620 deaths, along with 22,240 new diagnoses of ovarian cancer were estimated and 14,230 deaths. The findings that *BRCA* mutations sensitize (1000-fold) cells to PARP inhibitors paved the road to examine PARP inhibitors in the clinic in the mutation carriers, and a number of trials are either ongoing or are actively recruiting participants to test PARP inhibitors in various cancers (**Table**). However, all the drugs are currently in the development stage and are not yet close to being approved. Iniparib (Sanofi), which had presented promising phase 2 results, failed to generate significant improvements in overall survival (OS) or progression-free survival (PFS) when combined with gemcitabine and paclitaxel in a phase 3 trial in triple-negative breast cancer patients; however, it did improve OS and PFS in second- and third-line settings.[17] BioMarin, in collaboration with NCI, has started recruiting for phase 3 trials of BMN 673 following a clinical benefit response observed in 72% (13/18) patients with *BRCA1/2*-mutated breast cancer.[18]

Payers and BRCA Testing

Medicare recently announced that it will slash the reimbursement for BRCA1 and BRCA2 testing by 50% (down to $1440 in 2014 from $2795 in 2013).[19] This is a result of new competition afforded to Myriad Genetics by other companies (Quest Diagnostics, Ambry Genetics) that marketed their own tests at lower prices ($900 to $2900). Most insurance companies cover the cost of genetic testing recommended by a healthcare provider. Additionally, the Affordable Care Act mandates coverage for testing when recommended by a healthcare provider, as well as counseling to help decide a preventative course of medication to lower the risk of breast cancer.[20]

With the ever-changing landscape in the cancer genetics realm, further updates from the USPSTF are needed to promote increased communication between the healthcare providers, genetic counselors, and patients. This could improve disease outcomes, not just for the patients, who might be at an increased risk for other primary cancers, but also for their family members and relatives. However, patient acceptance of genetic testing is not at 100%. A recent survey conducted by the Huntsman Cancer Institute at the University of Utah found that 34% of the respondents would not seek genetic testing for cancer, 69% were concerned about an adverse effect on their coverage, and only 63% said they'd follow recommended screenings in case of a family history.[21] **EBO**

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Diagnosis

Controversial Findings on the Value of Mammography to be "Dissected" at Miami Breast Cancer Conference

Beth Fand Incollingo

A large Canadian study that has caused a stir by indicating that mammograms are of no use in women aged 40 to 59 years, and in fact can lead to over-diagnosis of breast cancer, is flawed and misleading, according to the program chairman of the Miami Breast Cancer Conference.

The Canadian National Breast Screening Study[1]—whose results were published in mid-February in the *British Medical Journal* and reported widely in newspapers and on television—will also be the subject of discussion during the conference, the chairman, Patrick Borgen, MD, said.

"The Canadian study is probably the single most flawed, confounded trial in the history of trials—certainly in trials of mammography," Borgen said. "This is a trial from 34 years ago using ancient technology and a very flawed randomization technique which put women with breast lumps into the mammography arm and normal-exam women into the control arm—and, of course, after 30 years, it showed no difference. Applying that to today is simply outrageous."

"We'll be spending a lot of time at the Miami Breast Cancer Conference dissecting this trial, talking about it, and, frankly, developing a group strategy for how to overcome it," he said. "Mammograms save lives, and we'll be getting that message out loud and clear at Miami."

In the study, Anthony B. Miller, professor emeritus at the University of Toronto, and 5 colleagues compared 25-year cancer outcomes in 89,835 women aged 40 to 59 who were randomly assigned to either receive or not receive annual mammography screening. The trial was launched in 1980, and the recruitment period continued through 1985.

In women who received mammography, screening took place over 5 years at 15 centers in 6 Canadian provinces. Two-view film screen mammography was used, with craniocaudal and mediolateral views taken until 1985; after that, in accordance with updated guidelines, craniocaudal and mediolateral oblique views were taken.

Women aged 40 to 49 years in the mammography arm and women aged 50 to 59 years in both arms received annual physical breast examinations, while women aged 40 to 49 years in the control arm received a single physical breast examination followed by usual care in the community, the authors wrote. All women in the study were taught breast self-examination by trained nurses prior to randomization.

During the 5-year screening period, 666 invasive breast cancers were diagnosed in the mammography arm (nearly three-fourths of them screen-detected), with 180 of those cancers becoming fatal within 25 years. In the control arm, 524 invasive breast cancers were diagnosed, 171 of them fatal within 25 years.

The overall hazard ratio (HR) for death from breast cancers diagnosed during the screening period by mammography was 1.05 (95% confidence interval [CI], 0.85-1.30). Age made virtually no difference in the survival outcomes of these women, according to the authors.

Over the entire study period, 3250 women in the mammography arm and 3133 in the control arm were diagnosed with breast cancer, and 500 and 505, respectively, died of the disease. The cumulative mortality from breast cancer did not significantly differ between women in the mammography arm and in the control arm (HR 0.99, 95% CI 0.88-1.12), Miller et al wrote.

Of the cancers found during the screening period, all those in the control arm and 68.2% in the mammography arm were palpable, but rates of node-positive cancer in the groups were similar (32.4% in the control arm and 30.6% in the mammography arm [$P = .53$ for difference]), the investigators found. Palpable cancers were generally larger than cancers detected only by mammography (2.1 cm vs 1.4 cm; $P < .001$), and were more likely to be node positive (34.7% vs 16.5%; $P < .001$), they wrote.

While the cancers detected strictly by mammography were associated with better survival outcomes than those that were palpable upon diagnosis, that result was not meaningful, the authors argued. "Although the difference in survival after a diagnosis of breast cancer was significant between those cancers diagnosed by mammography alone and those diagnosed by physical examination screening, this is due to lead time, length time bias, and over-diagnosis," they wrote.

After 15 years of follow-up, 106 cancers detected in the mammography arm were attributed to over-diagnosis, meaning they might not have otherwise become clinically apparent within the patients' lifetimes.

"Annual mammography in women aged 40-59 years does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available," the authors concluded. "Overall, 22% (106/484) of screen-detected invasive breast cancers were over-diagnosed, representing 1 over-diagnosed breast cancer for every 424 women who received mammography screening in the trial."

The investigators added that "In technically advanced countries, our results support the views of some commentators that the rationale for screening by mammography should be urgently reassessed by policy makers."

In discussing limitations of their findings, the authors contended that "The lack of an impact of mammography screening on mortality from breast cancer in this study cannot be explained by design issues, lack of statistical power, or poor quality mammography. It has been suggested that women with a positive physical examination before randomization were preferentially assigned to the mammography arm. If this were so, the bias would only impact on the results from breast cancers diagnosed during the first round of screening (women retained their group assignment throughout the study). However, after excluding the prevalent breast cancers from the mortality analysis, the data do not support a benefit for mammography screening (HR 0.90, 95% CI 0.69-1.16)."

In recent findings, contrary to those of the Canadian National Breast Screening Study, a different team of investigators reported that 4 large studies of mammography—previously thought to have divergent results—are actually fairly consistent in demonstrating that mammograms are associated with reduced breast cancer mortality. Those results[2] were presented in December during the 2013 San Antonio Breast Cancer Conference (SABCS) by Robert A. Smith, PhD, senior director of cancer screening at the American Cancer Society (ACS) in Atlanta.

Considered in that study were the Nordic Cochrane review, the UK Independent Breast Screening Review, the US Preventive Services Task Force (USPSTF) review, and the European Screening Network (EUROSCREEN) review. Each review had generated different findings regarding how many women must be screened with mammography in order to prevent 1 breast cancer death, with estimates ranging from 90 to 2000, about a 20-fold difference, Smith said.

"We wanted to understand why these estimates differ so much," he added in

(continued on SP143)

IN MBC, ONCOLOGISTS ARE CONSISTENTLY
EXTENDING THE CONTINUUM OF MEANINGFUL CARE[1-3]

With MBC treatment potentially extending to 6 lines and beyond, third-line chemotherapy can still be early in the fight for some patients[2]

MBC=metastatic breast cancer.

Indication

Halaven is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

Important Safety Information

Neutropenia

- Monitor complete blood counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days
- Severe neutropenia (ANC <500/mm^3) lasting more than 1 week occurred in 12% (62/503) of patients. Patients with elevated liver enzymes >3 × ULN and bilirubin >1.5 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels
- Grade 3 and Grade 4 neutropenia occurred in 28% and 29%, respectively, of patients who received Halaven. Febrile neutropenia occurred in 5% of patients and two patients (0.4%) died from complications

Peripheral Neuropathy

- Patients should be monitored closely for signs of peripheral motor and sensory neuropathy
- Grade 3 peripheral neuropathy occurred in 8% of patients, and Grade 4 in 0.4% of patients who received Halaven. Delay administration of Halaven until resolution to Grade 2 or less
- Neuropathy lasting more than 1 year occurred in 5% of patients. Twenty-two percent of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days)
- Peripheral neuropathy (5%) was the most common adverse reaction resulting in discontinuation

Pregnancy Category D

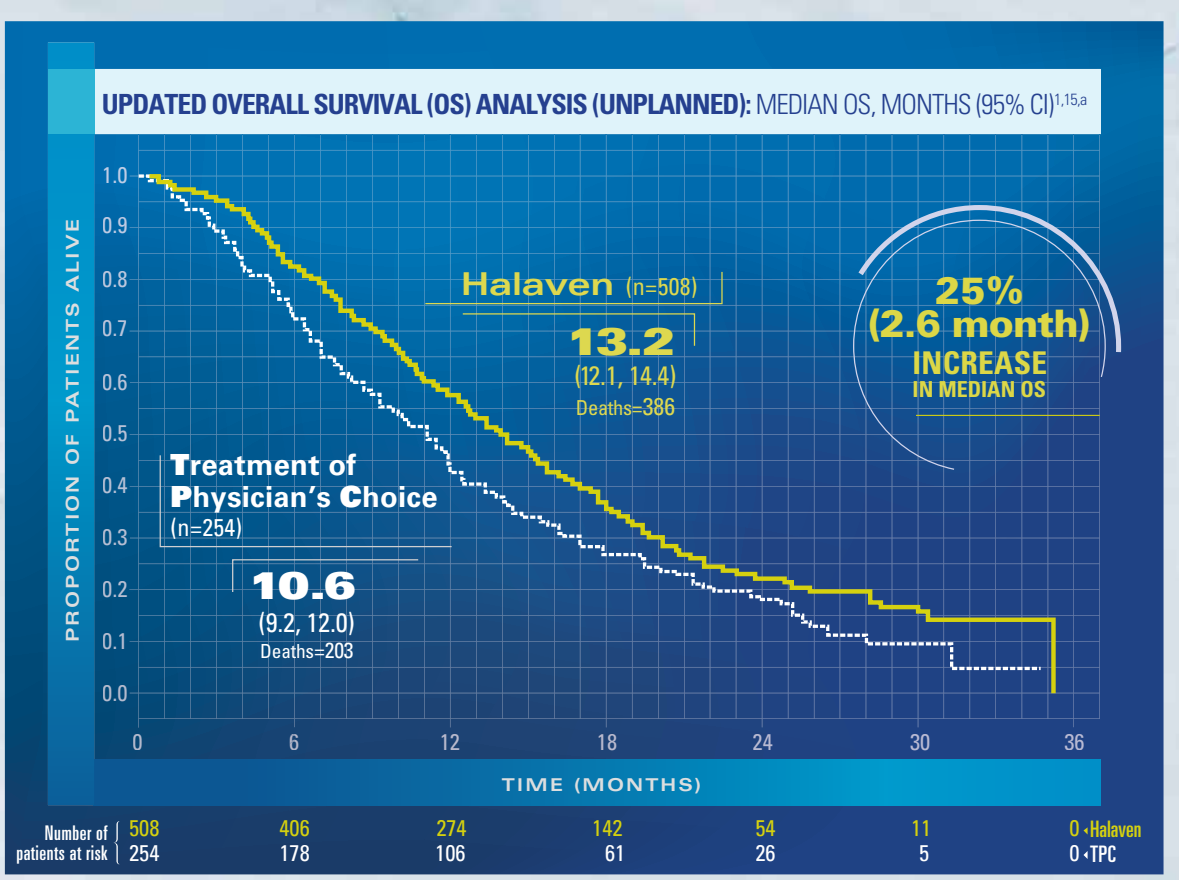
- Halaven is expected to cause fetal harm when administered to a pregnant woman and patients should be advised of these risks

QT Prolongation

- In an uncontrolled ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no prolongation on Day 1. ECG monitoring is recommended for patients with congestive heart failure; bradyarrhythmias;

GIVE YOUR PATIENTS AN OPPORTUNITY FOR MORE LIFE

The FIRST and ONLY single agent that significantly extended OVERALL SURVIVAL in third-line MBC[7-14]



Results from an updated, unplanned survival analysis of the Phase III, randomized, open-label, multicenter, multinational Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus E7389 (Eribulin) (EMBRACE) trial of Halaven versus Treatment of Physician's Choice (TPC) in patients with MBC (N=762), conducted when 77% of events (deaths) had been observed. The primary endpoint was OS. Patients were randomized (2:1) to receive either Halaven 1.4 mg/m^2 intravenously for 2 to 5 minutes on Days 1 and 8 of a 21-day cycle, or any single-agent therapy, selected prior to randomization. At baseline, all patients had received ≥2 prior chemotherapeutic regimens for metastatic disease and demonstrated disease progression within 6 months of their last chemotherapeutic regimen. All patients received prior anthracycline- and taxane-based chemotherapy, unless contraindicated. Therapies in the TPC arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxanes [included paclitaxel, docetaxel, nab-paclitaxel, and ixabepilone], 9% anthracyclines, 10% other chemotherapy), and 3% hormonal therapy.

CI=confidence interval.
[a]Conducted in the intent-to-treat population.

The updated OS analysis was consistent with the primary analysis[7]

- The primary analysis, conducted when ~50% of events (deaths) had been observed, demonstrated a median OS for Halaven vs TPC of 13.1 months (95% CI: 11.8, 14.3) vs 10.6 months (95% CI: 9.3, 12.5), hazard ratio=0.81 (95% CI: 0.66, 0.99) (*P*=0.041)[7,15]

concomitant use of drugs that prolong QT interval, including Class Ia and III antiarrhythmics; and electrolyte abnormalities

- Correct hypokalemia or hypomagnesemia prior to initiating Halaven and monitor electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome

Hepatic and Renal Impairment

- For patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic and/or moderate (CrCl 30-50 mL/min) renal impairment, a reduction in starting dose is recommended

Most Common Adverse Reactions

- Most common adverse reactions (≥25%) reported in patients receiving Halaven were neutropenia (82%), anemia (58%), asthenia/fatigue (54%), alopecia (45%), peripheral neuropathy (35%), nausea (35%), and constipation (25%)
- The most common serious adverse reactions reported in patients receiving Halaven were febrile neutropenia (4%) and neutropenia (2%)

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Please see accompanying brief summary of Halaven full Prescribing Information.

Visit **www.halaven.com/hcp.aspx**

Halaven®
(eribulin mesylate) Injection
ADVANCING SURVIVAL

HALAVEN® (eribulin mesylate) Injection BRIEF SUMMARY – See package insert for full prescribing information.

2.2 Dose Modification

Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose delays

- Do not administer HALAVEN on Day 1 or Day 8 for any of the following:
  - ANC <1,000/mm^3
  - Platelets <75,000/mm^3
  - Grade 3 or 4 non-hematological toxicities.
- The Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume HALAVEN at a reduced dose as set out in Table 1.
- Do not re-escalate HALAVEN dose after it has been reduced.

Table 1 Recommended Dose Reductions

Event Description	Recommended HALAVEN Dose
Permanently reduce the 1.4 mg/m^2 HALAVEN dose for any of the following:	1.1 mg/m^2
ANC <500/mm^3 for >7 days	
ANC <1,000 /mm^3 with fever or infection	
Platelets <25,000/mm^3	
Platelets <50,000/mm^3 requiring transfusion	
Non-hematologic Grade 3 or 4 toxicities	
Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity	
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue HALAVEN

ANC = absolute neutrophil count.

Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Severe neutropenia (ANC <500/mm^3) lasting more than one week occurred in 12% (62/503) of patients in Study 1, leading to discontinuation in <1% of patients. Patients with alanine aminotransferase or aspartate aminotransferase >3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin >1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Monitor complete blood counts prior to each dose; increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of HALAVEN and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days. Clinical studies of HALAVEN did not include patients with baseline neutrophil counts below 1,500/mm^3.

5.2 Peripheral Neuropathy

Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients in Study 1. Peripheral neuropathy was the most common toxicity leading to discontinuation of HALAVEN (5% of patients; 24/503). Neuropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.

5.3 Embryo-Fetal Toxicity

There are no adequate and well-controlled studies of HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

5.4 QT Prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid HALAVEN in patients with congenital long QT syndrome.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

• Neutropenia • Peripheral neuropathy • QT interval prolongation

The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of HALAVEN was peripheral neuropathy (5%).

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

In clinical trials, HALAVEN has been administered to 1,222 patients with multiple tumor types, including 240 patients exposed to HALAVEN for 6 months or longer. The majority of the 1,222 patients were women (82%) with a median age of 58 years (range: 26 to 91 years). The racial and ethnic distribution was Caucasian (83%), Black (5%), Asian (2%), and other (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1. In Study 1, patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received HALAVEN, and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2 Adverse Reactions with a Per-Patient Incidence of at Least 10% in Study 1

MedDRA ver 10.0	HALAVEN (n=503)		Control Group (n=247)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and Lymphatic System Disorders[a]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
Nervous system disorders				
Peripheral neuropathy[b]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
General disorders and administrative site conditions				
Asthenia/Fatigue	54%	10%	40%	11%
Mucosal inflammation	9%	1%	10%	2%
Pyrexia	21%	<1%	13%	<1%
Gastrointestinal disorders				
Constipation	25%	1%	21%	1%
Diarrhea	18%	0	18%	0
Nausea	35%	1%	28%	3%
Vomiting	18%	1%	18%	1%
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
Investigations				
Weight decreased	21%	1%	14%	<1%
Metabolism and nutrition disorders				
Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders				
Cough	14%	0	9%	0
Dyspnea	16%	4%	13%	4%
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[c]	10%	NA[c]

Table 2 (cont'd)

MedDRA ver 10.0	HALAVEN (n=503)		Control Group (n=247)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Infections and Infestations				
Urinary Tract Infection	10%	1%	5%	0

[a] Based upon laboratory data.

[b] Includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.

[c] Not applicable; (grading system does not specify > Grade 2 for alopecia).

Cytopenias: Grade 3 neutropenia occurred in 28% (143/503) of patients who received HALAVEN in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in <1% of patients. The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm^3) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte–macrophage colony-stimulating factor) was used in 19% of patients who received HALAVEN.

Peripheral Neuropathy: In Study 1, 17% of enrolled patients had Grade 1 peripheral neuropathy and 3% of patients had Grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received HALAVEN. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade and 2% (8/503) of patients developed Grade 3 peripheral motor neuropathy.

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of HALAVEN-treated patients experienced Grade 2 or greater ALT elevation. One HALAVEN-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; these abnormalities resolved and did not recur with re-exposure to HALAVEN.

Less Common Adverse Reactions: The following additional adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group: **Eye Disorders:** increased lacrimation; **Gastrointestinal Disorders:** dyspepsia, abdominal pain, stomatitis, dry mouth; **General Disorders and Administration Site Conditions:** peripheral edema; **Infections and Infestations:** upper respiratory tract infection; **Metabolism and Nutrition Disorders:** hypokalemia; **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, muscular weakness; **Nervous System Disorders:** dysgeusia, dizziness; **Psychiatric Disorders:** insomnia, depression; **Skin and Subcutaneous Tissue Disorders:** rash.

6.2 Postmarketing Experience

The following adverse drug reactions have been identified during post-approval of HALAVEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Blood and Lymphatic System Disorders:** lymphopenia; **Gastrointestinal Disorders:** pancreatitis; **Hepatobiliary Disorders:** hepatitis; **Immune System Disorders:** drug hypersensitivity; **Infections and Infestations:** pneumonia, sepsis/neutropenic sepsis; **Metabolism and Nutrition Disorders:** hypomagnesemia, dehydration; **Respiratory, thoracic, and mediastinal disorders:** interstitial lung disease; **Psychiatric Disorders:** anxiety; **Skin and Subcutaneous Tissue Disorders:** pruritus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category D

There are no adequate and well-controlled studies with HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In a developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.04, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area (mg/m^2). Increased abortion and severe external or soft tissue malformations were observed in offspring at doses 0.64 times the recommended human dose based on body surface area (mg/m^2), including the absence of a lower jaw, tongue, stomach and spleen. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at or above doses of 0.43 times the recommended human dose.

Maternal toxicity of eribulin mesylate was reported in rats at or above doses of 0.43 times the recommended human dose (mg/m^2), and included enlarged spleen, reduced maternal weight gain and decreased food consumption.

8.3 Nursing Mothers

It is not known whether HALAVEN is excreted into human milk. No studies in humans or animals were conducted to determine if HALAVEN is excreted into milk. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in human milk fed infants from HALAVEN, a decision should be made whether to discontinue nursing or to discontinue HALAVEN taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of HALAVEN in pediatric patients below the age of 18 years have not been established.

8.6 Hepatic Impairment

Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m^2 is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C).

8.7 Renal Impairment

For patients with moderate renal impairment (CrCl 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function. A lower starting dose of 1.1 mg/m^2 is recommended for patients with moderate renal impairment. The safety of HALAVEN was not studied in patients with severe renal impairment (CrCl <30 mL/min).

10 OVERDOSAGE

Overdosage of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day.

There is no known antidote for HALAVEN overdose.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Hepatic Impairment

A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=5) hepatic impairment. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 2.5-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function.

Renal Impairment

No formal PK trials were conducted with HALAVEN in patients with renal impairment. Available data suggests that geometric mean dose-normalized systemic exposure is similar for patients with mild renal impairment (CrCl 50-80 mL/min) relative to patients with normal renal function. However, for patients with moderate renal impairment (CrCl 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function.

12.6 Cardiac Electrophysiology

The effect of HALAVEN on the QTc interval was assessed in an open-label, uncontrolled, multicenter, single-arm dedicated QT trial. A total of 26 patients with solid tumors received 1.4 mg/m^2 of HALAVEN on Days 1 and 8 of a 21-day cycle. A delayed QTc prolongation was observed on Day 8, with no prolongation observed on Day 1. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.4 (19.5) ms.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies have not been conducted with eribulin mesylate.

Eribulin mesylate was not mutagenic in *in vitro* bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

The effects of HALAVEN on human fertility are unknown. Fertility studies have not been conducted with eribulin mesylate in humans or animals. However, nonclinical findings in repeated-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (mg/m^2) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (mg/m^2) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.64 times the recommended human dose (mg/m^2) weekly for 3 out of 5 weeks, repeated for 6 cycles.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs or symptoms of infection such as chills, cough, or burning or pain on urination.
- Advise women of childbearing potential to avoid pregnancy and to use effective contraception during treatment with HALAVEN.

Eisai

(continued from SP139)

a press release issued by SABCS. "What we found was that the estimates are all based on different situations, with different age groups being screened, different screening and follow-up periods, and differences in whether they refer to the number of women invited for screening or the number of women actually screened. When we standardized all the estimates to a common scenario—ie, the same exposure to screening, and a similar target population, period of screening, and duration of follow-up—the magnitude of the difference between studies dropped." After the adjustment, he said, there remained about a 2.5-fold difference between the estimates reported in the studies.

Otis W. Brawley, MD, chief medical and scientific officer of the ACS, has suggested that the medical community take a measured approach to the findings of the Canadian National Breast Screening Study.

"This study adds to the body of evidence, but that body of evidence still suggests that there is some benefit to mammography screening among women aged 40 and above," Brawley wrote in an article for the February 14 edition of *The Cancer Letter*. "The US Preventive Services Task Force assessed the total body of literature, including earlier reports from the Canadian trial, and said screening of women 40 to 59 likely produces a 15% relative reduction in the risk of death."

"While it is my concern that the benefits of mammography screening have been exaggerated, this does not mean that it does not save lives, or that women should not get it," he continued. "It means we need to use it with caution, explain its limitations, and realize we need to develop a better test." **EBO**

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Nutrition

Dietary Patterns, and Effect on Cancer, Get Attention From Advisory Panel

Mary K. Caffrey

Back in 1977, when a committee convened by then–US Senator George McGovern, D-SD, took the first official look at the American diet, the big concern was nutrient deficiency: in other words, what's missing that might make people sick?[1]

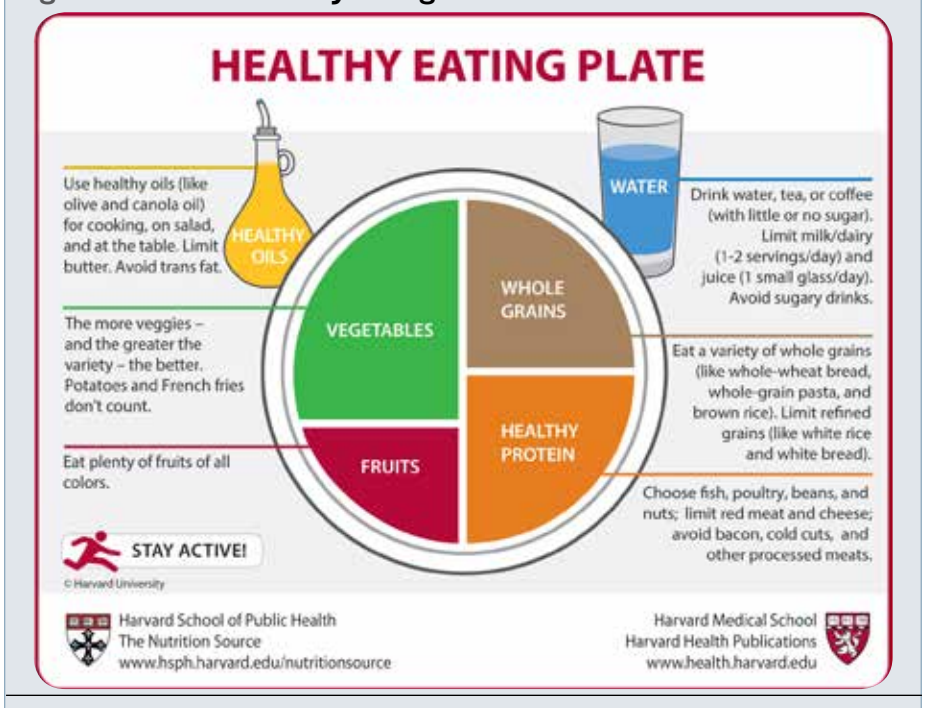
How times have changed.

On January 13-14, 2014, when the 2015 Dietary Guidelines Advisory Committee (DGAC) met in Bethesda, Maryland, the worries were generally not about too little but too much: Americans are making themselves sick alright, but most of the evidence concerns what we're *putting in* our diets, not what we're leaving out.

Rates of diabetes and obesity are soaring, especially in the Southeast, and at least part of this difference is attributed to the regional diet.[2] Institute of Medicine Senior Scholar J. Michael McGinnis, MD, MA, MPP, opened the session with an historical overview of the Dietary Guidelines process, and noted that 500,000 Americans now die each year due to poor diet and exercise habits—more than die from smoking.[1,3]

But as McGinnis and DGAC Chairwoman Barbara E. Millen, DrPH, RD, made clear, the 2015 guidelines cycle is not happening in a vacuum: the process, which occurs every 5 years and rotates between the US Departments of Agriculture and Health and Human Services (HHS), will unfold within HHS as the Affordable Care Act (ACA) takes hold across the country.

Figure. Harvard's Healthy Eating Plate



Source: http://www.hsph.harvard.edu/nutritionsource/healthyeating-plate-vs-usda-myplate/.

Looking to Improve Population Health

McGinnis, when asked how the guidelines could engage primary healthcare providers, said he was encouraged with the creation of accountable care organizations, as envisioned in the ACA. McGinnis noted that the ACA not only calls for the improvement of population health but for primary and specialty care providers to "look beyond the clinic doors" and speak to a "broad set of factors" that affect the health of every American, and require primary care physicians to be engaged.

The next day, after public testimony had concluded, Millen opened reports of the subcommittees with a clear link to healthcare reform. The 2015 guidelines, she said, have the potential to affect "the implementation of the Affordable Care Act, the accountable care organizations," national prevention strategy, as well as grant funding within the National Institutes of Health and the Centers for Disease Control and Prevention. She then outlined what is good and bad about both the food and the healthcare systems.

The US population, she said, has the finest healthcare innovations in the world, including the best cancer care, but access to care is "variable." The nation needs to shift its attentions from a preoccupation with treatment to a system based on prevention. Despite what employers and families spend on healthcare, there are wide healthcare disparities, Millen said. "We have preventable disease morbidity and chronic disabilities, and they account for half of the nation's health burden."

Is there a link between these facts and what Americans eat? Millen seemed to suggest so.

"One in 6 households are food insecure, and two-thirds of the population is overweight or obese…we suffer from poor dietary patterns," she said. "Foodborne illnesses have reached 76 million annually, accounting for 325,000 hospitalizations and 5000 deaths each year."

Despite the many strengths of the agriculture and food distribution systems, Millen said, many experts believe that the committee must find solutions to these problems, and it must act aggressively to tackle diabetes and obesity, to do something about healthcare disparities among certain groups, to moderate alcohol use, and to lower metabolic risk factors. "These are the questions that are on the minds of the DGAC," Millen said.

For the first time, Millen said, the committee will include in the evidence base what it finds about connections between dietary patterns and cancer risk, including not only known relationships, but also what can be done to reduce cancer risk in the population through the foods Americans eat.

A "Systems" Approach

Millen, DGAC Vice Chair Alice Lichenstein, DSc, and the 2 returning members from 2010, Miriam Nelson, PhD, and Rafael Perez-Escamilla, PhD, have formed a science review subcommittee that is ensuring that the committee takes a "systems approach," and examines dietary patterns and best practices, rather

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than just go food by food, or ingredient by ingredient. In fact, the third presenter at the January 13 session, Susan Krebs-Smith, gave the panel an overview of how to evaluate diets based on different systems approaches. Millen called for looking at "what works" at *both* a population level and at an individual level. The 2015 committee will continue its predecessor's work in examining the effects of the places where people eat, cultural factors, and access to quality food, but it will dig deeper to examine the connection with help outcomes, Millen said.

Milton Mills, MD

This approach is more novel than it might seem. Past DGAC reviews have been criticized for being captive to corporate food groups; indeed, those interests gave it their best during the morning session of January 14. A literal smorgasbord of professionals paraded to the microphone, representing sugar, salt, potatoes, California walnuts, the American Meat Institute, nonalcoholic beverages, Ocean Spray cranberries, McDonald's, juice products, Dannon yogurt, food technologists, egg farmers, the Tea Council, the National Cattlemen's Beef Association, candy and gum, pistachio growers, and the United Fresh Produce Association, among others. Most interests came armed with a registered dietitian, and everyone had studies to support giving their product a place at the table.

How food-specific the DGAC's recommendations will be remains to be seen. Anna Maria Siega-Riz, PhD, RD, who chairs the largest and most critical subcommittee on "Dietary Patterns, Foods and Nutrients, and Health Outcomes," explained in the afternoon session January 14 that her panel will first examine dietary patterns, and from those results will take its work into specific foods. She did not directly answer a question from Nelson on how the subcommittee would tackle thorny topics such as sugar-sweetened beverages, which has been the subject of important research since 2010, as well as high-profile public policy initiatives in New York City, Mexico, and the United Kingdom; and dairy, which dominated testimony in the public hearing January 14.

The Importance of Sustainability

Some topics of the January 13-14 meeting were anticipated: given the public flap over a May IOM study that did not support sodium intake below 2300 mg per day, it was hardly surprising when a Salt Institute lobbyist asked the committee to take the "courageous step" of calling for more salt in American diets.[4]

Comments received in the fall from John Hopkins' Center for a Livable Future[5] presaged the presentation from its visiting scholar, Kate Clancy, PhD, who spoke January 13 about food sustainability and food security; essentially, the idea that it's best for the sources of food to be as close to the people that consume them as possible, to protect both population health and the environment.

As the Hopkins center did last fall, Clancy addressed the beef industry's effects on the climate; she did not, however call for diets "bereft" of meat, but said "low-meat" diets produce many of the same benefits.

When it came to seafood, however, Clancy was clear: overfishing is a "wicked" problem, and the current dietary recommendations of 2 servings per week simply don't square with supplies of popular fish. The public needs better, more specific advice on what species to eat; the fish "conundrum," as Clancy called it, is part of a broader problem of food diversity. "There is biodiversity available to people, but when we look at what people eat, the message is not getting through," she said. "Just like anything else, a better diet would have more species in it."

Clancy said efforts to improve biodiversity and reduce portion size in school lunches in the largest districts and in college cafeterias have made some headway, but there's more to be done. The public has a huge role to play in food sustainability and food security through the choices it makes, she said.

Dueling Over Dairy

Opponents of meat and especially dairy were out in force January 14; 13 of 54 favored plant-based diets in some form,[6] and they ran the gamut: from the vegan mother who shared a typical daily menu, to the African American doctor who showed up in scrubs after an overnight hospital shift, to the actress Marilu Henner. Mona Sigal, MD, the former emergency room chief at North Shore Medical Center in Massachusetts who today educates the public about healthy eating, used her 3 minutes to lambaste the USDA's publicly funded promotion of cheese, which left the audience laughing when the moderator announced that the next speaker was from the National Dairy Council. But Sigal's message was serious: like other speakers, she cited studies that link dairy consumption with cancer.

The African American physician, Martin Mills, MD, is a graduate of Stanford University School of Medicine and has led a suit by the Physicians' Committee for Responsible Medicine against the dairy industry, seeking warning labels on milk.[7] Mills did not mention those credentials; instead, he cited statistics that unlike Americans of Northern European origin, most ethnic minorities are naturally lactose intolerant, including 70% of African Americans, 90% of Asian Americans, and 55% of Mexican Americans.

Moreover, Mills said, connections between milk and cancer are emerging, and the troubling disparities of prostate cancer among African American men[8] demands that the committee "stop holding Americans hostage to the marketing interests of the dairy industry."

While percentages in studies have varied, Mills' overall assertion that lactose intolerance is higher among minorities than persons of Northern European heritage is supported in the literature,[9-11] and his assertions about cancer links are supported as well.[12,13]

Thus, Mills likened the government's ongoing inclusion of recommended daily allowances of dairy in American diets to a form of "institutional government racism."

"Yes, I played the race card," he said.

Various dairy groups brought up past recommendations about "nutrients of concern," specifically calcium, potassium, and vitamin D, and cited studies showing that consuming dairy would contribute to meeting daily requirements.

Controversies over dairy recommendations are not new. The inclusion of a separate dairy cup to the side of the MyPlate graphic was a key criticism of the 2010 edition of Dietary Guidelines for Americans; Harvard's School of Public Health replaced the dairy cup with a glass of water in its "Healthy Plate" alternative, citing dairy links to prostate cancer as a reason.[14]

Next Steps

In opening the subcommittee sessions, Millen reminded the committee that its work is advisory in nature, and the final guidelines are set by the federal departments that oversee the group. Still, the committee has a significant role in shaping guidelines that Millen said shape massive federal programs and touch virtually "every American, every day."

The committee's work, she said, "must be thoughtful, it must be science driven, and it must be very careful."

Millen noted that the committee would consider online comments, in addition to those given in person at the hearing. The next committee meeting is set for March 14, 2014. **EBO**

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Ramucirumab Combination Improves OS and PFS in NSCLC

Christina Izzo

The second-line administration of ramucirumab in combination with docetaxel has shown a statistically significant improvement in overall survival (OS) and progression-free survival (PFS), compared with placebo plus docetaxel, in patients with non-small cell lung cancer (NSCLC), according to Eli Lilly and Company, the developer of the agent.

The phase 3 REVEL randomized double-blind trial compared ramucirumab and docetaxel with placebo and docetaxel in patients with NSCLC whose disease had progressed after failure of prior platinum-based chemotherapy for locally advanced or metastatic disease. More than 1200 patients, with both squamous and nonsquamous NSCLC, were enrolled across 26 countries.

"We are pleased with these phase 3 data of ramucirumab in non-small cell lung cancer, which accounts for most cases of lung cancer—the leading cause of cancer-related mortality worldwide. Despite currently available therapies, there continues to be a need for new second-line treatment options for patients with lung cancer," Richard Gaynor, MD, senior vice president, product development and medical affairs for Lilly Oncology said in a press release. "REVEL is the first positive phase 3 study of a biologic in combination with chemotherapy to demonstrate improved overall survival compared to chemotherapy alone in second-line non-small cell lung cancer."

The most common (>5% incidence) grade >3 adverse events occurring at a higher rate on the ramucirumab plus docetaxel arm compared with the control arm were decreased white blood cell count (neutropenia/leukopenia), febrile neutropenia, fatigue/asthenia, and hypertension.

Full data from the REVEL trial will be announced at an upcoming scientific meeting and Lilly said it intends to submit the first application of these data to regulatory authorities this year.

Ramucirumab, a fully human monoclonal antibody, targets vascular endothelial growth factor receptor-2. It is designed to directly inhibit angiogenesis, a process by which blood vessels supply blood to tumors.

In an open-label phase 2 study of 140 chemotherapy-naive patients, ramucirumab was investigated in combination with first-line chemotherapy in advanced nonsquamous NSCLC.

For patients who received pemetrexed (500 mg/m^2) plus carboplatin (AUC = 6) or cisplatin (75 mg/m^2) once every 3 weeks, the median PFS was 4.3 months. In patients who received ramucirumab (10 mg/kg), pemetrexed (500 mg/m^2) plus carboplatin (AUC = 6) or cisplatin (75 mg/m^2) once every 3 weeks, the median PFS was improved to 6.3 months (hazard ratio = 0.48; 90% confidence interval [CI]; 0.31-0.74).

Ramucirumab was also studied in combination with paclitaxel and carboplatin as first-line therapy in patients with advanced NSCLC. Forty patients received ramucirumab (10 mg/kg), paclitaxel (200mg/m^2), and carboplatin (AUC = 6) on day 1 of a 3-week cycle for up to 6 cycles, followed by maintenance ramucirumab.

The overall disease control rate (complete response + partial response + stable disease) reached 90% and PFS at 6 months was 59.0% (95% CI; 41.3-72.9). In this analysis, the median PFS was 7.85 months.

The REVEL lung cancer trial is the third positive phase 3 study of ramucirumab across multiple tumor types. The first, which studied ramucirumab in gastric cancer as a single agent, is the basis for initial regulatory submissions in the United States and Europe. The second study evaluated ramucirumab in gastric cancer in combination with paclitaxel and is scheduled for regulatory submission in 2014.

Top-line results for phase 3 trials of ramucirumab in hepatocellular and colorectal cancer are expected later this year. **EBO**

FDA Grants Accelerated Approval for Ibrutinib for CLL

Surabhi Dangi-Garimella, PhD

The US Food and Drug Administration (FDA) granted accelerated approval for the expanded use of ibrutinib, marketed as Imbruvica, for chronic lymphocytic leukemia (CLL) patients who have previously received at least 1 therapy. This approval was based on a phase 1b-2 open-label, multicenter study that was designed to determine the safety, efficacy, pharmacokinetics, and pharmacodynamics of Imbruvica in patients with relapsed or refractory CLL or small lymphocytic lymphoma.

FDA's approval comes after reviewing a study of 48 patients who had been diagnosed with CLL an average of 6.7 years prior to the study. They received orally administered 420 mg of ibrutinib until they experienced unacceptable toxicity or their disease progressed. Significantly, overall response rate (cancer shrinkage) was observed in 58% of participants over a duration of 5.6 to 24.2 months. It's still early, however, to establish impact on survival or disease-related symptoms.

"Today's approval provides an important new treatment option for CLL patients whose cancer has progressed despite having undergone previous therapy," said Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "The FDA completed its review of Imbruvica's new indication under the agency's accelerated approval process, which played a vital role in rapidly making this new therapy available to those who need it most."

According to the National Cancer Institute, CLL is the most common leukemia in adults; it affected 15,580 adults in 2013 and was responsible for 4580 deaths. The B-cell receptor signaling pathway, specifically the downstream protein Bruton's tyrosine kinase (BTK), has been shown to drive the disease. Following activation, BTK promotes cell survival by stimulating Akt, ERK, and the NF-κB signaling pathways along with the activation of cytokine-driven homing and adhesion of B-cells. This makes BTK an attractive target for inhibition in CLL therapy.

Ibrutinib is an orally bioavailable BTK inhibitor that demonstrated immense potential in several preclinical studies. The absence of toxic effects on normal T-cells distinguishes the drug from most other CLL regimens.

The most common side-effects observed in the trial included thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, pyrexia, rash, constipation, stomatitis, peripheral edema, nausea, sinusitis, and dizziness.

Ongoing trials for Imbruvica include randomized trials to compare the drug's safety profile with current CLL therapies, which include 2 phase 3 studies (RESONATE; ClinicalTrials.gov number NCT01578707 and RESONATE-2, NCT01722487).

The drug is being developed jointly by Pharmacyclics and Janssen Biotech, Inc. **EBO**

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Nivolumab Provides Favorable Results in Patients With Advanced Melanoma

Surabhi Dangi-Garimella, PhD

Programmed cell death-1 (PD-1) is a key immune inhibitory receptor expressed by activated T-cells and B-cells. Binding of PD-1 to its ligands PD-L1 and PD-L2, expressed on antigen-presenting cells and cancer cells, turns off T-cell signaling to the lymphocytes and allows tumor cells to shut off the immune response. Many solid tumor types express PD-L1, and its expression is often associated with a worse prognosis. Blocking PD-1 is the novel approach being evaluated in cancer treatment and it has been reaping extremely favorable results (**see "Targeted Programmed Cell Death in Lung Cancer Treatment," cover**).

A recent phase 1 trial report published in the *Journal of Clinical Oncology* evaluated the effect of intravenous nivolumab in 107 patients with advanced melanoma in an outpatient setting, every 2 weeks for up to 96 weeks. The patients were observed for overall survival (OS), long-term safety, and response duration after treatment discontinuation.

Patients receiving nivolumab had a median OS of 16.8 months; the 1- and 2-year survival rates were 62% and 43%, respectively. Of 33 patients with objective tumor regressions (31%), the estimated median response duration was 2 years. Of the 17 patients who discontinued therapy (not due to disease progression), 12 maintained a response for at least 16 weeks (range was 16 to 56 weeks).

Objective responses were observed in 33 of 107 patients, and 7 patients' experienced stable disease lasting at least 24 weeks. Durable responses were observed across all the tested doses (0.1- to 10-mg/kg) of nivolumab. Unconventional response patterns that did not meet response evaluation criteria in solid tumors (RECIST) were observed in 4 patients. Of the 11 patients in whom the disease progressed at doses of 0.1- or 0.3-mg/kg nivolumab, dose escalation to 1.0-mg/kg did not help. Tumor regression in the 33 patients was observed at various sites, in both primary and metastatic lesions.

Of 17 patients who discontinued therapy, 12 maintained a response for at least 16 weeks.

The most common adverse events observed included fatigue, rash, and diarrhea. Twenty-four of the 107 patients experienced grade 3 to 4 treatment-related adverse events. Treatment-related adverse events included skin disorders, GI events, and endocrinopathies. Although no drug-related deaths were observed in patients with melanoma, 3 treatment-related mortalities were observed in the overall population (2 patients with non-small cell lung cancer and 1 with colorectal cancer) associated with pneumonitis. Most adverse events were observed in the first 6 months of treatment; no cumulative toxicities were observed over a 2-year safety follow-up period. **EBO**

Physician Practices, Healthcare Organizations See Own Staff as Source of Security Breaches

Tony Berberabe, MPH

Results from the final report of the 2013 Healthcare Information and Management Systems Society Security Survey suggest that physician practices and health care organizations such as hospitals view their own staff members as the greatest source of patient information and confidentiality security breaches. In fact, 80% of respondents noted that they were concerned that human-related factors would put data at risk.

In the survey, respondents were most likely to identify human-related factors such as individuals circumventing controls or disclosing information in error as the greatest area of concern. Respondents were least likely to identify loss of information integrity, such as database corruption, as a concern. The respondents used a scale from 1 to 7, where 1 was not perceived as a threat and 7 represented an area that was of high-threat concern.

A security breach from an insider remains a major challenge, according to the 283 information technology and information security professionals who responded to the survey. The survey was supported by Medical Management Association and sponsored by the Experian Data Breach Resolution.

To prevent staff's prying eyes, hospitals and practices are adding technology to existing Information technology systems to prevent snooping into electronic records. These include user access controls and audit logs of each user's access to patient health records.

Additionally, two-thirds of respondents reported that they use at least 2 access control mechanisms, such as user-based and role-based access controls, for controlling employee access to data. Furthermore, the number of respondents indicating their organization is collecting and analyzing data from audit logs is also increasing. For instance, the number of respondents that report their organization analyzes data from their firewalls, applications, and servers has all increased in the past year.

Nineteen percent of respondents reported they had a security breach in the last year. The majority of these breaches involved fewer than 500 patients.

Lastly, healthcare organizations are more frequently auditing their information technology security plan to ensure they are ready in the event that a breach—internal or external—takes place.

Other key survey results include:

- *Risk Analysis*: The number of respondents working for physician practices that reported their organization conducted a risk analysis increased from 65% in 2012 to 78% in 2013.
- *Data Breach Response Plan*: More than half of the respondents (54%) reported that their organization has tested their data breach response plan.
- *Security Breaches*: Nineteen percent of respondents reported that they had a security breach in the last year. The majority of these breaches involved fewer than 500 patients. Three-fourths (79%) reported that they notified patients affected by the breach. Only 8% of respondents indicated that the security breach was the result of actions taken by a business associate. **EBO**

Understanding and Addressing Barriers to Recruitment

Jennifer L. Redmond, DrPH

Patients fear being a guinea pig or receiving a placebo, healthcare providers do not have time to keep up with all the clinical trial information or talk with patients in depth, conducting clinical trials are very expensive for healthcare systems and funding continues to decline for research. With all these barriers, it's not surprising that clinical trial recruitment remains around 1.7% for adults.[1]

Many professionals throughout the country, including oncology nurses, surgeons, medical oncologists and researchers, have identified best practices and resources to help overcome many of these barriers, improve informed decision-making and increase clinical trial recruitment. Six professionals, actively involved in clinical trial education, navigation, review, recruitment and research, provided their perspectives on barriers and best practices:

- Oncology nurses
  - Sue Childress, RN, MN, OCN, director of nursing at the Huntsman Cancer Institute, Salt Lake City, UT
  - Cindy Davidson, APRN, clinical operations manager at the Huntsman Cancer Hospital in Salt Lake City, UT
  - Joyce Schaffer, RN, MSN, AOCNS, clinical trials patient navigator with Scottsdale Healthcare in Scottsdale, AZ
- Physicians
  - Timothy Mullett, MD, cardiothoracic surgeon at the University of Kentucky, Lexington, Kentucky and director of the Kentucky Clinical Trials Network
  - Leigh Neumayer, MD, a general surgeon specializing in breast cancer at the Huntsman Cancer Institute, Salt Lake City, UT
- Researcher
  - Margaret Byrne, PhD, associate professor at the University of Miami, Florida, focused on new tools related to informed decision making and clinical trials.

Barriers and best practices can be found at many places in the clinical trial system. These relate to the patient and family who may be fearful or confused by the trial, the healthcare professional who has no time to spend on clinical trials, and the healthcare system that struggles with handling the cost and inefficiencies of conducting clinical trials.

Patient and Family

Barriers

Fear was touted as the greatest barrier for patients and families, particularly the fear of being a guinea pig or receiving a placebo rather than treatment. Patients may not know that clinical trials were an option, and if they did know, they may see participation as a last resort. Some also believe that a drug already approved by the US Food and Drug Administration (FDA) would be better than a drug that is not yet approved.

Clinical trials can be complicated and confusing. Some patients would rather just say "no" to participation because it is easier. When conducting in-depth interviews with 45 minority patients, Byrne asked about whether they participated in a clinical trial. After providing information on their treatment experiences, many patients asked her if they had participated in a clinical trial.

Sue Childress, RN, MN, OCN

Cindy Davidson, APRN

Joyce Schaffer, RN, MSN, AOCNS

Cost is another patient barrier. These costs include: travel, time off work, and cost of procedures, particularly if the patient is uninsured. Insured patients may be concerned that there will be unexpected costs that are not covered by their insurance. Some patients have limited insurance plans with minimal out-of-network benefits and many patients do not know the rights they have within their plans. Depending upon the way a patient asks the question, they may receive a different response. As Schaffer said, "If a person calls an insurance company and asks if they will provide coverage for a clinical trial, they will say "no", but if that person asks if they will cover the standard of care in a clinical trial, then they will say 'yes'."

There is also the impact of clinical trials on their families. Patients may not want to burden their families and will choose whatever is easiest for their families even if it may not be the best for them.

Best Practices

Everyone agreed that communication and education were essential in overcoming the fear-based patient and family barriers to clinical trials. Some specific approaches, mostly focused on healthcare professionals' involvement, included the following:

- Provide all the treatment options, including eligible clinical trials, to the patients and their families. Involve them in the decision making.
- Have everyone involved in the conversation, both the patient and close family members.
- Provide education on clinical trials so they know that it is a type of treatment rather than a placebo.
- Include all healthcare professionals in discussing clinical trials: nurses, social workers, primary care providers, surgeons, oncologists, and others.
- Have a dedicated research nurse to explain the clinical trials in depth.
- Utilize various types of media to educate patients regarding clinical trials including advertisements, Facebook, Twitter, and word of mouth.
- Develop relationships in the community by providing specific outreach and education to minority populations.
- Have a process for informed consent that includes the ability to address potential language barriers.

When addressing the cost concerns of the patients and families, the interviewees recommended the following:

- Connect patients to financial counselors or social workers to identify resources. Once they are off of a trial, treatment resources are often available by contacting the drug company directly.
- In partnership with private foundations, set up patient assistance programs in coordination with local hotels and businesses to help with travel expenses.
- With Institutional Review Board

The Specific Tools

Moffitt Cancer Center 8-minute patient video on clinical trials: http://moffitt.org/research--clinical-trials/clinical-trials/clinical-trials-video.

Margaret Byrne, PhD, has developed Web-based decision aids for clinical trials still in the research process. Once completed, these tools will be available for patients.

Specific Tools

Include a "pink sheet" or electronic reminder in every chart where the clinical trials coordinator/navigator can put the patient's name and tumor characteristics. Provide a space for the physician to make notes on the result of the discussion of the trial.

Role of Healthcare Professionals/Providers in Clinical Trial Recruitment

- Involve patients in decision making. Provide clarity on risks and benefits of each treatment option. Utilize many methods of communication including:
  - One-on-one conversations
  - Website tools and webcasts
  - Printed materials
- Stay as current as possible on treatment and clinical trial options.
- Admit to not having all the answers.
- Stay focused on what is best for the patient and be willing to refer a patient somewhere else if it is a better option.
- Include clinical trial recruitment as a metric for monitoring performance.
- Work together to advocate with the healthcare system leadership to hire and support a clinical trials coordinator.

THE AMERICAN JOURNAL OF MANAGED CARE®

Affordable Care Act

The law, effective for health plans newly issued or renewed after January 1, 2014, prohibits health plans or insurance issuers from:

- Denying participation of beneficiaries in clinical trials,
- Denying or limiting coverage of routine patient care costs, subject to the plan's out-of-network coverage policy, and/or
- Discriminating against the individual on the basis of participation in a trial.[3]

Potential Impact on Clinical Trials:

- More patients will have insurance so they will be able to reassure patients that they wouldn't have any additional bills, whether they were participating in a clinical trial or not.
- Cancer patients under age 26 years are able to stay on their parent's insurance plan and have coverage for standard treatments.
- Patients should continue to have insurance after their cancer and/or participation in the clinical trials because they cannot be discriminated against based on preexisting conditions.
- The reimbursement structure will change—which may or may not be beneficial—for clinical trials.
- Interpretation and full implementation of the Affordable Care Act is still unknown.

approval, provide reimbursement from the trial for some travel expenses, including food, lodging, and transportation.
- Write letters and advocate for patients to insurance companies.
- Encourage patient participation in the Health Insurance Exchange Marketplace

Healthcare Professional

Barriers

Lack of time was the most common barrier noted for healthcare professionals. As Neumayer emphasized, "Time is number 1-10, particularly when we are asked to see so many patients, get them through more quickly and are pushed and pulled in so many directions. Number 11 is remembering and 12 is identifying the appropriate patients."

Related to time was a lack of knowledge and ability to keep up with all the trials that might be appropriate for patients. Despite being aware of latest trials, in the midst of caring for patients, it becomes difficult to remember specific inclusion and exclusion criteria.

Lack of funding prevents institutions from hiring clinical trial coordinators who can provide guidance and chart reviews on identifying appropriate patients for clinical trials and communicating that information to the clinician. There is no reimbursement to clinicians for clinical trials work, and since it takes a lot of time to discuss clinical trials with patients, there are negative financial implications for physicians.

Fear among healthcare professionals was mentioned several times during the discussions. One fear, particularly seen among nurses, was of the unknown impact of treatment and the concern that the patient might not receive the best treatment possible. Another fear, particularly from community oncologists, was that they would lose their patients if they recommended participation in a clinical trial.

Best Practices

To address the lack of time and coordination barriers, have a dedicated research nurse, clinical trials coordinator or clinical trials patient navigator who:

- Focuses on keeping up with the latest clinical trials
- Reviews the patients' charts and types of cancers (prescreening)
- Identifies which patients would be eligible for particular trials
- Advises the physician to talk about certain clinical trials
- Coordinates the process.
- Talks with patients about clinical trials

Fostering communication and collaboration across researchers, nurses, physicians, and community oncologists increases knowledge of clinical trials and addresses some of the fear and cost concerns. Some practical ways to encourage this collaboration include:

- Meet periodically with researchers, physicians and community oncologists to share what clinical trials are available for patients
- Create opportunities to listen to the concerns of specific healthcare professionals—nurses, social workers, community oncologists, and other physicians—provide opportunities for discussion and ways to address their concerns
- Involve as many healthcare professionals as possible in discussing clinical trials at every opportunity
- Open trials in collaboration with community oncologists
- Develop communication pieces (newsletters, etc) on current clinical trials for nurses, community oncologists and other physicians
- Attend professional events and create opportunities to discuss clinical trials
- Require a percentage of continuing education credits focused on clinical trials
- Set goals, both individually and collectively, for clinical trial recruitment
- Celebrate successes and provide positive feedback

Timothy Mullett, MD

Leigh Neumayer, MD

Margaret Byrne, PhD

Healthcare Systems

Barriers

Most of the healthcare system barriers focused on funding, coordination and insurance coverage. The funding barriers included the limited funding for clinical trial research, particularly from national research organizations and lack of health system-level resources. Even when there is funding, it may be insufficient to be able to design the trial that would best test the treatment modalities. Funding is also targeted to particular types of cancers that may be disproportional to the disease burden. Many trials remain open and recruit a minimum number of patients, which can be extremely expensive.[2]

As Mullett explained, "Clinical trials are expensive, they disrupt the follow of clinical care, they require extra personnel and there are potential risks involved. Those in the ivory tower want us to take care of patients efficiently—and bill for it…there is just no way to justify the costs so there has to be a commitment from the enterprise that they are willing to take a loss on it."

Connected to the funding barrier is the lack of coordination as well as the requirement of significant documentation. There is often no easy way to find out which patients are eligible for what trials. If the facility or system has not funded a clinical trials coordinator, and there is minimal infrastructure provided, then it is difficult to get all the healthcare professionals working together on clinical trials.

There were varying responses related to the insurance component. Some of the interviewees had frequent challenges with insurance plans not covering care outside of their system or facility even though the system or facility didn't have the treatment options available to the patient. Others found that those with insurance had adequate coverage for standard of care. They all had concerns about the uninsured, and although some of them were often able to eventually find resources to support their care, uninsured patients sometimes delayed their treatment several months. The interviewees were hopeful that the Affordable Care Act would have a positive impact on reducing the insurance barrier.

Best practices

These 6 healthcare professionals provided several recommendations to improve the healthcare system's ability to recruit and conduct clinical trials.

The following focused on addressing the funding issues:

- Work together as an organization to advocate to legislative bodies for additional funding
- Collaborate with cancer center fundraising efforts to support clinical trials
- Identify private foundations interested in supporting clinical trials
- Support many different types of clinical trials from industry-supported, which often have adequate funding, to cooperative and investigator initiated ones
- Recognize the importance and support clinical trials with personnel, office space, and resources to achieve clinical trial goals
- Consider the clinician support and system capacity prior to conducting trials. Only conduct trials that would be most cost effective, with responsible conduct and good clinical practice

There were also several recommendations related to coordination challenges:

- Encourage healthcare system leaders to begin the conversation about clinical trials in order to promote positive publicity and raise awareness among cancer patients and communities
- Invest in at least 1 person dedicated to being a clinical trials coordinator/expert within the healthcare organization

- Ensure that new technologies, such as electronic medical records, will support clinical trials efforts
- Combine practices to create bigger networks that would support clinical trials
- Include clinical trial participation metrics into dashboards and other measures of performance

Although it may take time for a healthcare organization to implement these best practices, a priority consistently recommended by all 6 healthcare professionals included having a dedicated clinical trials person. As Byrne said, "There is agreement that it is important to have one person dedicated to being a clinical trials expert—a research nurse—where all she does is talk with patients about clinical trials, knows what trials are available and coordinates the process." **EBO**

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Technology

Proteomic Advances Hold Promise for Precision Medicine

Andrew D. Smith

The patient's metastatic cancer has resisted the trastuzumab and chemotherapy you initially prescribed, and she's relying on you to devise life-saving fallback treatment.

A realm of possibilities exist for this scenario: the same treatment at a higher dose, a different chemotherapy, a different monoclonal antibody, an angiogenesis inhibitor, an experimental medication, or any combination of the above.

What new tests can maximize the chances that your patient will obtain the right treatment for her particular case?

Lance A. Liotta, MD, PhD, explained the existing options and highlighted some promising research Friday during his presentation, "Application of Proteomics to Biomarker Discovery and Individualized Therapy."

"In the past, doctors had little option but to rely on 'gut feelings' that amounted to little more than guesswork," said Liotta, codirector of George Mason University's Center for Applied Proteomics and Molecular Medicine and medical director of its Clinical Proteomics Lab, during an interview in advance of his presentation.

"Unfortunately, studies conclusively show that it's nearly impossible to guess right, which is why it is so exciting and important that proteomics has advanced to the point that it can sometimes eliminate the guesswork."

Indeed, proteomic tests can provide much information that even genetic analysis cannot.

They can, for example, measure activity levels within the signaling pathways of individual tumors, and those signaling pathways functionally drive the growth, activity, and reproduction of cancer cells.

Proteomics may also provide narrower options for treatment.

"Genetic analysis tells you all the proteins a tumor is capable of making. Proteomics tells you what few proteins it actually does make and which ones are in use driving growth or invasion," Liotta said. "The first bit of information is interesting, but the second one is a lot more practical when you're selecting among drugs that only work when particular proteins are present."

Liotta's presentation will explain the capabilities of the few proteomic tests that are commercially available for breast cancer patients right now.

One test that measures the HER family of proteins, for example, builds a "molecular profile" of each tumor that measures the levels of EGFR (HER-1), HER-2 and HER-3 and then quantifies specific auto-phosphorylation sites that appear on each tumor and indicates the degree of activation.

The test then looks at downstream pathways such as the MAP Kinase pathway and the Akt/mTOR cell survival pathway.

In all, the test measures the concentration and activity levels of receptors and signaling pathways that are targeted by 10 separate drugs: cetuximab (Erbitux), erlotinib (Tarceva), gefitinib (Iressa), panitumumab (Vectibix), trastuzumab (Herceptin), pertuzumab (Perjeta), lapatinib (Tykerb), temsirolimus (Torisel), sirolimus (Rapamune), and everolimus (Afinitor).

The same test also looks for the activation and amplification of signaling pathways associated with resistance to many of those same therapies.

"You take a small biopsy, you mail it away and 2 weeks later you have a mountain of useful information, both pro and con, to help you decide among a large number of medications. It is, in many cases, hugely valuable," Liotta said.

Unfortunately, only a few such tests are commercially available right now, but Liotta sees other possibilities for doctors and patients who really need to tap the power of proteomics.

"In addition to discussing what's on the market for everyone, I will explain how doctors can find relevant trials and enroll patients when circumstances make that appropriate," Liotta said.

"The trials I talk about are not for patients with good prognoses under well-established standards of care. However, in cases where the alternative for choosing treatment is guesswork, trials may be a very good option."

Lance A. Liotta, MD, PhD

Liotta says that the Side Out Trial 2 that uses proteomics combined with genomic profiling to individualize therapy specifically for metastastic breast cancer, is a pioneering trial that directly addresses this need.

Another good option for many women is the I-SPY 2 trial.

That trial, which will assess up to a dozen experimental medications, doesn't assign those treatments entirely at random. It also uses commercial and experimental diagnostic techniques to characterize each tumor and select an appropriate treatment before surgery.

The care, moreover, improves as the trial progresses. Data from earlier groups of patients guide decisions about which treatments might be more and less useful for patients enrolled later in the trial.

In addition to summarizing I-SPY and other promising trials, Liotta will explain how doctors can use websites, such as NCI.gov, to find trials that would make sense for their individual patients.

"Proteomics is a big area of research right now," Liotta said. "There are a lot of trials at various stages of planning and enrollment, so it makes sense for doctors to learn how to look."

To make the discussion as practical as possible, Liotta will frame most of it in case studies, like that of the patient who led off the story, the one who did not respond to trastuzumab and chemotherapy.

Each case study will be one familiar to community oncologists who treat breast cancer, and each discussion will illustrate how advances in proteomics might help doctors and patients, either directly or through improved tests for other cancer biomarkers that range from microRNA to lipids, sugars and metabolites.

Liotta's presentation will focus mainly on what's available now, but it will also mention proteomics research that's expected to produce valuable new diagnostic tools in the near future.

"There are some very exciting blood tests in the works that could find cancers at very early stages," Liotta said, "and other tests that could be paired with mammograms to greatly increase the specificity of diagnosis and greatly reduce needless biopsies." **EBO**

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 $1568 per 3.5-mg vial as of January 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 ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

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

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

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

*Melphalan+prednisone.

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

VELCADE®
(bortezomib) FOR INJECTION

VELCADE®
(bortezomib) FOR INJECTION

Brief Summary

INDICATIONS:

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

CONTRAINDICATIONS:

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

WARNINGS AND PRECAUTIONS:

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

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

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

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

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

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

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

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

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

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

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

ADVERSE EVENT DATA:

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

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

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

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

DRUG INTERACTIONS:

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

USE IN SPECIFIC POPULATIONS:

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

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

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

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

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

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

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

Takeda MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

V-12-0306a 1/14

QOPI

(continued from cover)

Berwick, MD, who was then administrator of the Centers for Medicare and Medicaid Services (CMS), expressed interest in partnering with ASCO to raise the quality of service rendered to Medicare and Medicaid beneficiaries.[5] Subsequently, the 2014 ASCO annual report announced plans to position QOPI as a model clinical registry with CMS, through a provision made in the American Taxpayer Relief Act of 2012.[6]

Quality Improvement

Maintaining high standards for successful treatment requires efficient measures, as well as periodic review to ensure continuing improvement. QOPI was developed by world-renowned practicing oncologists and quality experts, using clinical guidelines and published standards such as the National Initiative on Cancer Care Quality, ASCO/National Comprehensive Cancer Network Quality Measures, and American Society for Radiation Oncology/ASCO/American Medical Association Physician Consortium for Performance Improvement Oncology Measures.[7] The program currently lists at least 160 measures, which are updated biannually, but these measures are dynamic and may improve with time and experiences.

James Brandman, MD, MS

From Idea to Reality

Simone, a pediatric oncologist who has served as the director of the University of Florida Shands Cancer Center, is the pioneer of the quality improvement program. In a 2009 commentary, he ascribed his inspiration for developing QOPI to multiple factors:

- the pediatric oncology model
- quality of cancer care recommendations that he was involved in drafting as a member of the NCPB
- the uproar created by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, which raised the essential question: "Where does the patient stand?"[2]

Subsequently, Simone initiated a steering committee that laid down a proposed model that was tested (2003) in 25 practices interested in quality-of-care issues. Consequently, QOPI was offered to all ASCO members in 2006.

Program Participation Basics

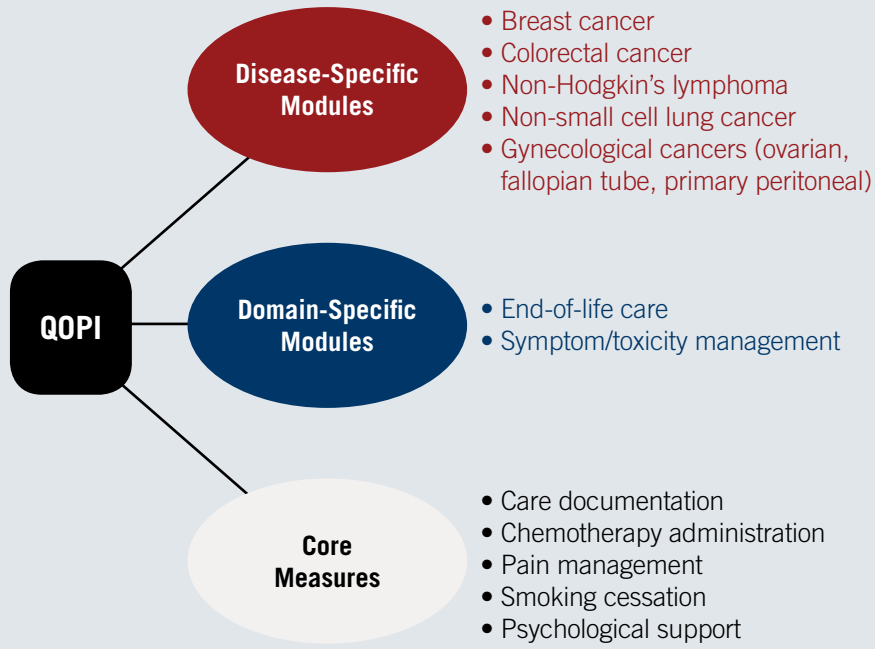
The program requires that a US-based participating practice have at least 1 active ASCO member in good standing. Currently, international practices can register, but they cannot participate in data collection, although efforts are under way to expand inclusion (iQOPI). Although participation in QOPI does not entail a fee, data abstraction would cost the practice staff time. Further, practices are encouraged to participate in multiple rounds for rapid quality improvement and to share their data among the entire practice staff. The program necessitates a 1-time registration, and it is recommended that the registration process be initiated at least 1 month prior to data collection.[7]

Quality Measurements

QOPI data collection is based on scoring on 7 modules: care at the end of life, symptom/toxicity management, breast cancer, colorectal cancer, and non-small cell lung cancer (**Figure**), resulting in nearly 160 quality measures. Participation in specific modules is determined by a clinic's patient population, and data collection measures are evidence-based, process-centric, and are reassessed every 6 months. The core measures include pathology report confirming malignancy, staging documented in the first month of an office visit, pain assessment and pain addressed appropriately, a documented plan for chemotherapy, consent, treatment intent, smoking status with adequate counseling for cessation, and emotional well-being of the patient. Practices with multiple locations can maintain a single or multiple accounts, with either staff or physician reporting.[3,7]

According to James Brandman, MD, MS, medical director of Northwestern Medicine Cancer Quality Practice and director of the Robert H. Lurie Clinical Cancer Center, "The Northwestern Medical Faculty Foundation (NMFF) was one of the first practices to enroll with QOPI, after it opened up for enrollment to ASCO members in 2006. Although our practice is well known for palliative care, QOPI assessment identified low pain control scores. This information was relayed back to the physicians and the necessary changes were implemented." The metrics that formulate QOPI helped design the annual quality projects of the Kellogg Cancer Center according to Thomas Hensing, MD, clinical associate professor at the Kellogg Cancer Center of NorthShore University Health System.

Figure. Measures and Modules



Source: Adapted from ASCO's QOPI program details; http://qopi.asco.org/documents/QOPI-Program-Details-Presentation-7-2013.pdf.

Data Sampling Technique

The sampling protocol is laid out to include patients most recently seen in an out-patient setting, with charts of patients with an invasive malignancy (identified <2 years earlier) who were evaluated in a recent 6-month period being included. Sample size is determined by the number of associated physicians and the number of modules selected. Registered practices are provided with updated information on data collection, both in the form of training material and webinars, as well as individual training sessions.[7] Data can be submitted through a Web-based application and reports are provided within 4 weeks that can help a practice evaluate where it stands compared to the aggregate results of QOPI to improve performance.[3] The entire process is compliant with the Health Insurance Portability and Accountability Act.

Thomas Hensing, MD

QOPI Benefits Over and Above Improved Quality of Care

In addition to improving how well a practice functions, physicians can obtain Continuing Medical Education credits for documenting the development and implementation of a performance improvement plan and maintenance of Physician Board Certification. Additionally, upon request from a participant, ASCO can verify participation or achievement of QOPI certification to health plans that participate in the program (a list of the current participating health plans can be found at http://qopi.asco.org/Health_Plan_Program.htm).[3,7] QOPI participation is a means to QOPI certification, which evolved out of the feedback received from oncologists and their staff asking to share their performance information with health plans and in marketing materials.[3]

When asked about the participation of the North Shore Cancer Center at Massachusetts General Hospital (MGH) in the program, Joel Schwartz, MD, director of oncology services at the cancer center, said in an e-mail response, "We were one of the beta test sites for QOPI, as one of the physicians actively involved in setting up QOPI, Joseph Jacobson, MD, was a member of our practice. We thought it would be a good idea to benchmark ourselves against similar institutions nationally and learn where we could do better in delivering the highest quality care to our patients….It has helped us enormously in understanding areas of practice where we can provide better care for our patients (eg, referral for fertility preservation)."

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On future plans of the cancer center with regards QOPI certification, Schwartz added, "In my new role as medical oncology network clinical director of the MGH Cancer Center, I have suggested that all hospitals joining our network apply for QOPI certification, as one of the ways to ensure a higher standard of care across the network."

QOPI Certification

The QOPI Certification Program (QCP), initiated in 2008 and promoted in 2010, served as the next step to advancing QOPI in attempts to standardize and improve patient care. QCP, which provides a 3-year certification for outpatient hematology-oncology practices, emerged following feedback provided by registered QOPI members,[3] based on the fact that a public recognition of QOPI participation, in the form of certification, would further raise the performance of the participating clinics. According to the Association of Community Cancer Centers, 80% of all adult cancer patients are treated by community oncology practitioners, and 70% of QOPI-certified practices are community-based.[8] For certification, the practice must complete a round of QOPI data abstraction, using the QOPI modules, sampling strategy, and appropriate sample size. The resulting report would determine eligibility for participation in QOPI certification. Certification is then achieved based on QOPI medical record abstraction measures selected for certification and QOPI certification site assessment.[3]

> *"The main challenge (with QOPI), and probably the most important effort, will be to find a way to track outcomes."*
>
> **—Joseph Simone, MD**
> pioneer of the QOPI initiative

QOPI certification review process includes audits prior to the certification, which confirm results, ensure program integrity, and improve learning opportunities for the program. The audit report is then shared with the practice and they may be awarded a QOPI certification-pending status for 1 year, during which period they can work on improving their shortcomings.[3,7] The certification includes 20 standards related to staff training, chemotherapy orders, patient education and consent, chemotherapy planning documentation, drug preparation, chemotherapy administration, patient monitoring and assessment.[7] The certification would prove a practice's commitment to quality to both payers and the patients.

Table. QCP Certification Site-Assessment Standards[14]

Standard	Description
1	Qualifications
2	Medical record documentation
3	Consent policy
4	Chemotherapy order standards
5	Double checking of order
6	Drug labeling
7	Intrathecal chemotherapy policy
8	Time of administration double-check
9	Extravasation
10	Emergency procedures
11	Medical record documentaiton at each site visit
12	Day-of-treatment assessment
13	Accillary services-referrals
14	Missed office visit follow-up
15	24/7 triage and toxicity communication
16	Toxicity assesment available before writing chemotherapy
17	Cumulative dosing

According to Brandman, the certification process "requires a village," and NMFF brought together the nursing group, the pharmacy group, and the physicians (represented by Brandman) to mobilize resources for the certification. A site visit by 2 oncology nurses ensued in April 2012 following application in fall 2011, and NMFF received certification in July 2012.

Joel Schwartz, MD

For Kellogg, the biggest challenge was documentation of the procedures to adhere to the QOPI metric. "Although electronic medical records were actively in use, the work-flow needed to be ironed out. We went through 2 to 3 cycles of internal auditing before certification", said Hensing. The cancer center registered for QCP in 2011 and were certified in 2012.

More than 200 practices are currently QOPI certified.[9]

QOPI and Health Plans

A number of health plans have been listed on ASCO's QOPI website as participants in the program,[10] and ASCO verifies program participation or successful completion to the listed health plan upon member participation in the QOPI Health Plan Program. However, ASCO does not share performance data with the health plans. Some of the participating health plans include Aetna, Anthem Blue Cross and Blue Shield, Health Alliance Plan, Humana, UnitedHealthCare.

Although initially frowned upon, health plans are now offering financial incentives to practices for adherence to quality improvement measures. Blue Cross Blue Shield of Michigan (BCBSM) was the one of the first health plans to provide a financial incentive to oncology practices that participate in QOPI. The Physician Group Incentive Program oncology initiative was formed in collaboration with ASCO, based on QOPI. BCBSM subsidized participation by practices, expecting that self-assessment and adherence to the QOPI measures would have a positive impact on the quality of life of patients, reduce off-label drug use, and reduce healthcare costs.[1,10] Following participation in QOPI, BCBSM established a new professional initiative, the Michigan Oncology Quality Consortium (MOQC), to improve performance, implement changes, and guide oncologists who were new to QOPI.[11]

Other health plans have now caught on with BCBSM. UnitedHealthCare took a different view with the incentives provided to doctors to improve care; by covering the entire cost of treatment upfront, rather than reimbursing later, they disengaged payment from drug selection. The pilot study, published in the journal *Health Affairs*, experimented with "bundled/episodic payment," wherein the physician-determined cost of the entire treatment period is paid to cover the standard treatment period of 6 to 12 months. With this practice, the oncologists' fee does not vary based on the drug selected for treatment, so practitioneres can choose a more cost-effective alternate. If the patient later needs treatment with a more expensive drug, the drugs are reimbursed at cost, mitigating any risk for the practice. Further, the payer has no say in drug selection,[12] thus the oncologist can determine the most cost-effective treatment option. However, considering the huge cost variations between patients, additional studies would be needed to determine the significance of this model. Other practices, including the Northwest Georgia Oncology Centers, are working with UnitedHealthcare to test the bundled payment model; CMS is also working with payers to adopt the model.[13]

NMFF has not yet contracted with insurance groups due to internal contracting procedures, but does see an advantage in doing so in the future, says Brandman. According to Hensing, the driver for certification at Kellogg was improving processes to meet the benchmark quality requirements, which is his primary interest, and he was not aware of collaborations with health plans.

Feedback Following Evaluation

Outside of QOPI, cancer clinics are working to achieve quality cancer care based on the IOM recommendations. The Florida Initiative for Quality Cancer Care (FIQCC) is one such initiative: a consortium of 11 medical oncology practices that evaluates the quality of cancer care across Florida.[14] FIQCC recently published a report following a reevaluation of 35 quality care indicators (QCIs) in medical records of colorectal cancer cases in 10 participating practices in 2009. The practices were first evaluated in 2006, and the results of the review were circulated to the relevant clinics to improve adherence. Despite an overall improvement in QCI adherence, the reassessment in 2009 observed a variability in adherence across practices in addition to lack of adherence to several indicators (accepted regimen of neoadjuvant chemotherapy, receipt of adjuvant ra-

diation treatment), pointing to a need for organized improvement efforts for those specific indicators.

ASCO, in collaboration with the Oncology Nursing Society, published a QCP report early last year evaluating the implementation of chemotherapy administration safety standards in outpatient oncology clinics.[8] By the end of November 2012, of the 206 practices that had applied for certification, 156 did get certified, 44 sites were in the process of certification and 6 had withdrawn their application. The study observed that of 111 practices that had completed an on-site review by the end of November 2012, only 2 (1.8%) sites completely met the 17 standard requirements (**Table**). Individual standard performances varied between 40.4% (qualifications, extravasation management) and 100% (toxicity assessment documentation), with a median of 75.3%.[8] QCP is definitely proving to be beneficial in terms of ensuring rigorous adherence to the established standards. The report identified that 98.2% of the practices that received on-site visits failed at some level in adhering to the 17 standards essential for certification. Certain standards seemed more challenging for the practices to meet over others, including qualification of the staff who prescribe, prepare, and administer chemotherapy, medical record documentation, meeting the requirements for the time of administration, and extravasation management (staff were aware of the procedure, but lacked documentation). Conversely, maximum adherence was observed for ancillary services such as referrals for supportive care and for documentation of toxicity assessment. Following evaluation, practices put in extra efforts to adhere to the standards and improve performance, with 1 clinic obtaining certification within 43 days from the certification-pending date (average time to certification was 4.4 months to 6.9 months over the various rounds).[8]

Simone, the pioneer of QOPI, said retrospectively in an e-mail, "Since its inception in 2003, I would say one of (QOPI's) major successes has been engaging a wide array of oncologists from across the country. I believe it was because it was built by and for them. When I had the idea, I had had many experiences of trying to get doctors to do things and the major lesson was that they must be in on the ground floor. Appealing to their better instincts—do good for patients—was an incentive, but so was curiosity to see how they performed compared to other oncologists. Doctors can be competitive in a good way, rather than just financially or by volume of work. We started small, did lengthy testing, and brought in small test groups before offering it to any ASCO member. This took several years and we managed to keep the commitment and interest of the practices engaged in building the program all that time."

In terms of where the program could lead the quality of cancer care he added, "QOPI, as it now stands, has only scratched the surface of what should be done. The main challenge, and probably the most important effort, will be to find a way to track outcomes. At the end of the day, that's all that matters to patients and that is the gold standard to test whether what we are doing is useful as well as informative."

So where does the patient stand with QOPI and QCP? For an oncology patient, quality of care is most important, but hospitals work on referrals and reputation. "Patients are usually ignorant of a practices' quality standards and certifications." said Brandman. "The influence of such accreditations on patient recruitment would be extremely difficult to measure." However, in the long run, the reputation of a practice emerges from the standard and quality of care, the ultimate goal of QOPI. **EBO**

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Drug Pipeline

Lung Cancer Treatment
(continued from cover)

if the pathway is inhibited, allow tumor cells to foil the immunotherapeutic system and grow unrecognized and without sparking a natural T-cell reaction. What makes this such a promising area is the fact that many solid tumor types express PD-L1. In fact, PD-L1 expression is often associated with a worse prognosis, because it is a sign that the patients' own immune system is likely not helping to combat tumor growth. However, recent research efforts indicate that by blocking the PD-L1 ligands, the body's T cells can be forced to recognize tumor cells, and the natural programmed cell death mechanism can then take over.[7]

Research has found that blocking the PD-1 pathway inhibits binding to both PD-L1 and PD-L2 ligands. There is potential to selectively block the PD-L1 receptor, which affects the CD80 pathway that is necessary for T-cell activation and survival.[4,7] The more specific targeting is preferable, as studies have indicated that targeting PD-L1 may lead to fewer toxicities (including pneumonitis) than targeting the overall PD-1 pathway.[7,8]

Table 1. Types of Lung Cancer

Types of Lung Cancer	% of Lung Cancer	Number of Stages
Non–Small Cell Lung Cancer • Adenocarcinoma (~50%) • Squamous Cell (epidermoid carcinoma) (~30%) • Large Cell (~10%) • Mixtures of above types	80–85%	IV Stages
Small-Cell Lung Cancer	15%	II Stages
Other	<5%	

Source: Eldridge L. Lung Cancer Types. About.com Lung Cancer September 15, 2013. http://lungcancer.about.com/od/typesoflungcancer/a/lungcancertypes.htm?p=1. Accessed January 23, 2014.

Several PD-1 and PD-L1 agents are currently being tested in clinical trials. Since several tumor types express these targets, the early investigational studies involve multiple solid tumor types. Once a drug candidate demonstrates PD-1 pathway activity, the clinical trials tend to home in on specific tumor types.

Ongoing studies should indicate whether anti-tumor activity is greatest with the PD-1 targeted agents versus those targeting PD-L1 alone.

PD-1 Targeted Agents in Development

Nivolumab. Nivolumab, a fully human IgG4-PD-1 immune checkpoint inhibitor, is currently in phase III trials. Nivolumab binds to the PD-1 receptors expressed on activated T-cells, which in turn inhibits the binding of PD-1 to both PD-L1 and PD-L2 ligands.[9]

Results of an expanded nonrandomized controlled phase I trial were pre-

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sented at the World Conference on Lung Cancer in October 2013.[10] A total of 129 patients with non-small cell lung cancer (NSCLC) who had been previously treated (74 with non-squamous cell cancer, 54 with squamous cell cancer, and 1 with unknown histology) were given an intravenous infusion of nivolumab every 2 weeks for 4 doses in an 8-week treatment cycle. Treatment with 1, 3, or 10 mg/kg was administered for a maximum of 12 cycles or until patients had a complete response (CR), unacceptable toxicity, progressive disease (PD), or withdrew consent. Patients were not tested for PD-L1-receptor expression. Twenty-two patients (17%) had either a complete response or partial response (PR), as measured by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The highest objective response rate (ORR; ORR = CR + PR) was seen with the 3 mg/kg dose across all of the NSCLC disease types. There was no differentiation with regard to response based on tumor cell type. Of the patients responding to therapy, 50% (11/22) saw improvement at 8 weeks. The median overall survival (OS) was 9.6 months across all doses and 14.9 month with the 3 mg/kg dose across tumor types. The 1-year OS rate was 42%, while the 2-year OS was 14%. Adverse events of any grade were observed in 41% (53/129) of the patients, with the most common relating to dermatologic (16%), gastrointestinal (12%), and pulmonary (7%) problems. Grade 3 or 4 adverse advents were seen in 5% (6/129) of the patients; 3 patients (2%) had pneumonitis. Pneumonitis was the cause of 2 early deaths.[10]

Phase III clinical trials are in progress for nivolumab for NSCLC (both squamous cell and non–squamous cell), melanoma, and renal cell carcinoma. The drug is being investigated as monotherapy and in combination with other drugs used to treat cancer. In 1 phase I trial, nivolumab and ipilimumab are being administered in combination for the treatment of advanced stage NSCLC. As of January 27, 2014, Bristol-Myers Squibb, the company developing the 2 molecules, did not have plans to initiate late-stage trials with this combination (nivolumab and ipilimumab) for treating NSCLC.[11]

Lambrolizumab. Mechanistically, lambrolizumab is similar to nivolumab. It differs only in that it is a humanized IgG4 rather than a fully human monoclonal antibody.[4] Phase III trials are currently in progress with this drug.

Interim data from a phase Ib expansion study were presented at the World Conference on Lung Cancer in October 2013. Patients with previously treated NSCLC were administered 10 mg/kg lambrolizumab via intravenous infusion every 3 weeks. PD-L1 expression was evaluated before the study was initiated, though it was not used to determine treatment. The ORR in the 38 patients diagnosed with squamous and non-squamous disease was 24%. Using RECIST criteria, the ORR was 21% (N = 9). Most of the responses were seen at the first planned assessment at week 9. The median duration of response had not been reached after 6 to 9 months of study. Adverse events were observed in 51% of the study participants, with the most common being fatigue, rash, and pruritis (6 patients each), with 12% experiencing diarrhea. One case of grade 3 pulmonary edema was reported; no patient died as a result of treatment.[12]

The presence of this PD-L1 expression was a statistically significant predictor of response—all confirmed responses were in patients with tumors that strongly expressed PD-L1.[12] A press release by Merck provided additional information[13]: high levels of PD-L1 expression resulted in a response rate of 57% or 67% (depending upon the assay utilized), whereas patients with zero or low levels of PD-L1 expression had a response rate of only 4% to 9%. Further studies will help fully understand the relationship between PD-L1 expression and response to therapy.

Pidilizumab. Pidilizumab is currently in a phase I trial, where it is being evaluated for multiple tumor types. This agent is different from nivolumab and lambrolizumab in that it a humanized IgG1 monoclonal antibody. An early study with this agent in patients with advanced hematologic malignancies showed no pulmonary adverse effects.[14] A small study has indicated that there may be a difference in the adverse event profile between IgG4 antibodies and IgG1 antibodies.

Other agents. Two other PD-1 agents are in phase I development: (1) AMP514/MEDI0680, a collaboration between Amplimmune and Medimmune, and (2) AMP224, a collaboration between Amplimmune and GlaxoSmithKline.[15] No early clinical trial results have been released to date.

PD-L1 Targeted Agents in Development

MPDL3280A. MPDL3280A, being developed by Genentech, is an anti-PD-L1 monoclonal antibody that enhances the anti-tumor T-cell response. In a trial of 53 patients with either squamous or non–squamous-cell NSCLC having prior therapy (surgery, radiotherapy, or systemic chemotherapy), the agent was given intravenously every 3 weeks for up to a year (median duration, 106 days).[16] Dosages administered were ≤ 1 mg, 10 mg, 15 mg, and 20 mg/kg. The ORR across dosages was 24% (9/37 patients evaluated for efficacy), and the PFS at 24 weeks was 48%. Overall, 34% of patients experienced grade 3 or 4 adverse events, including dehydration, dyspnea, and fatigue (all 4%), and pericardial effusion (6%). Severe pneumonitis or diarrhea was not reported.

The study also evaluated the correlation between PD-L1 tumor marker status and efficacy finding that those patients with a positive PD-L1 tumor status having an ORR of 100% while those with a negative PD-L1 tumor status of 15%. There was a PD rate of 0% in the PD-L1–positive tumor status group and a PD rate of 58% in the PD-L1–negative tumor status group.[16]

Smoking seemed to be a predictor of outcome: the response rate was 25% in the former or current smokers group and 14% in the group of patients who had never smoked.[17]

MPDL32801A is currently in phase II development; a trial in patients with locally advanced or metastatic NSCLC that was initiated in May 2013 has an estimated completion date of May 2015.

MEDI4736. Early clinical results for another PD-L1 monoclonal antibody were presented at the European Cancer Congress 2013 held August 31-September 2013. The preliminary results for the phase I trial of MEDI4736 showed that 8 patients receiving a median of 6 doses indicated tumor shrinkage as early as 7 weeks. No adverse events grade 3 or above were reported and there were no reports of pneumonitis or colitis of any grade.[18]

Table 2: The PD-1 Drug Pipeline

Drug	Drug#	Company	Phase	Study Information
PD-1 Inhibitors				
Nivolumab	BMS-936558/ONO-4538/ CA209-003 /MDX1106	BMS/Medarex/ Ono Pharma	III	• NCT01673867-non-squamous cell • NCT01642004-squamous cell
Lambrolizumab (new name is under review)	MK-3475	Merck	III	• NCT01905657 for NSCLC that is PD-L1 positive
Pidilizumab	CT-011	CureTech	II	• Not specific for lung cancer
	AMP514/ MEDI0680	Amplimmune/ Medimmune	I	• NCT02013804 (not specific for NSCLC)
	AMP224	Amplimmune/ GSK	I	• NCT01352884 (not specific for NSCLC)
PD-L1 Inhibitors				
	MPDL3280A/RG7446	Genentech/Roche	II	• NCT01846416-locally advanced or metastatic NSCLC (started May 2013; Estimated Completion May 2015) • Combination studies with bevacizumab & chemotherapy
	MEDI4736	Medimmune/ AstraZeneca	I	• NCT01693562 • NCT02000947 in combo with tremelimumab (CTLA-4 antibody) • NCT01975831 in combo with tremelimumab (CTLA-4 antibody)
	BMS936559/ MDX1105	BMS/Medarex	I	• NCT00729664 (not specific for NSCLC)

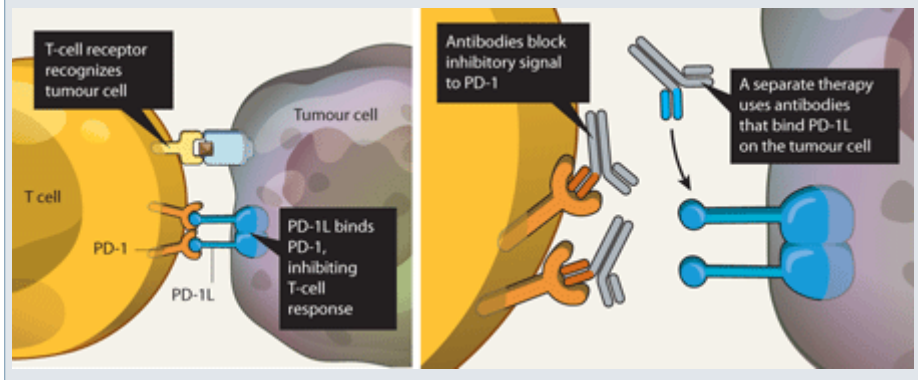
The drug is currently in phase I clinical development for patients with advanced solid tumors as well as for NSCLC. One study is evaluating the combination of MEDI4736 with tremelimumab, a CTLA-4 antibody for patients with NSCLC. These phase I clinical trials are not anticipated to be completed until November 2015 and October 2017, respectively.

BMS-936559/MDX1104. Bristol-Myers Squibb's agent is a high-affinity, fully human PD-L1 monoclonal antibody that inhibits the PD-L1 pathway. The drug was given to 207 patients with various cancer types in a phase 1 trial.[9] The efficacy population included 160 patients, with a subset of 49 patients with NSCLC. Three doses (1, 3, and 10 mg/kg) were given every 14 days in 6-week cycles for up to 16 cycles. Therapy was discontinued if the patient had a CR or if there was confirmed disease progression.

Five patients had an objective response at 24 weeks, and 6 patients had a PFS rate of 31% at 24 weeks. The response rate was 8% and 16%, respectively, in the patients receiving 3 and 10 mg/kg of drug. Across all tumor types, 91% of the patients were observed to have adverse events, with 9% experiencing a grade 3 or 4 adverse event. Twelve patients discontinued treatment owing to adverse drug events.[9] Although an apparently low level of response, this is of interest because no response was expected by the investigators—until then, NSCLC had been considered to be nonimmunogenic and therefore poorly responsive to immune-based treatments.

This agent is currently in phase I studies for multiple tumor types as well as in patients with HIV who have viral load levels below the limit of detection.

Figure 1. Schematic of T-cell PD-1 and tumor cell PD-L1 interaction. Therapeutic antibodies block the inhibitory signal to PD-1 receptors, allowing T cells to attach to the tumor cell's PD-L1 sites.



Source: Sheridan C. Cautious optimism surrounds early clinical data for PD-1 blocker. *Nat Biotechnol.* 2012;30:729-730.

Conclusion

The PD-1 inhibitors and PD-L1–targeted agents are in various stages of development, but application to the US Food and Drug Administration is not expected for any of these products until at least 2015. Very early results demonstrate some specific response when this pathway is blocked, and more data (both initial and supportive) are needed to quantify their expected efficacy in patients who express PD-L1 receptors.

One might expect PD-L1 overexpression to be a reliable biomarker for patients who would benefit from such targeted treatment. However, PD-L1 has not been conclusively found to predict response, and investigators studying Merck's lambrolizumab[12] indicated that further study is needed to better understand the role of PD-L1 as a biomarker.

Additional studies will continue to evaluate the efficacy and safety of these drugs as well as the potential to find a highly predictive biomarker that will accurately identify patients in whom the agents will be most efficacious. **EBO**

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50th Anniversary Report
(continued from cover)

Consequences of Smoking: 50 Years of Progress, is aimed at oncologists and payers, rather than smokers: According to Timothy McAfee, MD, director of the Office of Smoking and Health, the amazing advances in cancer therapy, which have created drugs with $100,000 pricetags, are not as important to survival as getting a smoker with cancer to quit.

"Does it make sense to spend this kind of money, $100,000 for a drug to add a few months to someone's life, and ignore somebody's tobacco status during treatment?" McAfee asked in an interview with *Evidence-Based Oncology*. All the evidence, he said, indicates that quitting smoking will do as much good for the cancer patient as "the best available chemotherapy," and yet there are cases where a cancer patient undergoes the rigors of treatment while his or her smoking goes unaddressed.

"In 2014, after this report, it isn't fair to individuals for smoking status to be ignored," McAfee said. "There are historical and cultural reasons why that was the case. But that doesn't make sense anymore."

McAfee's call to arms has implications not only for healthcare providers, but also for the US taxpayer. Demographic data contained in the report[3] and available from the Centers for Disease Control and Prevention (CDC)[2,7] show that while smoking has declined significant-

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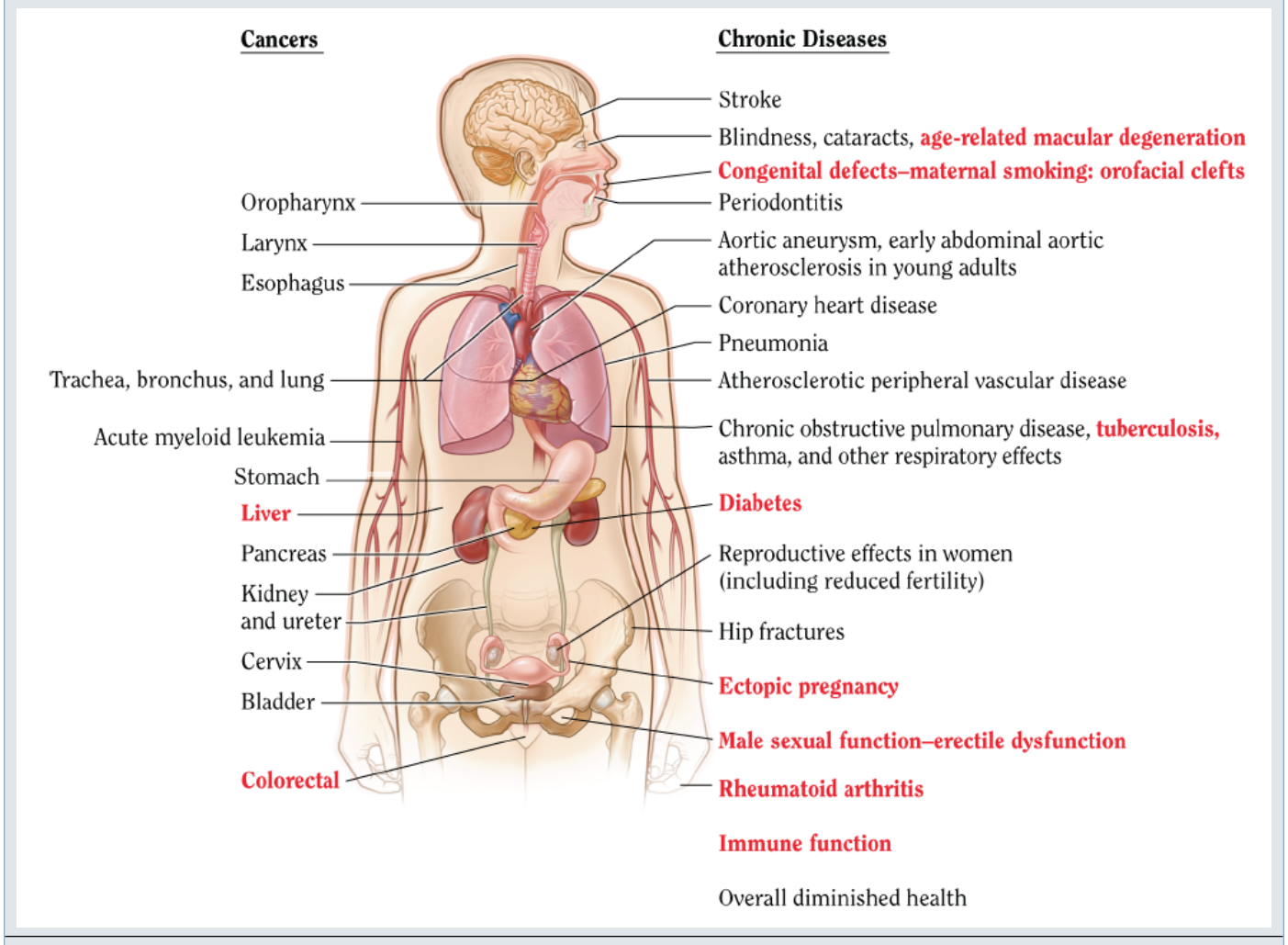
Figure 1. The Health Consequences Causally Linked to Smoking



Source: US Dept of Heath and Human Services 2004, 2006, 2010.
Note: The confition in red is a new disease that has been causally linked to smoking in *The Health Consequences of Smoking: 50 Years of Progress*.

ly since 1964, progress against tobacco is leveling off. Those who still smoke or who start smoking are more likely to be poor and have limited education[2,7]; this means without a renewed commitment to end smoking, the expanding ranks of Medicaid clients under the Affordable Care Act (ACA) will include a larger share of smokers than the population as a whole.

The Rise of Adenocarcinoma of the Lung

When Terry unveiled the first Surgeon General's Report in 1964, "lung cancer in men" typically meant squamous cell carcinoma of the lung. Men smoked more than women, and thus, accounted for more cases of lung cancer.[3] In the wake of the 1964 announcement, the tobacco industry's attempts to create "safer" cigarettes, coupled with efforts to market directly to women in an era of change, led to shifts in both the type of lung cancer diagnosed and in the makeup of who suffered, changes that are only now fully understood.[4]

A study of smokers by the American Cancer Society (ACS) from 1959-1965 had been an important source for the advisory panel that created the 1964 report.[3] Behaviors exhibited by those smokers informed scientists who created models to predict the number of future lung cancer deaths. They also informed tobacco company researchers, who created machines to measure supposedly lower levels of "tar" and "nicotine" on filtered and ventilated cigarettes that were put on the market in the decade after 1964.

This new Surgeon General's report chronicles how scientists missed the mark for years in predicting lung cancer deaths, until they began to account for the changes in smoking behavior that were a direct result of modifications to cigarettes, supposedly to make them "safer." Re-engineered cigarettes did not provide the same "hit" of nicotine, so smokers responded by puffing longer or holding smoke in their mouths, actions that fundamentally altered the nature of the way their bodies reacted to the 69 different carcinogens identified in cigarette smoke.[3-5]

Over time, health consequences of a different cigarette became clear. The United States and other countries saw falling rates of squamous cell cancer of the lung, which may first affect the bronchial areas and cause a patient to cough up blood. Among smokers, the United States in particular saw rising rates of adenocarcinoma of the lung, which develops in the far reaches of the lung tissue and may not cause symptoms beyond a cough until the cancer is in later stages. While overall death rates for men from lung cancer peaked in 1990 and for women in 2003, likely due to reduced prevalence of smoking, the climb of adenocarcinoma of the lung continues among those who do smoke, and rising incidence has been steeper for women[3,8] (see **Figure 2**). Differences in the composition and manufacturing practices of US cigarettes, compared with those in Canada and Australia, are believed to account for larger increases in adenocarcinoma incidence here than in those nations.[3,6]

> *Does it make sense to spend this kind of money, $100,000, for a drug to add a few months to someone's life, and ignore somebody's tobacco status during treatment?*
>
> **—Timothy McAffee, MD**
> Director, OSH

Key work in this area includes a 2011 study led by David M. Burns, MD,[5] which first factored the change in cigarette design in modeling to account for changing rates of adenocarcinoma; and the 2013 study in the *New England Journal of Medicine* led by Michael J. Thun, MD,[4] which tracked smoking-related mortality over a 50-year period. Thun and his coauthors concluded that the relative risk (RR) of lung cancer for women smokers, compared to women who have never smoked, are higher than ever: RR was 2.73 in the original ACS study, 12.65 in a follow-up study begun in 1982, and was 25.66 in a cohort ending in 2010. Women smokers today face higher lung cancer risks than men relative to their non-smoking counterparts; for men, RR of lung cancer in the 2010 cohort was 24.97.[4]

A panel of experts convened recently by *The American Journal of Managed Care* to discuss non-small cell lung cancer said the increased understanding about adenocarcinoma of the lung has changed treatment over the past decade, putting more onus on the pathologist to properly evaluate tumor types.[10] It has also caused the US Preventive Service Task Force to recommend lung cancer screening among smokers and former smokers who meet certain criteria (**see related story, page SP160**).

McAfee said that while lung cancer screening is important and will save lives, the CDC is working hard to craft an education message that does not lead smokers to believe that screening is a substitute for quitting; in fact, the CDC hopes that being screened will provide an opening for a conversation with a smoker about how to stop. "We are working very closely with our cancer prevention control office on this specific issue," McAfee said. "How do we turn this into a positive, educational opportunity?"

Smoking's Links to Other Cancers

While smoking is most associated with lung cancer, successive Surgeon General's Reports (SGRs) have assembled evidence of its ties to other cancers. Reports are careful to never overstep what is known at the time; thus, when any

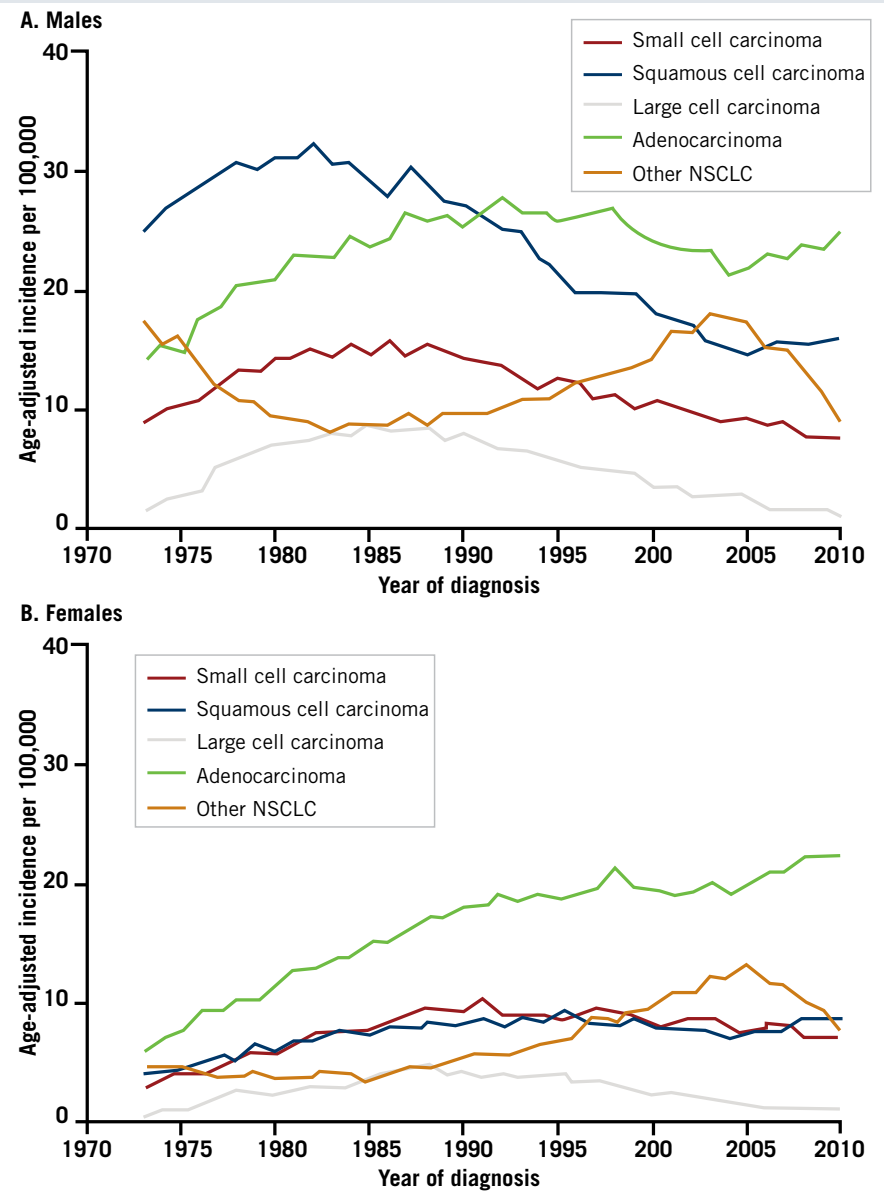
report says for the first time there is a "causal relationship," it is an important step, as no SGR has ever had to reverse a previous finding, according to Terry F. Pechacek, PhD, associate director for science at the Office of Safety and Health (OSH), and a veteran of crafting multiple reports.

So, the finding for the first time that "the evidence is sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer,"[3] is a critical statement, especially since colorectal cancer is now the second-leading cause of cancer deaths in the United States, according to CDC statistics.[9]

The report also examined possible connections to liver, prostate, and breast cancers and found:

- The evidence is sufficient to infer a causal relationship between smoking and hepatocellular carcinoma.
- The evidence is suggestive of no causal relationship between smoking and the risk of incident prostate cancer; however, there is evidence suggestive of a higher risk of death from prostate cancer among smokers than nonsmokers.
- In men who have prostate cancer, the evidence suggests a higher risk of advanced-stage disease and less well-differentiated cancer in smokers than nonsmokers.
- Besides the evidence of mechanism by which smoking may cause breast cancer, the report says there is "suggestive but not sufficient" evidence to infer a causal relationship between smoking and breast cancer. The same characterization was made of evidence linking secondhand tobacco smoke and breast cancer.

Figure 2. Standardized Incidence of Lung Cancer, by Gender and Histology (age-adjusted to 2000 US population), 1973–2010



Source: Surveillance, Epidemiology, and End Results (SEER) Program, public use data.
Note: Other non-small-cell lung carcinoma (NSCLC) includes code 8046 from the SEER Registry, as well as others. In the most recent years (2001–2010), most of the "Other NSCLC" were 8046. Before 2001, most "Other NSCLC" were coded as 8010 "Carcinoma, NOS." Around 2004 there were changes in how lung cancers were coded in the SEER Registry data (Travis et al. 2004, 2011; Johnson et al. 2007). There were also advances in diagnosis and treatment around 2004 (erlotinib or gefitinib for patients with EGFR mutations, bevacizumab for patients with non-squamous NSCLC) that make accurate histologic classification important (Langer et al 2010; Kulesza et al 2011; Conde et al 2013).

Smoking Hinders Cancer Care, Survivorship

The anniversary report bolsters the message long-term smokers most need to hear: Quitting improves health at any age, no matter how long a person has smoked, except perhaps in very final stages of cancer.

But for the smoker who has received a cancer diagnosis, the need to quit immediately comes through as never before. Not only is there clear evidence that smoking harms a cancer patient's overall health and chances of survival, but evidence is accumulating that smoking interferes directly with cancer treatment, making it less effective and rougher on the patient.[3]

For the first time, the Surgeon General's Report features a section on what happens when cancer patients continue to smoke, and the simple answer is: It certainly doesn't help, and it probably causes greater harm.

Evidence is "suggestive but not sufficient" of a causal relationship between smoking and poor responses to cancer treatment, increased toxicity, and cancer recurrence, adding weight to McAfee's call to put the highest priority on getting smokers to quit if they are about to undergo cancer treatment.

The report evaluated 16 studies that examined whether cigarette smoking affects patients' response to cancer therapy, and found that in 72% of the studies, smoking had a statistically significant association with a worse response. Of 82 studies examining the relationship between smoking and increased toxicity, 80% found that smoking made treatment more toxic. In 49 studies that included a category of "current smoking," the association with increased toxicity was even higher, at 88%.[3]

While major groups, including the American Society for Clinical Oncology (ASCO), have called for increased efforts to help cancer patients quit smoking, the SGR raises the bar with provocative questions: do the optimal approaches to treat cancer differ in patients who are current smokers compared with nonsmokers? And, is it better to make smoking cessation an initial priority before implementing the patient's cancer treatment regimen?[3]

"This needs to be a serious discussion," McAfee said. The nation still loses more than 400,000 lives each year due to smoking, a statistic he said, "would not be tolerated" if the offending substance was something other than cigarettes. Americans moved quickly to remove threats like asbestos and lead paint, yet tobacco remains part of the landscape.

"It didn't take 50 years to remove lead paint," he said. "This shouldn't take another 50 years." **EBO**

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Compared with Mammograms, Experts See Lack of Awareness to Screen for Lung Cancer

AJMC Panel Discusses Current Treatment of Non-Small Cell Lung Cancer

A screening recommended in the summer of 2013 to detect early stage lung cancers in chronic smokers has not gained the awareness level it merits, given that lung cancer causes the most deaths in the United States among both men and women. That was the assessment from Corey J. Langer, MD, professor of medicine, Abramson Cancer Center, University of Pennsylvania, who took part in a panel discussion on non-small cell lung cancer (NSCLC) convened by *The American Journal of Managed Care*.

Corey J. Langer, MD

Breast cancer has the pink ribbon and a monthlong campaign every October to get women screened. Colonoscopies experienced the "Katie Couric effect," an upsurge attributed to the popular former host of the Today Show, who had an onscreen exam after losing her husband, 42-year-old lawyer Jay Monahan, to colon cancer in 1998.[1f]

> *"The issue of imaging and early detection certainly resonates with payers...not only for economic but also ethical considerations."*
>
> **—Steven Peskin, MD**
> Senior Medical Director
> Horizon Healthcare Innovations

But according to Langer, screenings for lung cancer, which each year kills more Americans than colon, breast, and prostate cancer combined,[2] did not see a similar surge last summer when it was recommended for the roster of tests for which insurance must pay under the Affordable Care Act. On December 31, 2013, the US Preventive Services Task Force (USPSTF) finalized its recommendation for annual lung cancer screenings with low-dose computed tomography in adults ages 55 to 80 years who have smoked 30 "pack-years."[3] A pack-year means the person has smoked at least a pack a day for a year; a person who smoked 2 packs a day for 15 years would have 30 pack-years.

The draft recommendation, based on results from the National Lung Screening Trial,[4] received plenty of press attention when it came out July 29, 2013. Yet, "It's amazing how few patients or family members are aware of this," Langer said. "The impact and the general notice of the NLST has not penetrated."

Langer's comments were part of a wide-ranging discussion on treatment strategies for NSCLC, including new and emerging agents, the need for precision in pathology to identify the characteristics and stage of the disease, and the use of molecular-level tests and agents.

David J. Sugarbaker, MD

Michael Chernew, PhD, a health economist at Harvard University and co-editor-in-chief of *The American Journal of Managed Care,* led the discussion that also included David J. Sugarbaker, MD, chief of thoracic surgery at Brigham and Women's Hospital in Boston, and Steven Peskin, MD, senior medical director, Horizon Healthcare Innovations, Horizon Blue Cross Blue Shield New Jersey.

Langer did not offer a reason for the lack of awareness. On its website, the American Lung Association said the stigma associated with cigarette smoking has clouded efforts to promote lung cancer screening.[5] That's quite a shift from the state of affairs in 1964, when the US Surgeon General unveiled its landmark report that showed cigarettes cause lung cancer in men and "probably" in women. At that time, 43% of Americans smoked; today fewer than half that share do. According to the Lung Association, 160,340 people in the United States were expected to die from lung cancer in 2012.[5]

Steven Peskin, MD

Some questions about who should be screened and how often come down cost-effectiveness. Overuse of scans generally has been a hot topic in cancer care, with the American Society of Clinical Oncology recommending against some scans in its Choose Wisely initiative.[6]

Sugarbaker noted that the costs of screening for lung cancer had to be weighed against the expense of end-of-life care for a patient with stage IV lung cancer, which Chernew said can easily exceed $100,000 a year. Too often, he said, lung cancer is diagnosed after surgery is no longer possible, and a patient's only options are expensive chemotherapy or targeted therapy treatments. "Early detection and early resection... saves a lot of money," Sugarbaker said.

But when the evidence clearly supports screening, it makes sense for everyone, said Peskin. "The issue of imaging and early detection certainly resonates with payers, including myself, and not only for economic but also ethical considerations."

Both Langer and Sugarbaker said screening and payment protocols are still evolving at major academic centers, with some centers offering the baseline screening for free for chronic, long-term smokers. Some patients don't quite fit the 30 pack-year criteria, or may not be old enough, but does waiting make sense? Langer, who said he had doubts about the NLST when it began, noted that one-fourth of the high-risk population it targeted "had some abnormalities on their scan."

The USPSTF recommendations call for ending annual scans once the patient has quit for more than 15 years, or if the patient develops some other medical condition that would make him or her unable or unwilling to be treated for lung cancer. Unlike the initial trial, scanning goes on to age 80 years.[3] **EBO**

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GRANIX™ (TBO-FILGRASTIM) Injection

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

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

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

5.2 Acute Respiratory Distress Syndrome (ARDS)

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

5.3 Allergic Reactions

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

5.4 Use in Patients with Sickle Cell Disease

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

5.5 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

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

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience

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

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

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

Leukocytosis

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

6.2 Immunogenicity

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

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

No case of overdose has been reported.

TEVA Oncology

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GRX-40188 January 2014

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

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Injection

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.

TEVA Oncology