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Evidence-Based Oncology

Quality Care

Accountable Care Organizations: How to Define Quality?

Cyril Tuohy

These days, talk about "quality" factors into every discussion of healthcare. So how do the nation's 449 accountable care organizations (ACOs) and ACO-like entities sponsored by hospital systems, physicians groups, insurers, and community organizations[1] around the country define quality?

Kelly Kelleher, MD

There's no shortage of data and metrics surrounding how effectively hospitals and doctors' groups claim to be delivering care, yet pinning down what it means to deliver quality care is difficult.

Trying to define quality may well prove elusive, as ACOs are less rooted in amending the patient experience than they are in turning industry work flows and hierarchies upside down.

"ACOs are not an attempt to change the patients, but an attempt to change the (healthcare) delivery system," said Jeffrey Brenner, MD, founder and executive director of the Camden Coalition of Healthcare Providers.

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Breast Cancer

Yale's Matloff Reports Shift in Views on Genetic Testing, Prophylactic Surgery

Sees Drop in Costs After Supreme Court Ruling

Lauren M. Green

The decision about whether to get tested for a genetic mutation that may predispose a person to certain cancers is a difficult one for many patients to make. Even more difficult for mutation carriers is deciding whether to undergo a prophylactic surgical procedure.

How would cancer genetics specialists themselves make these tough choices? Have their perspectives changed over the years, with increased knowledge about genetic testing, surveillance, and treatment?

Ellen T. Matloff, MS, CGC

Ellen T. Matloff, MS, CGC, director of the Yale Cancer Genetic Counseling Program at the Yale School of Medicine/ Yale Cancer Center, in New Haven, Connecticut, is getting more interest than ever in these questions in light of the June 13, 2013, US Supreme Court decision involving Myriad Genetics, in which she was a plaintiff. Myriad had vigorously enforced patents to control a monopoly in genetic testing for mutations

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Status in the States

Leveraging Health Reform to Combat a History of Cancer

Kentucky to Expand Medicaid, Increase Clinical Trials as U of K Markey Center Gains NCI Status

Mary K. Caffrey

Governor Steve Beshear did not sugarcoat the data May 9, 2013, when he said Kentucky would take an offer it couldn't refuse.

With his state ranked worst in the nation in smoking and cancer deaths, and not far behind in heart disease, Beshear was "tired of being at the bottom."[1] It was time for strong medicine–in the form of $608 million in new healthcare spending, which will come January 1, 2014, when Beshear accepts federal help to put 308,000 new people on Medicaid.[1] Another 800,000 Kentucky residents are already in the program.[2]

Regan Hunt, Kentucky Voices for Health, and Governor Steve Beshear on May 9, 2013.

The decision followed Beshear's 2012 call for Kentucky to create its own ex-

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From the Publisher

As we approach October 1, 2013, when open enrollment will start under the Affordable Care Act, there is a sense that each of us will experience healthcare reform differently, depending on where we live or work. From the decision to create an exchange to sell coverage, to the choice whether to expand Medicaid, each state possesses the power to shape reform within its borders. To reflect this, *Evidence-Based Oncology* will examine how cancer care may be affected by health reforms in individual states. Our August issue looks at Kentucky, whose governor expanded Medicaid expressly to combat the highest cancer mortality rates in the country. Despite its complex history as a tobacco producer, with high numbers of smokers, Kentucky is home to a vibrant community of advocates trying to curb smoking in the next generation. In July, the University of Kentucky raised the bar when its Markey Cancer Center received NCI designation. Kentucky's embrace of managed care for its Medicaid recipients has been challenging, with providers complaining that a too-rapid transition left much to be desired. Hope remains, however, that the accountability of managed care will encourage those unaccustomed to routine care to engage the system before they are gravely ill.

Kentucky's march to managed care was driven by a need to control costs: Too much was being spent on a population too ill to achieve good outcomes. That phenomenon drives much of the healthcare spending in the United States, and it's one of the things reform aims to fix.

Kentucky's march to managed care was driven by a need to control costs: Too much was being spent on a population too ill to achieve good outcomes. That phenomenon drives much of the healthcare spending in the United States, and it's one of the things reform aims to fix. Reimagined delivery systems, new entities like Patient-Centered Medical Homes (PCMHs) and Accountable Care Organizations (ACOs) will change the landscape for oncology and beyond. The miracle of targeted agents that can stop cancer in its tracks must be balanced against the enormous cost to the employer, the patient, the taxpayers, and society as a whole.

How oncology saves lives in the new world of ACOs will be part of the discussion on November 14-15, when *The American Journal of Managed Care* hosts Patient-Centered Oncology Care: Real World Perspectives at the Royal Sonesta Court in Baltimore, Maryland. Topics include the role of companion diagnostics in targeted treatments, and collaborations between payers and the pharmaceutical community. For information and registration, see http://www.ajmc.com/meetings/oncologycare13.

We hope you can join us. Until then, visit www.ajmc.com for updates, and thank you for reading.

Brian Haug
Publisher

EDITORIAL MISSION

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

In This Issue...

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Current Issues in Breast Cancer Treatment

Chernew Leads Discussion with Swain, Newcomer on New Agents, Cost of Care

Produced by Nicole Beagin

Last month, *The American Journal of Managed Care (AJMC)* hosted a panel discussion on current issues in breast cancer treatment. Participants were the moderator, Michael E. Chernew, PhD, co-editor-in-chief of *AJMC*, Professor of Health Care Policy, Harvard Medical School; and panelists, Sandra M. Swain, MD, immediate past president of the American Society of Clinical Oncology (ASCO) and medical director of the Washington Cancer Institute, MedStar Washington Hospital Center, and Lee N. Newcomer, MD, MHA, senior vice president for Oncology, Genetics and Women's Health at UnitedHealthcare.

The panel continued a 2012 *AJMC* discussion regarding pertuzumab (Perjeta) which had been just received approval by the US Food and Drug Administration as a first-line treatment for HER-2 positive metastatic breast cancer in combination with trastuzumab (Herceptin). Concerns have arisen about market access, as the cost of this combination therapy is more than $180,000 for an 18-month course. The July panel opened with an overview of a new combination therapy. This article presents highlights from the panel's recent discussion of the cost of new treatment therapies in breast cancer.

Chernew: Today, we would like to examine the use of another combination therapy, trastuzumab and [panzene] which is [Typhila] and pertuzumab, which is Perjeta. So, as we talk through this issue, concerns about which patients get these different therapies, their relative cost, and implications for outcomes will become important. I will start with Dr Swain…to understand the current treatment landscape and overview. Who are the patients eligible for these different types of therapies, and how big is the patient population?

Swain: As far as the use of pertuzumab, the current indication is for the patient to either present with metastatic HER-2 positive breast cancer, or for the patient who has had adjuvant treatment and then a recurrence, so it is first-line treatment for HER-2 positive breast cancer. The indication is for the use with trastuzumab and a taxane. For TDM-1, the indication is in patients who have had previous treatment already with HER-2 targeted therapy and usually chemotherapy, and so it is not the first-line treatment; it is either second- or third-line or later-line treatment. We probably have about 8000-9000 patients that either have recurrent disease in the first-line setting or present with stage IV disease. Of those 8000 or 9000 patients, approximately 4000-5000 would actually be eligible to get pertuzumab with trastuzumab in the first-line setting. Many of those patients will have ER-positive disease also, and the physician may not want to start with chemotherapy. Not all would get chemotherapy in the first-line setting, but it could be higher.

Chernew: And that number of patients is basically over the course of a year nationwide?

Swain: Yes. For TDM-1, I don't know the exact numbers; Dr Newcomer, if you know those numbers, it may be somewhat higher.

Newcomer: I couldn't give you an exact number either, but I sure agree with your estimate of 8000-9000 as a nation.

Chernew: And so, either of you, Dr Newcomer if you want to start or Dr Swain, can you provide a brief overview of the EMILIA trial?

Swain: Sure, I would be happy to do that. This trial, EMILIA, involved almost 1000 patients who were randomized to either get lapatinib and capecitabine or to get TDM-1; this was after they had previous treatment with HER-2 targeted therapy. This trial had incredible results. The TDM-1 group had a statistically significant improvement and progression-free survival of about 3 months. The difference was 6.4 months with the lapatinib/capecitabine compared with 9.6 months with TDM-1. And, not only did the trial show these results, but there was a survival benefit, and the survival for the TDM-1 was almost 31 months versus 25 months. That's a really significant increase of survival of 5 months with the use of TDM-1.

Newcomer: That's probably one of the best responses we have seen in breast cancer in almost a decade; that would that be a fair statement.

Swain: I think also with the CLEOPATRA data, which was the first-line study with pertuzumab, trastuzumab and docetaxel versus the combination with the placebo without the pertuzumab, also showed a very significant progression-free survival of 6 months and a survival benefit, too. So, I think both of them are pretty spectacular results.

"What I hear from this discussion is…the pace of innovation is quite rapid, but…the fiscal consequences can be substantial."

—Michael E. Chernew, PhD

Chernew: How are physicians, particularly oncologists, using these agents in practice? Is the information of the trial filtered through the practice?

Swain: I would have Dr Newcomer answer this, but I think what I see is that the doctors are not necessarily using the docetaxel with pertuzumab first line but they are also using paclitaxel, and interestingly, most recently at the ASCO meeting (May 31-June 4 in Chicago) there was a study from Memorial Sloan-Kettering using weekly paclitaxel with pertuzumab and trastuzumab showing a very high response rate. I think it was about 50%, so it was a very high response rate. So, I think the taxane really doesn't matter there. The issue is it is very effective dual-targeted therapy with trastuzumab and pertuzumab.

Newcomer: And we did see an immediate request for those drugs as soon as they became available on the market. We are limiting the use to the actual trial from the label, so the paclitaxel would not be authorized by us, but certainly the docetaxel is and usage was immediate. I think people are very aware of these studies, because it is such a significant drug and the breast cancer patients were following this news just as closely as the physician.

Chernew: That's wonderful. Maybe one of you can provide an overview of the MARIANNE trial.

Swain: This was a trial that was also on HER-2 positive breast cancer, the same as the other ones that we have already discussed, and it was over 1000 patients who had been randomized. The study actually closed, I think, last year, so it hasn't been reported yet; it is predicted to be reported in 2014. This was a 3-arm study and the patients were randomized to get trastuzumab with either docetaxel or paclitaxel; the paclitaxel was weekly and the docetaxel every 3 weeks. Arm B was the TDM-1 plus pertuzumab. And arm C was the TDM-1 plus a placebo for pertuzumab. So I think this is a really important study, too, to see if the TDM-1 can be moved to first line.

Chernew: Genentech has applied for approval for the use of pertuzumab regimen before surgery…So I gather there are 2 other trials that's based on, the NEOSPHERE study and the TRYPHAENA study.

Swain: Right, and we have seen in several of the neoadjuvant trials, which

are fairly small trials, you know, several hundred patients, that dual-targeted therapy really does give a much higher pathologic CR, and pathologic CR means that there is no tumor in the breast and sometimes no tumor in the nodes depending on how you define it. But, for example, in the NEOSPHERE study, when they used the pertuzumab, trastuzumab, and docetaxel, the pathologic CR rate was 46%. When you only used trastuzumab and docetaxel, it was 30%. So it is much higher with the dual-targeted therapy. I was a co-chair of an FDA workshop in March addressing this question of whether pathologic CR could be used as a surrogate for approval, so (Genentech) is the first one going in to try to see if they can get approval for the pertuzumab in the neoadjuvant setting.

Newcomer: Just to make sure, because I am not sure everyone understands this, pathologic CR is associated with much better survival rates in other studies, correct?

Swain: Well, it is associated with survival rates and that was a big discussion that we had, and it is really not absolutely proven that survival will be better, because the neoadjuvant trials that have been done haven't really [proven this] except for 1 trial. The NOAH trial did show a better outcome for those patients who had the highest path CR, but the other ones really don't have that outcome data. So that was a big discussion and I am sure with this, if (Genentech) gets approval, it will be an accelerated approval, meaning that this is a surrogate endpoint and that they need to have a follow-up study that relates to the outcome data, as you mentioned, like survival or disease-free survival benefit.

Chernew: So as a non-physician, what I hear from this discussion is it's an extremely exciting time in this particular clinical area and I was wondering, first, do you agree? It seems like the pace of innovation is quite rapid, but…the fiscal consequences can be substantial. Second, I was wondering what your broad thoughts are; specifically, for Dr Newcomer, how are payers assessing the value of these agents, and how are they addressing when there are other options that are available for lower cost?

Newcomer: I think we should begin with the fact that these drugs are having a very significant clinical effect. These are not drugs that help just a tiny bit, but they are making a substantial impact on both survival and how long the tumor stays away. So that has very real value. The question is, how much we can afford to pay for those kinds of responses? There are 2 things, though, that help make this more plausible for both UnitedHealthcare and for society in general. This is not a large number of patients, as Dr Swain said, 8000-9000 a year, and not all of those are eligible for therapy. So, as you spread that cost over a large population of insured patients, it isn't very big. So, I think it will cost more money, there is no question about that, these are extremely expensive medications when they are successful and we are going to have to pass that cost on to others, but again because of the very real and significant response rate, there is value there.

Chernew: So, does that imply that both the small population and the value of the treatment are encouraging plans in some ways to promote access to these medications because of the health benefit, as opposed to discouraging access because of the cost?

Newcomer: Well, I don't know that any health plan that I am aware of is discouraging access to these drugs. If a patient is seeing a medical oncologist with HER-2 overexpressed disease, they are going to hear about these options. I believe, and I will ask if Dr Swain agrees, but I can't imagine oncologists not talking about this to their patients, and I can't imagine a health plan telling an oncologist not to talk about it. The key question is just how we budget so that we have enough money to pay for these therapies.

Swain: I think it is not only that the insurance plans pay for it, but with the huge high drug cost, the copays are really high for these patients. So, a lot of them can't afford that. So I think we really do need to look at this and address the exorbitant cost of these drugs.

Chernew: So are they being placed on a specialty tier?

Newcomer: They aren't at UnitedHealthcare, and I would point out at least in our plans that the maximum out-of-pocket expense is met by every one of these patients. So plans typically have an amount of money where once you have paid that amount, everything else is covered 100%. That amount will be set by the employer; it can vary from as little as $1000 to as high as $10,000, but there is a limit. And at that point, the patient doesn't have to pay any more. So $10,000 out of pocket may seem like a lot of money, but when you are considering the fact that this is a life-prolonging therapy, it should be worth that both to the patient and to their family.

Chernew: And that out-of-pocket limit for a breast cancer patient, it is just what they are paying for drugs, or their overall treatment? It might be that the added cost of these medications for the patient is relatively small, because they would come close to hitting their maximum out-of-pocket anyway. Or am I wrong about how I have done that math?

> *"These are not drugs that help a tiny bit…The question is, how can we afford to pay for those kinds of responses?"*
>
> —Lee N. Newcomer, MD, MHA

Newcomer: The maximum out-of-pocket applies to all of their healthcare for all of their family. So once their family has paid that amount of money, they no longer have any more coinsurance or any other expenses. And you can't have breast cancer in today's modern age without hitting that maximum out-of-pocket.

Chernew: Even if you don't get these drugs?

Newcomer: Yes. Because by the time you finish your surgery, radiation, other medications, it doesn't take very long to hit $10,000.

Chernew: So, in fact, although the person with an out-of-pocket max is paying $10,000, they are going to be paying $10,000 whether or not they have access to these particular new medications; so if I understand correctly, what the specialty tiers do or some of the other cost-share requirements, is they push you up for someone who happens to get breast cancer, they push you up for that out-of-pocket max, but they wouldn't really influence your treatment decisions because pretty much any treatment decision you make is going to take you to that out-of-pocket max in most cases.

Newcomer: So there are 2 things we should add to that. First, these drugs are given in physicians' offices as infusions, and specialty tiers, rarely if ever apply to those. Second, I have been talking about UnitedHealthcare plans and there may be other plans out there that put more of a burden on the patient, but the reason those plans are structured that way is to get the cost of the insurance down. So the less you cover, the cheaper the insurance, and that's a decision in a triad that the people make when they buy their insurance or their employer does. So, we would encourage good insurance plans but they are expensive, there is no question about that today in the Unites States.

Swain: And what about with Medicare, do they still have that $10,000 out-of-pocket limit?

Newcomer: They don't. Medicare patients are clearly disadvantaged there, and they are paying coinsurance or copayments forever.

Chernew: Depending on their Part D plan or their MAPD plan, if they are in United Medicare Advantage Plan, then there would be some differences?

Newcomer: Medicare Advantage Plan looks a lot more like a traditional, commercial insurance plan, in that there would be maximum out of pocket so there would be better benefits than standard Medicare. Standard fee-for-service, Medicare, that Dr Swain was talking about, their coinsurances go on indefinitely.

Swain: And those are the patients who really will be hurt by the high prices because we know about two-thirds of patients with cancer actually are in the Medicare range. So a lot of these patients that we are talking about would be getting Medicare.

Chernew: So those people of course would have (insurance)…90% of them are on some sort of Part D or other supplemental plan, but it raises a question about another population—the Medicaid population. What are states doing, if anything, related to access to these medications?

Swain: I can just talk for DC and we only get a set amount of money, which is very, very low for anything we give, we give Cytoxan or we give TDM-1, we get X amount of dollars, which is very little. So they don't do it by drug here in

(continued on SP202)

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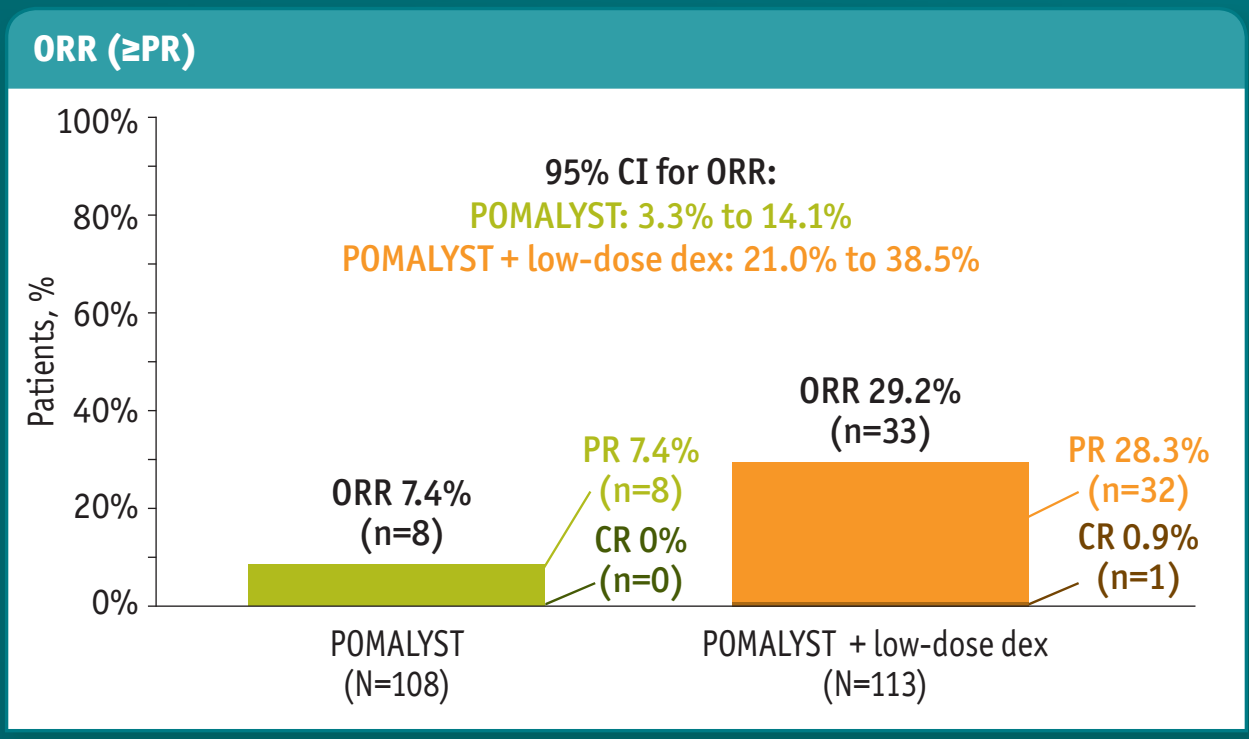

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WARNINGS AND PRECAUTIONS

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Venous Thromboembolism: Patients receiving POMALYST have developed venous thromboembolic events reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or antithrombotic treatment. The rate of DVT or PE was 3%. Consider anticoagulation prophylaxis after an assessment of each patient's underlying risk factors.

Hematologic Toxicity: Neutropenia of any grade was reported in 50% of patients and was the most frequently reported Grade 3/4 adverse event, followed by anemia and thrombocytopenia. Monitor patients for hematologic toxicities, especially neutropenia, with complete blood counts weekly for the first 8 weeks and monthly thereafter. Treatment is continued or modified for Grade 3 or 4 hematologic toxicities based upon clinical and laboratory findings. Dosing interruptions and/or modifications are recommended to manage neutropenia and thrombocytopenia.

Hypersensitivity Reactions: Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.

Dizziness and Confusional State: 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced grade 3/4 dizziness, and 3% of patients experienced grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice.

WARNINGS AND PRECAUTIONS (continued)

Neuropathy: 18% of patients experienced neuropathy (approximately 9% peripheral neuropathy). There were no cases of grade 3 or higher neuropathy adverse reactions reported.

Risk of Second Primary Malignancies: Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

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- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common adverse reactions (≥30%) included fatigue and asthenia (55%, 63%), neutropenia (52%, 47%), anemia (38%, 39%), constipation (36%, 35%), nausea (36%, 22%), diarrhea (34%, 33%), dyspnea (34%, 45%), upper respiratory tract infection (32%, 25%), back pain (32%, 30%), and pyrexia (19%, 30%)
- 90% of patients treated with POMALYST alone and 88% of patients treated with POMALYST + low-dose dex had at least one treatment-emergent NCI CTC Grade 3 or 4 adverse reaction
- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common Grade 3/4 adverse reactions (≥15%) included neutropenia (47%, 38%), anemia (22%, 21%), thrombocytopenia (22%, 19%), and pneumonia (16%, 23%). For other Grade 3 or 4 toxicities besides neutropenia and thrombocytopenia, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion
- 67% of patients treated with POMALYST and 62% of patients treated with POMALYST + low-dose dex had at least one treatment-emergent serious adverse reaction
- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common serious adverse reactions (≥5%) were pneumonia (14%, 19%), renal failure (8%, 6%), dyspnea (5%, 6%), sepsis (6%, 3%), pyrexia (3%, 5%) dehydration (5%, 3%), hypercalcemia (5%, 2%), urinary tract infection (0%, 5%), and febrile neutropenia (5%, 1%)

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with POMALYST. Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp). Coadministration of POMALYST with drugs that are strong inhibitors or inducers of CYP1A2, CYP3A, or P-gp should be avoided. Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

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Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Nursing Mothers: It is not known if pomalidomide is excreted in human milk. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from POMALYST, 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: Safety and effectiveness of POMALYST in patients under the age of 18 have not been established.

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Renal and Hepatic Impairment: Pomalidomide is metabolized in the liver. Pomalidomide and its metabolites are primarily excreted by the kidneys. The influence of renal and hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Avoid POMALYST in patients with a serum creatinine >3.0 mg/dL. Avoid POMALYST in patients with serum bilirubin >2.0 mg/dL and AST/ALT >3.0 x ULN.

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Panel Discussion
(continued from SP197)

DC, and I don't know what other plans do.

Newcomer: Each individual state has its own Medicaid rules. So, there is no common answer. It is very clear, though, that each state in the country right now is facing a budget crisis in Medicaid. So I wouldn't be surprised to hear that other states are putting up the same kind of problems that Dr Swain just described.

Chernew: And are you worried about access to these medications for people in the Medicaid population?

Swain: I am very worried about it. I am in a safety net hospital and we do give it to the patients that need it but we also have 340B pricing. So we basically can cover some of it but it is a big problem, it is a huge loss for us.

Chernew: So it would probably be useful if you said something about 340B pricing.

Swain: I just can say it this way: At our

hospital, a safety net hospital, we do have a substantial number of Medicaid patients and there are big losses for us when we use these drugs, but we do use them in the patients that need them.

Newcomer: I think it is worth pointing out that 340B was—the original intent of that regulation was—to address this kind of situation that when states couldn't pay properly for the drugs that there would be a discount for safety net hospitals, and that was the intent of the program. The hope was it would help defray the cost that Dr Swain was talking about.

Swain: And because it does probably affect 60 million people or more, who are going to be on Medicaid, I think it is a really good question.

Chernew: Absolutely. To what extent do you think the patchwork of payers and financing will impede the access to patients who might benefit from these novel therapeutic agents?

Swain: I think it will affect them great-

ly, because what we are already seeing is the patients are coming to hospital settings who are on Medicare and are not being treated in their doctor's office and their infusion center because the doctors can't afford to do it, they actually lose money, so they are coming to a higher-price facility, a hospital, to get their infusion. So I think it is really going to affect, not on the patients but the economy in general.

Chernew: There are some paradoxical things that arise in our financing system where we may end up spending more money in efforts to save money.

Newcomer: Well, it is important to realize, though, that Medicare doesn't think that way because Medicare actually pays a hospital less for chemotherapy than they do a physician office and they underpay both of them. So, a hospital today is reimbursed at ASP + 2%; that's obviously quite low. A physician is paid at ASP + 6%, going to 4%, going 3%. So, it is easy for me to understand that neither entity can make

money and be profitable getting that kind of reimbursement for these expensive medications. Medicare doesn't pay more if the patient goes to the hospital or the office and they are indifferent to that.

Chernew: So again, I am going to push a little bit on this because I want to know. That's certainly true for the drug, but what about situations where if you push someone to the hospital out of the office, there is a series of other services that may be ancillary to the drug where they may pay more in the hospital setting as opposed to the physician office. Does that happen, is that a concern?

Swain: Well, the facility fee, yes.

Chernew: But not necessarily for the drug. I think what Dr Newcomer is saying, and again this is just from my knowledge, the facility fee portion is not what's going on for the drugs, it's all the other services or is that being built in the fragmentation the way payments are working? So the drugs may be cheaper, but all of the other things that must be delivered along with the drugs are more expensive?

Swain: Dr Newcomer may know this better than I do, but I don't know if they are more expensive, but they are added to. You know you have a facility fee where you wouldn't have it in a private doctor's office.

Newcomer: Dr Swain is absolutely correct; the hospital gets to charge a facility fee for all the other things that are necessary like the lab test, the IV, etc, and that fee is more costly than it would have been to get those same services in a physician office. It pales by comparison to the cost of the drug, but it is more expensive. I think the reason that the Medicare program isn't quite as sensitive to the fact that the patient is going to hospitals is that on the whole the costs are pretty close. Hospitals, on the other hand, have to make up those differences, as do physicians, by overcharging commercial plans. They have to make it up somewhere. So the pressure by the federal policy is applying great pressure on the private insurance programs by making their prices much higher, which they in turn have to pass on to employers. It is really a hidden form of a tax.

Chernew: Just to clarify, despite some of the efficiencies, you think that the episode cost for someone going to a hospital is in fact not that much greater than the episode cost to someone in the office because the drug price difference swamps some of the higher charges or fees for the related services?

Newcomer: For the Medicare, yes. There have been a couple of studies trying to look at that question and they have come up with an equivocal result. So, whether or not other things happen to that patient when they are at the hospital is more expensive, I think it is still a debatable point. What is clear, at least on the commercial side is that a private physician office can deliver those therapies at less cost. In the Medicare program, it is probably about the same. It doesn't make sense to overburden our hospital systems which are already crowded and overtaxed with things that can be done in a physician's office. It would be a better policy to have those done when possible in a private practice.

"We do have a substantial number of Medicaid patients and there are big losses for us when we use these drugs, but we do use them."

—Sandra M. Swain, MD

Chernew: So my next question has to do again with the patient population. In a lot of areas the concern is that the treatment move beyond those with particular indications. You mentioned early on, Dr Newcomer, that you are only approving access in the situations where the FDA has granted approval… How do plans or other payers address this, and frankly is it a good or bad thing? It might be the case that practice moves faster than approvals.

Newcomer: The key concept for us is the evidence there to support moving beyond the FDA label? And, we are already talking in this discussion about some early trials showing benefit of pertuzumab in neoadjuvant settings, smaller studies as Dr Swain pointed out. But there is evidence to support an off-label indication. We are ready to support that with coverage, but we want the evidence. We don't want someone saying, "I think this is a good idea. I am going to try it in my patient without the evidence to support it." We are asking for and getting some of the studies done and if the evidence shows there is a benefit, then it is worth being paid for.

Swain: Can I ask, why are you not allowing the use of paclitaxel with pertuzumab, trastuzumab?

Newcomer: It was because of the original label indication. I think the evidence is coming out…and we will eventually broaden. Our policy today is to use the NCCN recommendations and I am not aware, I would have to go check whether or not NCCN has actually changed its recommendations to allow paclitaxel at this point. So rather than UnitedHealthcare trying to monitor these things (because we don't have the expertise here), we have relied upon the National Comprehensive Cancer Network to set the guidelines for coverage and if they change the paclitaxel, we will as well.

Swain: Okay, I think that's good because it is so much easier to give patients paclitaxel and docetaxel. I know we had a big discussion about that, one of the people who wrote the protocol and because your up-use is a lot of docetaxel, that's why that was chosen, because it was a worldwide study. But I think the paclitaxel is much better for the patient.

Chernew: So this raises another related question about how often UnitedHealthcare or other private insurers revisit their pathways to refine them. I gather from your answer, Dr Newcomer, that you follow other organizations and when they change you change, but there is not a set schedule for revisiting what must be a plethora of pathways and guidelines that you have?

Newcomer: No, the schedule is actually set by the NCCN and their policy is to add a recommendation for any major announcement and then they also have regularly scheduled updates for less major changes. It is not a perfect system, but I think as a general rule, they have been quite responsive. They have anticipated FDA approvals very well and get those changes made very quickly. I want to pick up on a comment…that hormonal therapy could be an early intervention for these patients. We just recently looked at our population at UnitedHealthcare that had newly diagnosed metastatic breast cancer and the patients were estrogen receptor-positive, and we were surprised to find that a very small percentage of those people are being treated initially with hormonal therapy, about 20%. And, it would be great, I was delighted to hear that because hormonal therapy can be extremely effective, it is less toxic, its responses last longer. And I wonder, Dr Swain, if some of our younger physicians may not have as much experience with hormonal therapies and may be a little less likely to use it.

Swain: Are you talking about this overall in all patients or HER-2 positive patients?

Newcomer: This was overall in all patients, not HER-2.

Swain: Well that shocks me actually.

Newcomer: Me too. I was really surprised.

Swain: We have got work to do to train our young doctors because clearly hormonal therapy gives better quality of life and in reference to the HER-2 positive population, when I give these lectures and talk about it, I always mention that because you can get some good mileage out of hormonal therapy with trastuzumab alone, for example in the first-line setting if you have someone who presents with really low volume disease, you certainly can use it and I have used it in patients and have them on it, maybe for a year or two. It certainly should be considered.

Newcomer: That's why I put an emphasis point on it, because I think in all the enthusiasm about this drug, and it is a good one, but sometimes we lose sight of the fact that there are still some old standards that can really derive a lot of benefit for patients.

Chernew: That's really a useful thing to remember, I think, both in this situation

and just generally true. But I do want to switch for a moment to talk about companion diagnostics. A lot of these treatment regimens require different diagnostic tests to be run and I was wondering if you think that they are being used appropriately and if the payers are covering them appropriately, and the use of diagnostics isn't or is a barrier to access to appropriate therapy?

Swain: I'll just start out, that it is pretty standard in the Unites States to get immunohistochemistry testing for HER-2, or some places do FISH upfront looking for HER-2, and I think that's really standard and it really doesn't limit the use of [this] even in patients who are in areas where they may not have access to the high-priced drugs, so I don't think that's a limitation.

Newcomer: I couldn't agree more. We actually measure this and our compliance rate of HER-2 testing in breast cancer patients is 99.5%. So I think the US oncologists are well aware of the biomarkers and using them.

Chernew: And are the payers assessing outcomes as they are using medications or do they rely on the evidence being generated externally?

Newcome: We are relying on the evidence externally. We are developing measurement tools that allow us now to look at relapse rates and overall survivals for regimens. So, we have tested this in our episode pilot group and I think we are getting pretty comfortable now that that's something that we will be able to track over time. It is important because as new regimens get approved, we will be able to do postmarketing analytics on these to say, okay, here is what the regimen is getting for a response rate in the real world, both in terms of relapse rates and in terms of ultimate survival rates. As we use the preauthorization process to basically create an intent-to-treat trial, and someone says this is the regimen I am going to use, we can then follow that patient in our databases and find out when they do relapse and start creating survival curves for regimens in clinical practice. Those patients are much different than the ones that are used in clinical trials and I think that's going to be important information to feed back to the oncologist to say, "Here is what really happens in US with this particular regimen."

Chernew: I have 1 last question and then I will see if you want to add anything that I have missed. There are a lot of changes going on in the American healthcare system now and a lot of talk about moving to new payment models. I know that certainly United is at the forefront of some of those changes. I wonder what your thoughts are as to how some of the incentives that are being placed upon physicians will influence their access to [nanotechnology] in general in these types of treatments in particular, for example, when risk is being pushed down to the provider level and we are moving away from our traditional fee-for-service system. Do you see or are you worried about physicians changing their practice patterns in a way that might be detrimental?

"We have got to find a way to produce these drugs less expensively if we are going to continue to make them accessible to US patients."

—Lee N. Newcomer, MD, MHA

Newcomer: I am concerned we can create incentive programs that would in fact discourage the use of a good drug. Our Episode program was designed to avoid that and in the Episode program, what happens is, when pertuzumab came out—and this actually occurred when we were in the middle of that pilot, we always pay the drug at cost. So the physician did not lose money by switching his patients to pertuzumab; they didn't make more money either. So in the current fee-for-service world, when pertuzumab comes out and they get a percentage of that as a profit margin, it is an expensive drug, they would have made more money for using it. In our Episode program, they were able to switch to the program without any penalty whatsoever because they are not at risk for the cost of the drug, but they didn't make more money either. We change our Episode payment for caring for the patient based on outcomes and if we see that these patients are in fact living longer or having fewer hospitalizations because their disease isn't controlled, then that will raise the Episode payment, but it won't be raised because they switched to an expensive medicine. On the other hand, there is no penalty or no barrier for them making that switch if they believe it is a better medicine. That was set up deliberately. We have to be a little careful about capitation programs where there is a fixed pot of money because that may be too much of a barrier to using newer medications that are effective.

Swain: I agree with that and I think I am concerned about that with a high-price drug. So I think that's why the drug pricing goes into all of it—that we need to be really careful because these drugs that we are talking about today are exceptional. I mean, they clearly, as you said before, have a value for use and they need to be given to patients. There are many drugs that you could argue that aren't. So I think that we need to be really careful about this.

Chernew: And Dr Newcomer, do you think the program that you described at United is industry standard or do you think it is somewhat atypical, particularly the inclusion or exclusion of drugs in the bundle? I am familiar with some plans in which the drugs are in the bundle, and then the question of course, as you alluded to, would focus on how the bundle is updated when there are new treatment options.

Newcomer: Let's put this in perspective. Clearly the standard today in the United States is still fee-for-service and that's still probably representing 95% of the way oncology is paid for here. These other programs are small, they are pilot, they are being tested, and we have got a lot of learning to do. I don't think Episodes is ready to become the payment method for the United States today. We are still trying to run the analytics this summer to find out if it has actually been effective in changing cost patterns and we should know that by the fall. We still have to do these experiments, though, because we can't afford the current rate of care. We are going to have to do something to figure out how we take waste out of this system, how we remove those unnecessary things to allow some payment for drugs that make a difference, and pharma has a responsibility to get its cost down. We have got to find a way to produce these drugs less expensively if we are going to continue to make them accessible to US patients.

Swain: And I think that's very true because we can't keep piling on these costs. If you would look at melanoma, for example, all the drugs are coming out at $10,000 a month, it has really accelerated over the last year or so. So we have to definitely look at cost. And I think what you said is really important too, is to look at these pilot programs. Because you can have unintended consequences when you do these things that you don't predict. So I think that's really important not to [administer to] everyone but to have the data before you implement it in all programs.

Newcomer: We need the evidence for testing these programs. We need just as much evidence for development here as we do for the drug responses.

Swain: I agree.

Chernew: Well that's actually music to the ears of a health economist. So I think this is a fine place to wrap up this discussion. **EBO**

AJMC TV

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Sequester Forcing Chemo Treatments into Hospitals Costing Taxpayers More in the End

Stanton R. Mehr

The federal sequester trims Medicare payments for cancer patients receiving chemotherapy in doctors' offices in an effort to save the government money. Instead, it will end up costing more in the long run, according to the president of the American Society of Clinical Oncology (ASCO).

ASCO President Clifford A. Hudis, MD, said most community-based oncology practices that operate under the "buy-and-bill" system, in which providers purchase chemotherapy drugs for on-site treatment and then bill Medicare, cannot afford to absorb the cuts imposed under the Budget Control Act of 2011, popularly known as the "sequester."

So, Hudis and others told *Evidence-Based Oncology*, these providers have been forced to refer patients seeking certain chemotherapy treatments to hospitals, where reimbursements—and costs to Medicare—are greater. It is not yet known how much this practice is costing the federal government.

"This is one of the true disappointments of the whole sequester—it's converting lower total costs associated with physician office care into higher costs incurred at the hospital-based setting," Hudis said. "It's going to significantly increase the cost of delivering the same care while making it frequently less convenient."

"It's quite an amazing paradox," he said.

Since the financial sequester took effect in April, medical providers, patients, and health plan administrators have worked to adjust to both immediate and long-term implications. The picture in cancer care has many aspects: There are effects on patients undergoing care, and there are effects on research into new treatments for future patients.

While other areas of the federal government sustained deeper cuts by the Budget Control Act, Medicare payment cuts were limited to 2%. This applies to payments to Medicare Advantage plans and providers while also affecting physicians who purchase part B medications, administer them onsite, and seek reimbursement from Medicare (referred to as "buy-and-bill"). A 2% cut may not sound like much, but it is having alarming effects.

The already-slight margins on office-based infusible products means that oncology practices are making extremely difficult decisions regarding whether to continue providing infused chemotherapy to their patients. For some, the choice involves whether to continue treating these patients or lose money on their medications. "If we treated the patients receiving the most expensive drugs, we'd be out of business in 6 months to a year," according to Jeff Vacirca, chief executive of North Shore Hematology Oncology Associates in New York.[1] He told the *Washington Post*, "The drugs we're going to lose money on, we're not going to administer right now," noting that Medicare beneficiaries comprised more than half of his practice.

The result, according to Hudis and other clinicians, is that patients are being directed to hospitals or clinics to receive the treatments, with the result being greater expense to Medicare. A study by Milliman, the actuarial consulting firm, estimates that chemotherapy given in a hospital costs on average $6500 more annually than chemotherapy provided in a community-based location.[2]

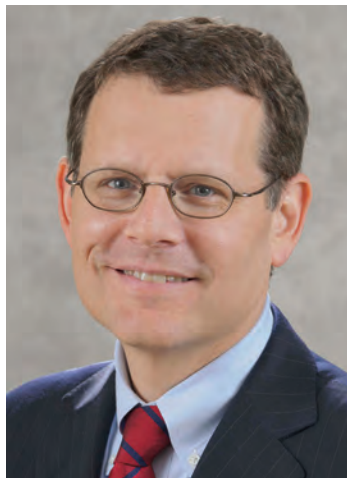
Furthermore, the question arises as to whether hospitals can handle the increased load: In 2011, Milliman found that 33% of patients were receiving their chemotherapy in a hospital setting. This may actually be exacerbating a trend toward administering chemotherapy in hospital-based outpatient centers. A study of fee-for-service Medicare data found that this shift has been continuing since the implementation of average sales price (ASP) pricing. Preliminary results from a study by the Moran Company revealed that in 2005, fully 87% were receiving chemotherapy in physician offices compared with just 13% in hospital settings.[3]

William T. McGivney, PhD, principal of McGivney Global Advisors, stated, "Sometimes, federal government policies are 'misdirected.' The sequestration cuts in reimbursement for oncologic drugs and biologics (therapeutic and supportive care) fall into a new category of 'undirected misdirection.' " McGivney, the former CEO of the National Comprehensive Cancer Network (NCCN), added, "Gaps in current federal reimbursement levels for oncologic agents have been amplified by the sequestration cuts, and this, in turn, has exacerbated an already difficult situation into one that jeopardizes patient access."

The Numbers Game

When clinics and physicians purchase chemotherapies for administration at their facilities, they had been receiving reimbursement of the ASP of the agent plus 6%. According to ASCO, the sequestration has reduced this reimbursement effectively to ASP plus 4.3%. This change is enough to erase their small margins and put their practices into the red, especially when purchasing expensive infusible products. This is driving oncologists and their practice administrators to advise patients that they are no longer providing chemotherapy at their offices.

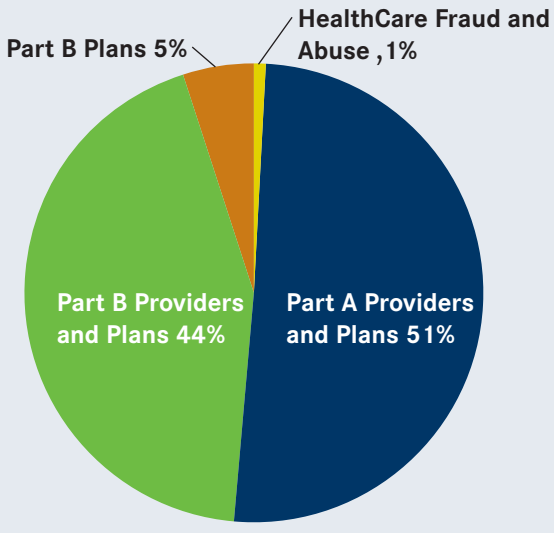
A survey of 500 oncologists by ASCO revealed that close to one-half were "no longer able to continue caring for Medicare patients unless they had supplemental insurance."[4] The survey, completed in May 2013, also specified that 50% of practices were reportedly sending their Medicare patients who need chemotherapy to hospital outpatient infusion centers **(Table).** A total of 14% reported that they no longer



The sequester will "significantly increase the cost of delivering the same care while making it frequently less convenient. It's quite an amazing paradox."

—Clifford A. Hudis, MD

Figure. Estimated impact of sequestration on Medicare spending for FY 2013.



Total Sequestered Spending, FY2013 = $11.085 billion

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accept Medicare patients. Hudis pointed out that the results of this survey should be interpreted with caution, as it was voluntary in nature (ie, selection bias may be an issue).

The results of a separate survey of 326 practices by the Community Oncology Alliance do support ASCO's findings, however. In addition, one-fifth of practices reported that they have reduced administrative staff, and two-fifths expected that they would do so should the cuts remain in effect through midsummer. Interestingly, 14% of practices surveyed indicated that they are now considering renewed discussions with hospitals to form closer relationships, including being acquired by them.

Table. Key Results of ASCO's Survey: Early Effects of the Sequestration on Oncology Practices

25% no longer participate in clinical research
74% now have difficulty paying for chemotherapy medications
80% indicate that the sequestration has affected their practice
50% send their Medicare patients elsewhere for chemotherapy
14% have stopped accepting Medicare patients
22% will close satellite or outreach clinics
27% will no longer accept patients covered by Medicare Advantage plans

Source: ASCO sequestration impact survey: One month out, sequestration affecting care of Medicare cancer patients. American Society of Clinical Oncology May 9, 2013 (www.asco.org/press-center/asco-sequestration-impact-survey-one-month-out-sequestration-affecting-care-medicare). Accessed June 14, 2013.

A cancer clinic "had to send several patients to the local hospital…The patients are very frustrated. Most of them are sick and would benefit from staying with their clinic."

—US Rep. Renee Ellmers

Effect on Clinical Trials

Intensive clinical research continues to be a force behind advances in cancer treatment. Sequestration seems to be affecting oncology clinical research at the national level and local level.

As part of sequestration, the National Institutes of Health (NIH) took a 4.7% hit to its operating budget, including clinical research trial grants. Since NIH is a major source of funding for drug trials, this will certainly result in fewer cancer drug therapy investigations over time, and possibly, slower delivery of oncology medications to the FDA for drug approval.[5]

Patients participating in active clinical trials may be especially hard hit in less-populated areas. In areas with few cancer treatment centers, there may be no option for those patients if their treatment center decides to turn away patients—any facility participating in a clinical trial must be individually approved. That patient may be forced to go across state lines to continue in the trial at an approved facility.

In clinical trials, the chemotherapy under investigation is usually provided to the patient free of charge, but this may not be the case with supportive or ancillary therapies for their care.

From a practical view, Hudis believes that less will seem different at the community level than meets the eye. "The community is so dedicated to doing clinical trials, and frankly has a history of doing clinical trials even when they represented a financial loss," Hudis explained, "that most patients are likely to keep getting their care in studies that are ongoing. So the impact of this could arguably not be fully appreciated for many months to years—new trials are not started, and the old trials that close aren't replaced."

A Fix in the Works?

It is expected that the next federal fiscal budget will address the current across-the-board cuts, retaining much of the savings obtained through the sequestration. The situation compelled some legislators to take immediate action.

Marilyn B. Tavenner, CMS administrator, responded to a request by more than 100 legislators to avoid chemotherapy reimbursement cuts, replying on June 3, "The Department of Health and Human Services assessed whether the law allows discretion to administer the sequestration reductions in a manner that is different from the across the board approach that has been used to implement it. We do not believe that we have the authority under the Budget Control Act of 2011 to exempt Medicare payment for Part B drugs."[6]

Since CMS does not believe that it has the authority under the Budget Control Act to decide where cuts can be avoided, congressional intervention will be necessary to effect a change in the law. A bill introduced by US Rep. Renee Ellmers (R-NC) has received bipartisan support in the House, capturing 101 co-sponsors by late July. The legislation, the Cancer Patient Protection Act of 2013 (H.R. 1416), would exempt chemotherapy from the 2% cut in payment. It has been referred to the House Budget Subcommittee on Health.[7]

In an interview with *Evidence-Based Oncology,* Ellmers said, "What's needed is momentum and public awareness. Many members were waiting to hear from CMS before they would agree to a legislative fix. Now that CMS has responded and said they will not act, members of Congress know the ball is in their court." Ellmers continued, "Furthermore, support for this bill has been enhanced by evidence from oncologists across the country that they are sending patients to the more expensive hospital setting because of CMS's application of the cuts."

She has seen negative effects in her own district, spurring her to act. "I have heard from numerous oncologists and cancer centers throughout the second district of North Carolina," she stated. "They have reported that, already facing small profit margins, their centers are concerned that CMS's application of these cuts will put them out of business.

"I have also heard from the Blood & Cancer Clinic in Fayetteville, North Carolina. They have had to send several patients to the local hospital. This is unfortunate because most of the patients have received several treatments in their office already, but are now suddenly forced to transfer to the hospital. Their patients are very frustrated. Most of them are sick and would benefit from staying with their clinic," according to Ellmers.

This would be a welcome change in attitude, based on ASCO's initial meetings on Capitol Hill. Hudis stated, "The last time we actually spoke with representatives and senators about the impact of the sequester, we pointedly highlighted the exemption that they carved out for the air traffic controllers and the FAA. Our arguments, though, seemed to fall on relatively deaf ears."

"The near-term probability of relief, legislative or regulatory, seems modest," McGivney told *Evidence-Based Oncology.* "Thus, providers likely will to have to deal with staying afloat as the delivery/payment system remains awash in cuts, mandates, and change." **EBO**

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Accountable Care Organizations

(continued from cover)

Under the 2010 Affordable Care Act (ACA), the nation's healthcare system bears financial risk for delivering better care, and the industry is experimenting by rearranging the relationship between those who provide care—doctors, nurses, specialists and technicians—and those who pay for it, such as insurance companies, major employers who self-insure, and federal and state governments.

ACOs, which integrate care across healthcare providers, are catching on, and ACOs and ACO-like entities operate in as many as 45 states.[1] Between 25 million and 31 million Americans are receiving healthcare services through an ACO, and more than 40% of Americans—126 million people—live in areas with at least 1 ACO, estimate Rick Weil, partner, and Niyum Gandhi, associate partner, in the Health and Life Sciences Practice of the consulting firm Oliver Wyman.

As of November 1, 2012, there were 328 ACOs, up from 221 at the end of May 2012, and 164 in September 2011, according to Leavitt Partners.[2]

While the near-term growth of ACOs seems assured, the jury is still out on the question of whether ACOs can deliver the requisite quality of care to have any measurable impact on long-term costs.

Even if there is no consensus about what quality care entails, initiatives in the marketplace hold clues to the future of how ACOs plan to deliver better care.

Nationwide Children's Hospital (NCH) in Columbus, Ohio, a sponsor member of the Partners for Kids ACO, which serves more than 300,000 children, tracks its metrics with impressive granularity.

Quality and Metrics

Future healthcare quality can't be improved unless hospitals and doctors know how well or poorly they are performing today. It's no surprise, then, that ACOs are sticklers for metrics.

Nationwide Children's Hospital (NCH) in Columbus, Ohio, a sponsor member of the Partners for Kids ACO, which serves more than 300,000 children, tracks its metrics with impressive granularity.

Drug errors, surgical infections, bloodborne infections, and rates of pneumonia associated with ventilator use are reported quarterly and monthly. Even staff compliance with washing hands is plotted on a graph.

Patient-centered models are designed to help patients maintain an ongoing relationship with the same doctor.

The hospital, which serves a pediatric Medicaid population in a 34-county area in central and southeastern Ohio, reports that the number of catheter-associated bloodstream infections has dropped to 0.5-per-1000 catheter days in the first quarter of this year, from an average of 5.1 per 1000 in 2004.

Data collected in separate quality indicators show the hospital doing very well, and that is 1 measure of better quality. "We try to show metrics of kids getting better," said Kelly Kelleher, MD, vice president of community health at NCH and a research adviser to Partners for Kids.

Kelleher said that fewer children with asthma and neurologic problems have been admitted to NCH's emergency department, and the decline in the rate of pre-term births compared with that of other regions is a sign that the quality of care has improved. "That's how we've improved outcomes," he said.

Even with a 1% decline in the use of neonatal intensive care units (NICUs), multiply that by every child admitted to the NICU at $3000 a day over the course of a year, and the numbers start to add up, he said.

NCH participates in pediatric quality measurement programs promulgated by the Centers for Medicare & Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ), and quality measures are set by the government.

For all of NCH's measurements, the question of whether the quality of its care improves the lives of children is, to some extent, one ultimately inferred from the data.

Short of going out and conducting large-scale surveys of families and the progress of their children, which is expensive and not reimbursed by Medicaid, Kelleher said, it's difficult to know if the quality delivered to a child today is truly any better than the care received 5 years ago.

Quality and Providers

Like an anchor tenant in a retail mall, ACOs have traditionally been clustered around big, institutional hospitals.

More recently, it is the doctors' groups that are forming the nucleus of the ACO, as ACOs seek to remain focused on the patient—a key to delivering quality.

Under this model, local primary care doctors, who see their patients regularly and know the family intimately, are in a much better position to determine what is most appropriate for the patient.

Atrius Health, a collection of 7 community-based health groups serving more than 1 million adult and pediatric patients in eastern and central Massachusetts, takes its commitment to improving the quality of care to heart—literally—as quality care "is at the heart of our mission," the Atrius website promises.[3]

Atrius, a Pioneer ACO built on the initiative sponsored by Centers for Medicare & Medicaid Innovation Center, was selected as one of 32 healthcare providers for its ability to deliver "high quality, coordinated care," according to Atrius' website.

Medicare beneficiaries are not locked into a restricted list of providers as are Medicare Advantage patients, or like regular patients were with the managed care networks in the previous generation.

Under the Pioneer ACO model, Medicare beneficiaries seeing doctors who participate in an ACO maintain the ability to see any doctor or healthcare provider, even as they continue to receive the full benefits of Medicare.[4]

Among the medical practices participating under the Atrius brand are 7 primary and multispecialty medical groups, and a hospice care group that delivers care to patients at home.

Atrius' model of delivering quality care was further cemented last year when South Shore Medical Center received the Level 3 Patient-Centered Medical Homes designation from the National Committee for Quality Assurance (NCQA).

Patient-centered models are designed to help patients maintain an ongoing relationship with the same doctor, who leads a team of healthcare experts at a single location, and who takes responsibility or ownership for care of a patient from beginning to end.

The goal with medical homes is to reclaim the importance of the primary care doctor as the gatekeeper to deliver more personalized, coordinated, and efficient care.

Elevating the central role of primary care services instead of more expensive specialty services has been shown to cut hospitalization rates, lower rates of Medicare spending, and improve quality.[5]

Quality and Payers

The 32 Pioneer ACO healthcare organizations were chosen by CMS to test different payment models and to spur competition to deliver higher quality and more affordable care than patients receive now under fee-for-service models.

All 32 ACOs in the program improved quality of care. On the cost side, while only 13 of the 32 ACOs were able to lower costs, the costs for the entire group of 669,000 beneficiaries in the Pioneer ACOs rose only 0.3% in 2012, less than

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the 0.8% increase for similar beneficiaries in 2012.[6]

The 13 ACOs produced a savings of nearly $88 million in 2012, partly due to fewer hospital admissions and readmissions, according to a recent study of the Pioneer ACO pilot.[6] Two of the Pioneer ACOs ended up spending more on the beneficiaries than the Medicare fee-for-service model.[6]

Of the 19 Pioneer ACOs that weren't able to cut costs in the first year, 7 announced they would leave the Pioneer program for the Medicare Shared Savings Program model, and 2 more said they would leave the Medicare accountable care arena.[6]

Fee-for-service models have rewarded volume, not the quality of the health services rendered, and have been blamed for driving the cost of healthcare upward, even as there's little evidence that the United States is healthier than nations that spend far less.

Under new payment schemes, hospitals and doctors, for instance, are being asked to take on more risk so that if procedures go awry and patients need to be readmitted, hospitals or doctors don't get reimbursed. The incentive is to get it right the first time, and to penalize mistakes by not paying the bill when things go wrong.

Value-based purchasing, which encourages pay-for-performance, tilts the system in favor of the patient. "The idea is to stimulate the competition among the healthcare system and make health care accountable," said. Jim Frazier, MD, system vice president for medical affairs with Norton Healthcare, an ACO serving Louisville, Kentucky, and southern Indiana. Norton is currently involved in a pilot reimbursement program with the health insurer Humana.

Payment redesign is being structured and recalibrated to take account of providers' readiness to accept financial risk, with health plans, hospitals, and doctors collaborating among themselves to negotiate goals around quality and cost reduction.[7]

Risk-sharing among providers and payers, and bundled payments, are changing the way hospitals and doctors are reimbursed so that the healthcare system moves "from volume to value," said Karen Ignagni, president and CEO of American Health Insurance Plans.[8]

"The challenge is that until the reimbursement (model) is changed, it makes it difficult to make it a true ACO," Frazier said.

Will ACOs and alternative health payment models be enough to control the rising cost of healthcare? The past 3 years have seen healthcare costs level off, but many experts point more to the weak economy as the primary reason, as opposed to structural change within the healthcare system.

Brenner says the nation is in the midst of a 30-year experiment in redefining how to deliver healthcare, and that to succeed at the individual level will mean patients will have to feel cared about and know exactly what happened, why things happened, and how they can prevent their ailments in the future.

For doctors and nurses, it will mean looking forward to taking care of patients and bonding with them every day, he says. At the macroeconomic level, it will mean offering better care at lower costs.

The US healthcare system in still the most expensive in the world by far, and whether the nation achieves better quality by rearranging the provider side or the payment side of the delivery system, "we've got a long way to go," said Brenner.

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Status in the States: Kentucky

(continued from cover)

change to sell health insurance under the 2010 Affordable Care Act (ACA). In theory, all 640,000 uninsured Kentuckians should be able to gain health coverage.[3] Cutting Kentucky's cancer rates is a tall order, and Beshear is candid about the link between that grim history and his state's economic conditions. Taking the Medicaid money, in his view, was the only choice that made sense.

Stephen W. Wyatt, DMD, MPH

"Kentucky is one of the least healthy states in the nation. In 2012, Kentucky's overall health ranking was 44th. Kentucky is at or near the very bottom of many national health rankings," Governor Beshear told *Evidenced-Based Oncology*. "A multitude of state and national reports have shown the positive impacts on health status that occur when an individual becomes insured. They are more likely to get preventive care and seek out medical treatment when they need it. They miss fewer days of work and school. And they live longer and more productive lives.

"By the time we reach 2020, I believe we will have seen such a measurable impact on prevention of disease, management of chronic health problems, and overall health of our workforce that to withdraw or shrink from Medicaid expansion would be unthinkable."

Beshear, a prostate cancer survivor, feels he is on solid footing, morally and practically. The expansion affects single persons with incomes of up to $15,856 per year or a family of 4 with an income of up to $32,499;[3] many of these are working poor. The infusion of healthcare spending will create 17,000 jobs and $15.6 billion in economic activity,[1] reduce absenteeism, and improve job performance to make Kentucky workers more attractive to industry.

Over time, Beshear believes, healthier children will miss fewer days at school, and the commonwealth will see economic benefits from a healthier population.[4] All this will require confronting Kentucky's historic links to coal and tobacco, and resulting rates of cancer, especially lung cancer.

"While my primary concern is for the improved health outcomes that will be possible for many of our citizens through the expansion of Medicaid, my decision was not solely based on the obvious health benefits that extending insurance coverage will provide to the people of Kentucky. It was also based on the far-reaching economic benefits of expanding Medicaid," Beshear said.

"If a company was willing to invest $15.6 billion in Kentucky in the next 7 years, creating nearly 17,000 jobs and significantly reducing the uninsured population, while greatly improving the health of our citizens, we would not hesitate to welcome them into our state. Medicaid expansion is no different."

Kentucky health officials must overcome political and logistical hurdles, not to mention cultural ones. A fee-for-service delivery system, saddled by ignorance, poverty, and occasionally the belief that "God's will" would determine the outcome, had to be replaced by one that relied on regular screenings and outreach. Healthcare advocates and observers said the record of failure meant that when the state's poor interacted with the medical system, there were few expectations.

"Folks are not accustomed to getting healthcare and having healthcare work," said Susan Zepeda, PhD, president of the Foundation for a Healthy Kentucky. "They may have family members who were diagnosed so late that the diagnosis was a death sentence."

But critics of Kentucky's approach say the state has rushed too quickly into managed care, in a quest to upend delivery systems that caused some low-income or rural residents to wait too long to seek treatment.[5] In the breathtaking sprint to move 70% of the state's 800,000 Medicaid recipients into managed care organizations (MCOs) for the first time, Kentucky Medicaid Commissioner Larry Kissner admits there were many bumps.

Over the long haul, however, Kissner insists the accountability of managed care under health reform will make a difference: In the first year, he said, officials are reaching more than 80% of Medicaid patients for regular screenings; once that baseline is established, officials will be able to track progress

in measurements like blood sugar over time. Better still will be when more consistent healthcare shows up in higher test scores among school-age children, or lower smoking rates in the next generation of adults.

From academia to government, those who know Kentucky's system hope to finally bridge a gap that has long existed: In a commonwealth with world-class healthcare at universities in Louisville and Lexington, there are aching needs among some of the most isolated, impoverished poor in the nation.

On paper, Kentucky envisions a system of federally funded health centers and managed care networks, providing regular screenings like colonoscopies and mammograms. Telephone calls would remind cancer patients when to come in for care, and will provide follow-up that the old system never could.

It remains to be seen whether cancer care delivery under Kentucky's new model can serve a rural population. Steven W. Wyatt, DMD, MPH a veteran of the Centers for Disease Control and Prevention (CDC) who returned to his native state to become dean of the College of Public Health at the University of Kentucky, said getting more rural people enrolled in Medicaid is only the first step.

"Just because you remove the cost barrier doesn't mean you are going to increase the access," Wyatt said. "It's all about other things that surround the payment of services." Things like transportation, or missing work, or not having anyone to watch a child or grandchild, or just the fear factor of coming to a modern campus like the Markey Cancer Center in Lexington. "Navigating a university setting can be intimidating," he said.

Susan Zepeda, PhD

Zepeda concurred. Although Kentucky has a "more robust" network of federally funded health centers than existed even 5 years ago, she said, expanding Medicaid rolls and subsidized insurance mean "there will be capacity issues, particularly in rural areas of the state."

Open Enrollment Approaches

With open enrollment under the ACA set to begin October 1, 2013, the pace of change remains swift. On May 9, Governor Beshear declared the Medicaid expansion "the single-most important decision in our lifetime for improving the health of Kentuckians," and invoked his right to change Medicaid eligibility by regulation, not by statute as occurs in most states. Until 2017, when the expansion will require state matching funds, there is little the Legislature can do.[6]

Within days, Kentucky had launched a website (www.kynect.ky.gov) to help residents understand healthcare reform and to shop for coverage. A series of forums with the state's Medicaid providers followed, allowing them to get information and to vent about the rapid conversion to managed care.

Kentucky's healthcare efforts appeared in the national press almost daily in July; on some days the news was positive, like when the National Governors' Association (NGA) included Kentucky in a demonstration project to reduce the number of "super-utilizers" in its emergency departments.[7] On other days, the reviews were poor: Kaiser Health News and *The Washington Post* offered a brutal assessment of the Medicaid program's transition to managed care, with critics stating that its only aim was to fill a $1.3 billion budget hole.[5]

July 12 offered the biggest news of all: After years of effort, the University of Kentucky's Markey Cancer Center received a National Cancer Institute (NCI) designation, giving Markey eligibility to compete for millions in additional funding and the best faculty in the world. In their announcement, Markey officials said that Kentucky residents would gain access to better chemotherapy agents and to clinical trials.[11]

University of Kentucky President Eli Capilouto, in making the announcement, said the designation strengthens Markey's potential "to roll back this scourge in Kentucky."[12]

Fighting Lung Cancer

Kentucky's fight against lung cancer starts with this fact: According to the Department of Public Health, 28.4% of the commonwealth's adults smoke.[9] It's not easy to curb tobacco use when generations of farmers have grown it, and when tax coffers have relied on its sale (**Figure 1**).

"Our disease burden is heavily driven by lung cancer," said Wyatt. While there are some other anatomical cancers with elevated rates relative to the rest of the country, such as breast and colon cancer, Wyatt said nothing comes close to lung cancer. "Take out lung cancer, and we look closer to the rest of the country."

State-by-state mortality rates bear out Wyatt's observation. SEER data, published by the NCI and the CDC, show lung cancer death rates in Kentucky of 71.7 per 100,000 residents among whites and 76.7 per 100,000 among African Americans for 2006 to 2010; corresponding rates for the United States were 48.1 among whites and 50.7 among African Americans.[10] While rates for some other cancers exceed US rates, nothing comes close to lung cancer (**Figure 2**).

It's not hard to understand why: At 87,641 acres, Kentucky devotes more land to growing tobacco than any other state except North Carolina, according to the US Department of Agriculture.[11] But over the past decade, tobacco's hold on the state's economy has slipped. In the mid-1990s, University of Kentucky economist Will Snell estimated sales of Kentucky tobacco at $900 million; by 2009, a combination of fewer farms and lower prices had cut that figure to $390 million.[12]

People around the nation were quitting, driven by greater knowledge, higher state taxes, indoor smoking bans, or a combination of the 3. And bans weren't just happening elsewhere: On July 1, 2003, the college town of Lexington was the first in Kentucky to pass a smoking ordinance, which was upheld by the Kentucky Supreme Court the following year.[13] As of July 1, 38 Kentucky towns or counties had indoor bans of varying degrees.[13] In February 2013, a statewide indoor ban passed a Kentucky House committee for the second year in a row, although its prospects in the Senate were unclear. Governor Beshear has publicly endorsed the indoor ban.[14]

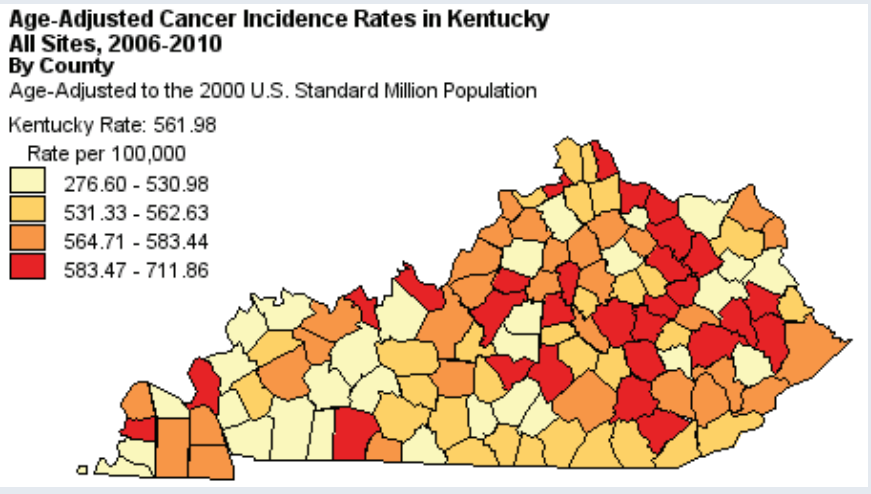
Sarah Walsh, Foundation for Healthy Kentucky program director, said polling data from early 2013 show that for the first time, more than half of adults in Kentucky of both parties support an indoor smoking ban. This is important politically, because it reduces fears of elected officials that they would be challenged in a primary for supporting a smoking ban. Overall, the poll, which was funded by the Foundation and conducted by the Institute for Policy Research at the University of Cincinnati, found that 59% of adult Kentuckians support an indoor smoking ban. These findings confirmed a University of Kentucky study that found support for smoke-free laws in rural areas.[15,16]

Commissioner Kissner said healthcare reform, and the expansion of Medicaid in particular, will allow Kentucky to reach a whole new population with programs to help people quit smoking. This will follow a near doubling of the program from 2011 to 2012, when Governor Beshear expanded it. Participation nearly doubled from 3431 to 7015, and expenditures rose from $234,517 to $527,289.[17]

Before 2011, Kissner said, Medicaid only funded programs for pregnant women. Now, "we pay for everyone."

He knows, however, that progress

Figure 1. Kentucky by the Numbers



Population (2010)	4,339,367
Cancer Cases (2006-2010)	131,205
Cancer Rates, Age-adjusted	561.98 (per 100,000)
Adults who smoke (2012)	28.4 %

Source: U.S. Census, NCI, Kentucky Cancer Registry, Kentucky DPH.

Photo Credit: NIH/CDC

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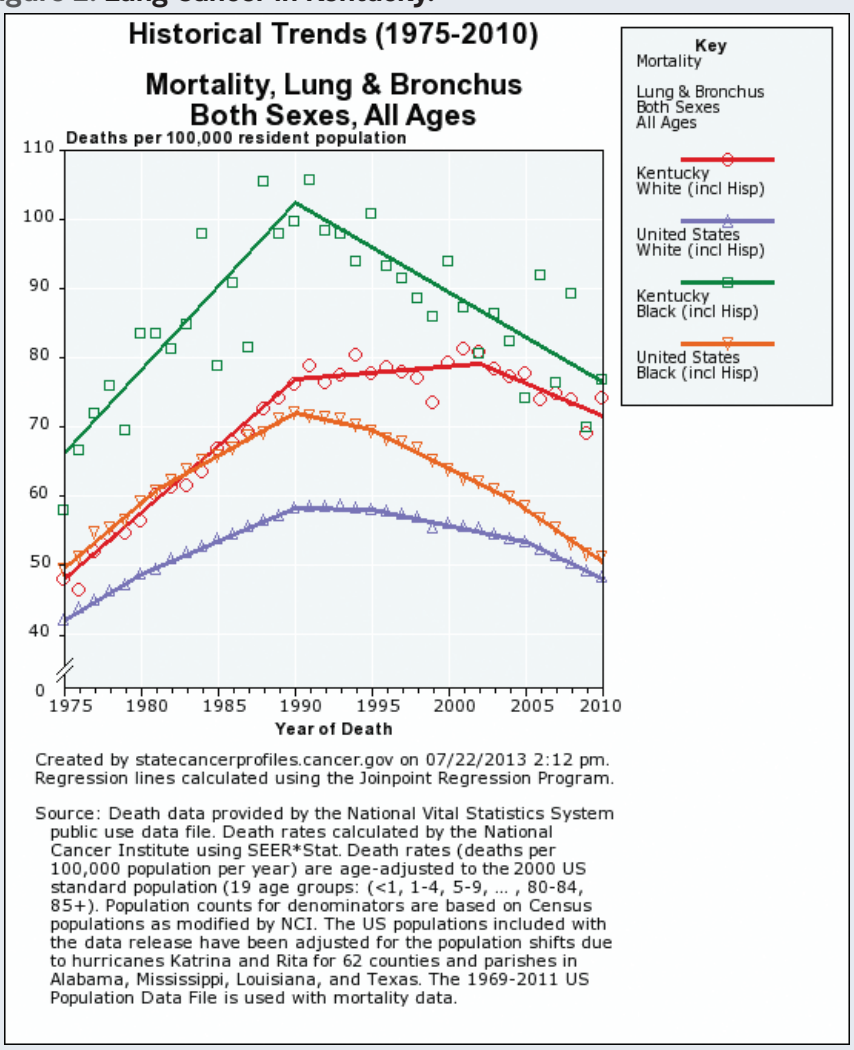
Figure 2. Lung Cancer in Kentucky.



among adults will be slow. Tucked in the most recent CDC figures, hope comes from data showing the share of teenagers aged 12-17 who took their first cigarette fell dramatically between 2002 and 2009, taking Kentucky out of the worst ranking into 10th.[18]

Managed Care Revolution

When Kissner became Commissioner in July 2012, Kentucky's march to managed care was at full throttle. Faced with a need to trim $1.3 billion from its Medicaid budget, Kentucky had announced in April 2011 that it would move beyond a managed care pilot in Louisville and enroll 560,000 Medicaid recipients into MCOs—which had to be publicly noticed, bid and awarded—between April and November 2011.[19] That schedule avoided more dire consequences like cutting reimbursements 35% or pushing recipients off the rolls.

By March 2013, providers were complaining, and 1 MCO, Kentucky Spirit, wanted out. Providers wrote op-eds and petitioned the Legislature about slow payments, contract cancellations, inadequate networks, or patient referrals to far-off providers.[20] In Eastern Kentucky, which is especially rural and poor, patients complained of inadequate mental healthcare.[21] The Kaiser story profiled a family denied payment for a child's nutrition supplement that had been covered under the old system.[5]

In an interview, Kissner acknowledged the complaints; he had just completed 8 regional forums with other health officials, where providers offered feedback ahead of the Medicaid expansion. "The biggest complaint was the speed" with which the changeover occurred, he said. Providers accustomed to just dealing with "Medicaid" suddenly could be dealing with any one of 3 vendors, and each had a slightly different authorization system.

Kissner insists that in time, the "3-legged stool" of better care coordination, education, and preventive care will be positive for patients, both for catching cancer early and for treating it. Health experts who spoke with *Evidence-Based Oncology* (*EBO*) all said Kentucky's high cancer mortality rate has been driven by the number of tumors caught late when there is little that can be done. That's where managed care can do a better job of making sure patients get preventive screenings to catch cancer early, Kissner said. And once treatment starts, he believes MCOs are better equipped than the old system, through telephone calls or other means, to remind patients to stick with treatment.

"The managed care companies do a much better job of care coordination than we did with fee-for-service," Kissner said.

Ultimately, experts who spoke with *EBO* said the test once healthcare reform arrives is whether health officials can change the way the population thinks. But they know it won't be easy.

"There's a fatalism," in some parts, Kissner said. "A thinking that says, 'Everyone in my family dies of cancer.' ... Hopefully managed care can help address that."

By keeping people insured, either through expanded Medicaid rolls or greater use of subsidized insurance, the hope is that fewer people will come on and off insurance. If they get insured and stay there, and their children stay there, chances are greater the family will get into the habit of seeking medical care regularly, not just when a crisis arises.

Wyatt knows it will take time. Even though he grew up in Kentucky, he said it's easy to forget how challenging it can be to make changes in rural areas. Working with churches can help, getting to know local opinion leaders can help. For the HPV vaccine, he said, it's not enough to convince parents; sometimes healthcare workers must convince grandparents.

"Removing the geographic barrier is very, very hard," Wyatt said. **EBO**

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Moving from Reacting to Health Crises to Stopping Them Before They Happen

Jennifer Redmond, DrPH

"It's the Right Thing to Do"

That was the sentiment of 5 healthcare executives who took part in the Kentucky Chamber of Commerce Business Summit on July 23, 2013, in Louisville, when discussing the need for increased access to insurance coverage and care for Kentucky patients.

Bruce D. Broussard, president & CEO, Humana, Inc, began the discussion on The Future of Health Care in America. He was followed by a panel featuring Kentucky's leading health executives discussing Health Care: ACA and What It May Mean to Kentucky.

Bruce D. Broussard

Panelists were Ruth W. Brinkley, CEO, KentuckyOne Health; Stephen C. Hanson, MPH, FACHE, president and CEO, Baptist Health; Michael Karpf, MD, executive vice president for health affairs, University of Kentucky; and Stephen A. Williams, president & CEO, Norton Healthcare.

Several themes emerged from presentations, including the importance of technology, changing payment structures, integrated delivery models, potential unmet expectations, partnerships, and cancer care.

"It's the Right Thing to Do"

The healthcare executives emphasized that Kentucky organizations need to work together to address issues related to access to care and population health in Kentucky. They also agreed on the importance of expanding Medicaid in Kentucky, which Governor Steve Beshear announced will happen effective January 1, 2014.[1] Karpf insisted that "it is morally, ethically, and socially unacceptable to have so many people uninsured; therefore, we must expand the mandate for healthcare and Medicaid."

Ruth W. Brinkley

Brinkley reminded participants of the impact of health on the economy. "If we want to thrive and be economically successful as a state, we have to have healthy and well-educated employees," she said. Hanson emphasized, "It's important; we shouldn't do it because we have to, we should do it because we are the leading systems in healthcare and we should do it because it's the right thing to do."

Technology

Humana's Broussard and the other healthcare executives challenged the participants to consider the use of technology in order to improve the health of populations and to consider healthcare more as "an experience rather than a transaction." He challenged organizations to make things as simple as possible. Although healthcare is very complex, he proposes that "the world in technology has made things so accessible and so easy to use....This raises the expectation that if you're not easy and you are complex, you will get penalized over time."

Broussard also suggests that technology will provide solutions to physician shortages found in rural, remote areas of Kentucky, with particular emphasis on telemedicine. Other solutions outlined by several of the healthcare executives included virtual care, lay providers, and "retail" access points.

Although some technology that rely on broadband infrastructure, such as online and mobile devices, can be difficult to access in some rural areas within the state, Broussard suggests that "It's a problem today but probably won't be in the future." He noted that technology-based companies are watching changes in healthcare closely and are figuring out a way to be involved, which will impact future service areas.

Humana provided an example of social network connectivity without the technology. Through partnerships in Bell County, Kentucky—part of rural Appalachian country—Humana created a social-based wellness program designed to address chronic diseases. At the end of the program, he said, 95% of participants have seen health improvements.

Stephen C. Hanson, MPH

Collaboration and Partnerships

All the healthcare executives highlighted the need for partnerships with multiple organizations in order to meet the responsibility for improving population health. These include healthcare providers, government, health departments, schools, members, and employers. Hanson discussed the need for partnerships to address more aspects of wellness, such as mental health, dental health, chemical dependency, and spiritual health, and Brinkley described a program in which hospitals partner with health departments to prevent hospital readmissions.

> *"If we want to thrive and be economically successful as a state, we have to have healthy and well-educated employees."*
>
> **—RuthW. Brinkley**
> CEO, Kentucky One Health

The changing healthcare system is "driving consolidations, collaborations, and alignments; developing a new world order in Kentucky and beyond," Williams said.

"We all compete, but we need to collaborate at a higher level," Hanson said.

Changing Payment Structures

Funding healthcare reform, reduced reimbursements, and increased costs were a concern for all the healthcare executives. Two aspects were highlighted during the conference that affect the changing payment structures for healthcare. First is the shift from fee-for-service to a payment structure that rewards better health outcomes, quality, and lower cost. Second, the financial risk has shifted to physicians.

All the healthcare executives recognized challenges in the current system where organizations and physicians are paid and incentivized based on the volume of services rather than improved health outcomes. "People are getting older, people are unhealthier, and the structure is flawed—the more you do, the more you get paid," Humana's Broussard said. "There is an inherent conflict especially if you don't have transparency and understanding of the cost."

(continued on SP216)

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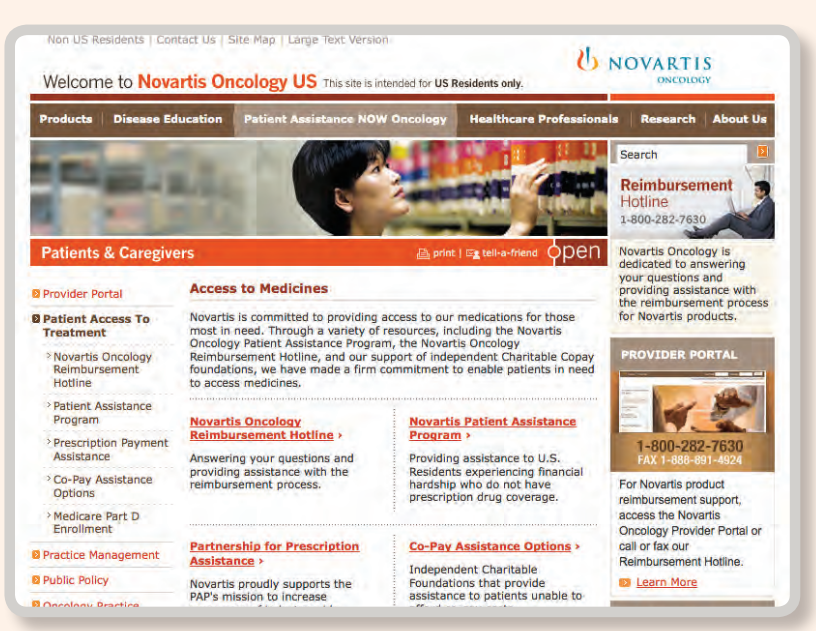

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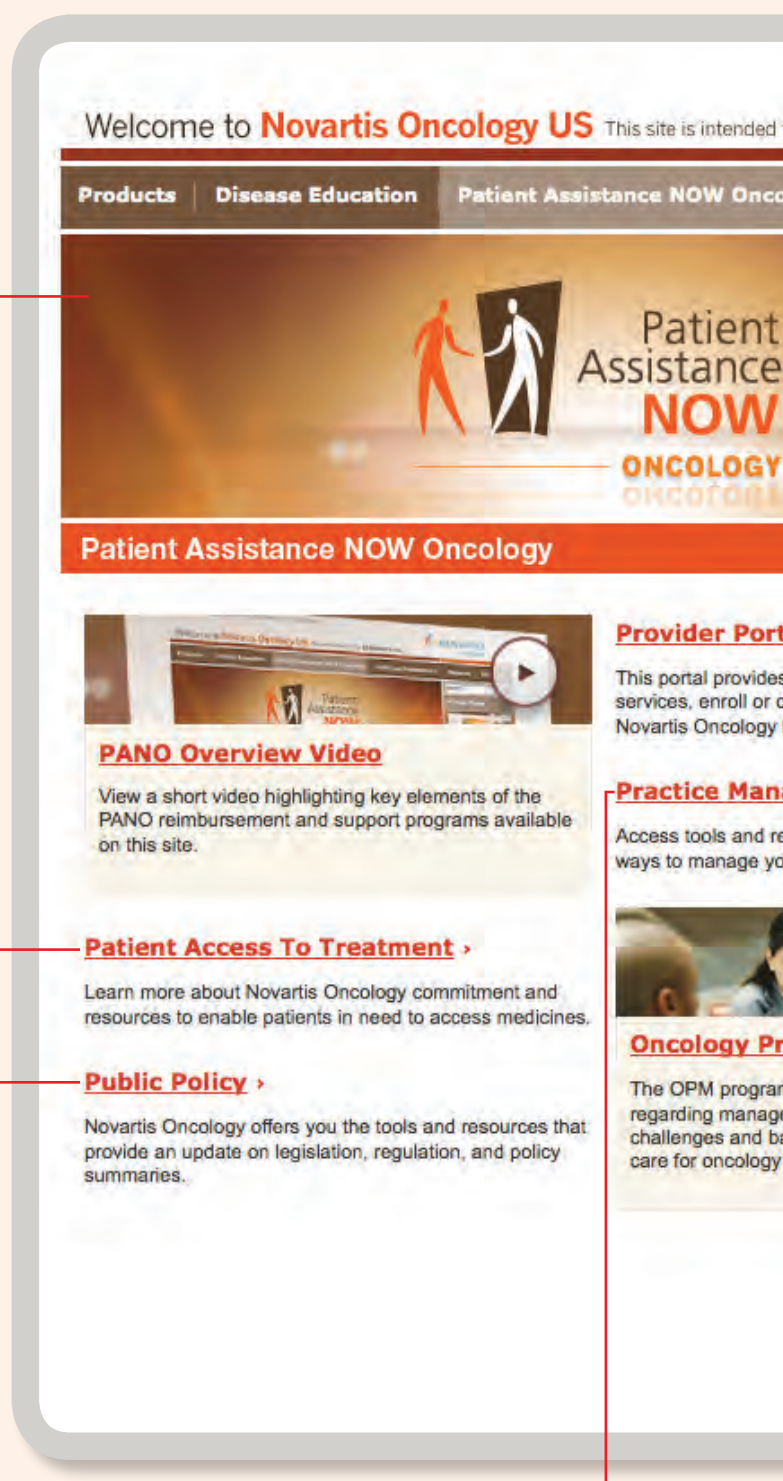

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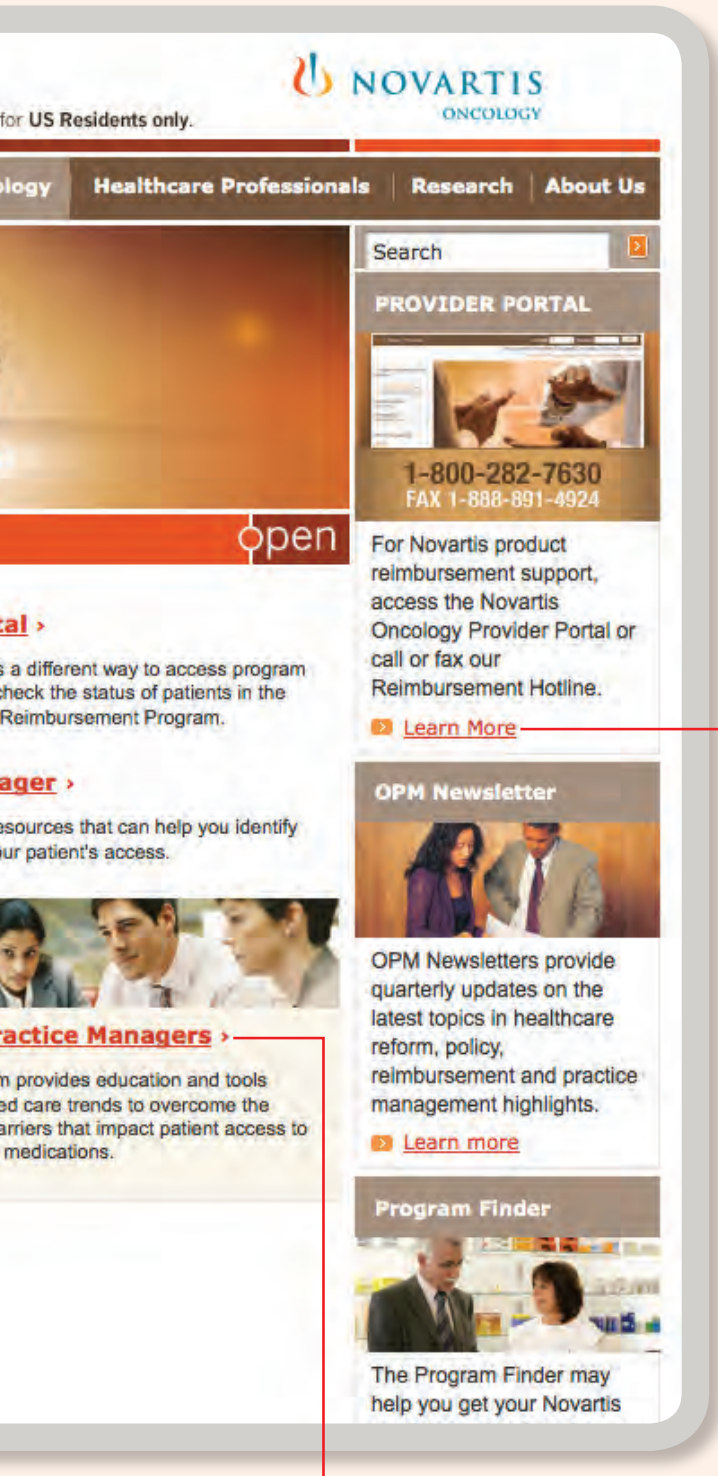

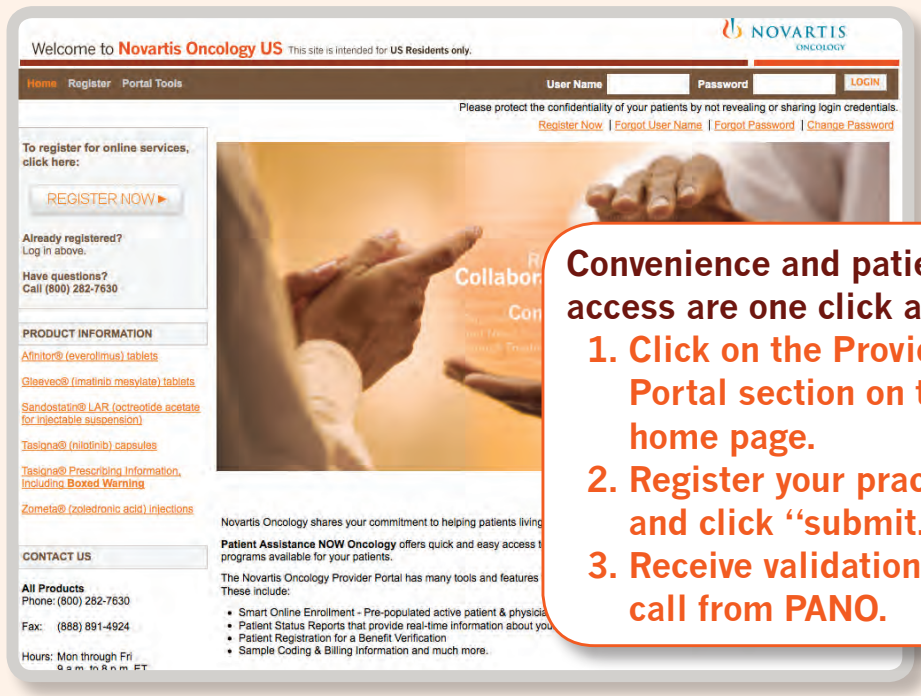

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Healthcare Executives
(continued from SP213)

For Humana, 26% of their current members are focused on relationships based on quality and cost of service through their Medicare Advantage program. Of the $40 million Humana makes annually, $26 million is paid on fixed reimbursement, incentivizing the insurer to improve quality and overall health among members. "The better we do, the more we get paid," Broussard said. "I have a whole team of people whose purpose is to improve quality."

He gave a specific cancer example to highlight this fixed fee. "If you are in stage III cancer, you are taking the most expensive treatments, and you select Medicare Advantage, we have a responsibility to take you on. Our motivation is to keep people healthy." Although Humana is required to take on this high-risk patient, there are differences in the rates based on preexisting conditions.

Since the payment structure is moving to promote healthy outcomes, an increased risk has shifted to physicians. Through bundled payments, there is an incentive to do less, be efficient, and focus on quality of care more than quantity of procedures. Broussard highlighted a program from Humana known as "path to risk" in which the company dedicates resources to help primary care physicians make the transition. Humana gradually increases bonus payments for improved quality and reduced cost, and it reduces fee-for-service payments over time.

Michael Karpf, MD

Integrated Care Delivery Models

Aligning with the changing payment structure, the executives said the healthcare system is moving from a skilled and fragmented delivery system to integrated primary care delivery systems and models. Hanson highlighted the need for coordination of care across the continuum: from prevention, screening, treatment, home health, rehabilitation, to long- term care and hospice.

Broussard attributes the growth and uniqueness of Medicare Advantage to the combination of fixed costs and the integrated care delivery model. The member relationship and experience around health has become a higher priority. Although Medicare Advantage is currently the only plan implementing this model, Humana plans to expand to other benefit plans.

One important aspect of the integrated care model includes the ability to provide education and navigation to patients who will be newly insured under ACA, so that they will understand how to utilize their new coverage. Williams explained that Norton Healthcare will train staff to be navigators who provide support to patients using "decision trees."

> *"The greatest costs of cancer are in the last 30-60 days of life. Decisions will need to be made based on value for the cost."*
>
> **—Michael Karpf, MD**
> University of Kentucky

Cancer Care

The healthcare executives agreed that concerns about cost and improved outcomes require better cancer prevention. When fewer cancers occur, there are fewer patients who need treatment. In announcing plans to add 308,000 people to Medicaid, Kentucky's governor said he was "tired of being at the bottom" of the nation's rankings of cancer deaths.[1]

When cancer is not prevented and patients must be treated, Karpf, of the University of Kentucky, said he confident that the patients would not receive different care based on the type of health insurance they carried. He believes that there will be increased standardization of treatments and participation in clinical trials, speaking just days after the University's Markey Center received a National Cancer Institute designation that was years in the making.[2] NCI designation allows funding for increased clinical trials.

"The greatest costs of cancer are in the last 30 to 60 days of life. Decisions will need to be made based on value for the cost," Karpf said. "If treatments are $15,000 per month and it prolongs life 3 months, the treatment may not be covered on a population level. Parameters have to be set based on impact to society."

He also emphasized the need for the best care for families and patients, which may involve hospice care, which can both decrease the cost of care and increase the degree of satisfaction for patients and their families at the end of life.

Hanson proposed that genomics and personalized medicine may become more common once populations have a medical home. He believes this aspect of medicine can impact both the screening and the treatment of cancer in the future.

Stephen A. Williams

Unmet Expectations

Although there are many potential benefits for Kentuckians with the increased access to care, there is also potential for disappointment. While Karpf stated his support for healthcare reform and increased access, he also described scenarios that may result in unmet expectations during the implementation process:

- Kentuckians will have the choice of a plan, but they may not have the choice of a provider or a network. There will be well-defined referral patterns within plans and systems providing fewer choices for patients.
- Kentuckians may also not have the choice in the types of diagnostics and therapeutics due to increased standardization.
- When Kentuckians sign up for an exchange plan, they may not fully realize the difference between the bronze, silver, gold, or platinum plans and their respective copays or deductibles.
- There will be fewer "Cadillac" plans because taxes on companies are increasing. One way to absorb the tax may be to offer fewer benefits in their health plans.
- When the employer mandate is implemented, some employers may choose to pay the fine and let the employee find his or her own insurance. These personal insurance plans may offer fewer benefits than employer-sponsored plans once did.
- Healthcare, which is already expensive, may become more expensive than anticipated. When Massachusetts implemented health reform, costs exceeded projections. Massachusetts had only 7% to 8% of the population uninsured, compared with Kentucky's 20%. If Kentucky spends more money than planned, there may be more reform required.

Another area leading to unmet expectations involved the Obama administration's decision in early July to delay the employer mandate. Brinkley emphasized that the only thing to change in the mandate was the date of implementation; however, both she and Hanson agreed that the delay in the employer mandate will probably not be the only delay in implementation due to the complexity of the ACA.

As Williams reminded the conference attendees at the end of the session, "ACA is a framework. Fix what doesn't work and accelerate what does work." **EBO**

Jennifer Redmond, DrPH, is a research assistant professor at the University of Kentucky College of Public Health. She provides expertise in partnership sustainability, program development, and group facilitation, especially related to cancer prevention and control, health promotion, and overall chronic disease prevention.

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1. Gov. Beshear Expands Health Coverage to over 300,000 Kentuckians. May 9, 2013. Governor Steve Beshear's communications office. Frankfort, Ky. Commonwealth of Kentucky. http://migration.kentucky.gov/Newsroom/governor/20130509medicaid.htm. Accessed July 21, 2013.
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Shifting Views on Genetic Testing
(continued from cover)

of the *BRCA1* and *BRCA2* genes, indicators of the likelihood of developing breast or ovarian cancer.

In light of the ruling, Matloff's research on the willingness of genetic specialists to be tested for mutations, or even undergo surgery, seems even more timely. She discussed her results at the March 2013 annual meeting of the American College of Medical Genetics and Genomics in Phoenix, Arizona. She presented findings of a follow-up survey of 216 active members of the National Society of Genetic Counselors' Special Interest Group in Cancer.[1] In late June, Matloff offered a presentation to members of the medical community in New York City, portions of which were broadcast nationally on FOX News.

"We originally conducted this study in 1998, when cancer genetic testing and counseling was in its infancy, and we had little or no data to tell us what would be the efficacy of prophylactic surgery, surveillance, or chemoprevention for carriers," Matloff explained in Phoenix. The follow-up, Internet-based, anonymous survey was conducted in July 2012; male respondents were asked to answer questions as they would for a close female relative.

Much has changed in the 14 years since the 1998 survey—notably, the fact that now 58.3% of the specialists surveyed said that they would opt for bilateral prophylactic mastectomy if they tested positive for a deleterious BRCA mutation at age 35. When that question was asked in 1998, only approximately 25% said that they would choose to have their breasts removed if they were found to be BRCA mutation carriers.

Decreased risk (57.9%) and avoidance of fear/worry (49.1%) were cited most often by respondents who said they would choose mastectomy if found to be mutation carriers. Twelve percent indicated that a lack of confidence in surveillance would be a factor in their decision to have their breasts removed.

"This was a very controversial issue in 1998, and it still is to some extent in 2012," said Matloff. Those who would choose not to have the prophylactic procedure listed confidence in surveillance (33.3%), negative impact of surgery on body image and sexuality (22.2%), and the fact that the surgery would not provide 100% protection against recurrence (10.6%). On the question of whether to undergo BRCA testing if risk for the mutation was determined to be 50%, a large majority of respondents to both surveys said that they would choose to be tested: 84.5% of those responding to the 1998 survey and all but 2 of the respondents in 2012 (99.1%). Among the reasons 2012 respondents gave for choosing to be tested were that the information would aid in medical management, it would be helpful to their families, and it would lessen uncertainty; 55.6% of the affirmative respondents said they would choose to be tested for the 50% probability that they would test negative.

Within the next few years, Matloff believes that the costs associated with testing will decline from $4000 for 2 genes to under $1000 to sequence the entire exome. This decrease in costs will bring genetic testing into the average marketplace with broad applications for reimbursement.

Matloff added that she did not present data on whether BRCA mutation carriers would have their ovaries removed, because the percentage was high in both surveys and not statistically significant.

The researchers also found statistically significant differences in attitudes toward prophylactic surgery for Lynch syndrome between the 2 surveys. When asked if they would choose prophylactic colectomy if positive for a deleterious HNPCC mutation at age 35, only 16 respondents to the 2012 survey (7.4%) said they would, compared with 27 people (17.4%) who answered affirmatively in 1998. Respondents in 2012 indicated confidence in colonoscopy, lowered quality of life and body image, and a willingness to postpone surgery until detection of a lesion or polyp as reasons for this choice.

Ellen T. Matloff is interviewed by FOX News in New York City about genetic testing.

However, when the same question was asked with regard to removal of the uterus or ovaries due to an elevated Lynch syndrome risk, participants were more inclined to respond affirmatively. Nearly 80% of 2012 respondents said they would have their uterus removed if found to carry the HNPCC mutation at age 35, compared with 54.1% in 1998. Similarly, nearly 78% of respondents in 2012 indicated that they would have their ovaries removed versus 52.4% in 1998. The survey also explored the issue of anonymity in genetic testing with respect to health insurance, and the results indicate that respondents are for the most part confident that billing their insurance company for testing would not be detrimental, with 94.9% of the 2012 respondents replying that they would, compared with just 23.9% in 1998. "I find this particularly interesting because I'm not sure we would even think to ask these questions in 2012, but these were top of mind in 1998," Matloff observed.

Matloff explained that gauging the perspectives of experts on issues related to genetic testing and possible interventions is especially important, insofar as the specialists surveyed "arguably have the most education and clinical experience in cancer genetic counseling and testing."

"We now know that genetic testing is well established, as compared with 1998, and that more clinicians know about BRCA and Lynch syndrome," said Matloff. She added that more clinicians are treating patients who carry mutations, and they can see both the natural progression of disease and also the stress inherent for people who test positive, as well as the stress among unaffected carriers, as they undergo surveillance, chemoprevention, and prophylactic surgery.

Another factor that may affect genetic testing is cost, which Matloff expects will come down in light of the Myriad decision. Within the next few years, Matloff believes that the costs associated with testing will decline from $4000 for 2 genes to under $1000 to sequence the entire exome. This decrease in costs will bring genetic testing into the average marketplace with broad applications for reimbursement, Matloff believes.[2] As more competitors enter the testing marketplace, choices and costs will improve for consumers, she explained. **EBO**

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2. http://www.onclive.com/onclive-tv/Ellen-Matloff-on-the-Supreme-Court-Gene-Patenting-Decision/

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

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Important Safety Information

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

Kyprolis™ (carfilzomib) for Injection

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

ONYX PHARMACEUTICALS

Kyprolis™ (carfilzomib) for Injection

KYPROLIS™ (carfilzomib) for Injection

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

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

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

Table 1: KYPROLIS Dosage Regimen for Patients with Multiple Myeloma

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

[a]If previous cycle dosage is tolerated.

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

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

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

(continued)

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

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

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

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

Table 3: Stability of Reconstituted KYPROLIS

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

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

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

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

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

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

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

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

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

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0.
[b]One event was Grade 5 severity.

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

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

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

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

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

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

ONYX PHARMACEUTICALS

Manufactured for: Onyx Pharmaceuticals, Inc., 249 East Grand Avenue, South San Francisco, CA 94080
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Early Results Robust for New Immunotherapy Agent

Anita T. Shaffer

An antibody that targets the programmed death ligand 1 (PD-L1) to unleash the body's immune system has demonstrated a 21% response rate in a phase I study of patients with multiple solid tumors, setting the stage for an advance in immunotherapy with broad implications for treatment.

MPDL3280A produced durable responses with no dose-limiting toxicities and a favorable adverse-event profile in heavily pretreated patients, according to Roy S. Herbst, MD, PhD, a professor of Medicine at Yale Cancer Center and chief of Medical Oncology at Smilow Cancer Hospital at Yale-New Haven in Connecticut.

"This therapy has the potential to be used in almost every tumor type," Herbst said in an interview. "It's just the tip of the iceberg so far. We're still figuring out exactly what the right biomarker is going to be to predict the most responsive population."

Herbst previewed the findings during a press conference held in advance of the 2013 ASCO Annual Meeting.

In the study, MPDL3280A was administered intravenously every 3 weeks to patients with metastatic tumor types including non–small cell lung cancer (NSCLC), melanoma, colorectal cancer, gastric cancer, and renal cell carcinoma. Responses were assessed with computed tomography scans every 6 weeks for 6 months, and then every 12 weeks.

In all, 29 of 140 evaluable patients (21%) exhibited tumor shrinkage according to RECIST criteria, with the highest overall responses in patients with NSCLC and melanoma. Of the 29 responders, 26 patients continued responding as of their last assessment. Responders were on the study from 3 months to more than 15 months.

In a biomarker analysis, responses were better among patients with higher levels of PD-L1 expression. The response rate among PD-L1-positive patients was 36% (13 of 36 patients), compared with 13% (9 of 67 patients) who were PD-L1-negative.

The role that PD-L1 expression might play as a biomarker is still being explored, Herbst said. Methods of measuring the protein, the nature of the tumor samples used to analyze its expression, and the levels that would predict a response to therapy are among the questions that remain unanswered.

For the safety analysis, results were available for 171 patients. A total of 43% of patients experienced grade 3/4 adverse events (AEs), most commonly hyperglycemia (5%), fatigue (4%), and increased alanine aminotransferase levels (3%). However, investigators determined that 13% of the grade 3/4 AEs were attributable to the drug, and there were no treatment-related deaths, Herbst said.

Moreover, only 2% of the participants (4 patients) experienced grade 3/4 AEs that were deemed to be immune-related, and only 1 patient discontinued treatment because of an immune-related AE.

"We didn't see any high-grade pneumonitis, which makes us feel very optimistic that this drug, because it's hitting only the PD-L1, is probably sparing some of the mechanisms that would allow for the lung to become inflamed," Herbst said in the interview. "We saw a couple of episodes of hepatitis and liver inflammation, but really, it's a very mild toxicity profile."

Findings Generate Excitement

MPDL3280A is the latest example of the checkpoint blockade anticancer strategy pioneered with the development of ipilimumab (Yervoy), which unlocks the power of the immune system by targeting CTLA-4. The US Food and Drug Administration approved the melanoma drug in 2011.

One of the highlights of the ASCO meeting last year was research into BMS-936558, now called nivolumab, which targets PD-1. Research into the agent was also presented at this year's meeting.

Herbst said the efficacy demonstrated thus far in attacking PD-L1 and other immune checkpoints "gives us the opportunity to open up a whole new avenue of therapy in cancer."

Tumor cells express PD-L1, which in turn binds to the T-cell receptors PD-1 and B7.1, Herbst said. "As long as there's PD-L1 on the surface of the tumor, the T cell PD-1 sees it as a friend," he said. "It is cloaked and it doesn't recognize the tumor as a foreign body and it doesn't kill it. But as soon as that PD-L1 goes away—by blocking it with an antibody—the tumor becomes visible, the target can be lit up, you go after it, and the T cell attacks and kills it."

Herbst said the therapeutic strategy could apply to a variety of cancers. "Any tumor type that has mutations is going to have the potential to be immunogenic and to work in this way to activate the immune system," he said, adding that "a lot of patients don't have a driver mutation that's easily targetable."

Since MPDL3280A has been engineered for enhanced safety, the agent could potentially be combined effectively with targeted therapies or with chemotherapy, Herbst noted. "The ability to combine this is going to be extraordinary," he said.

The MPDL3280A study is continuing with an expanded cohort of patients with a larger range of solid tumors and blood cancers; more than 275 patients have been enrolled, according to an ASCO press release.

Genentech, which is developing the drug, also is investigating MPDL3280A in separate phase I trials in combination with vemurafenib (Zelboraf) in patients with *BRAF* V600 mutation-positive metastatic melanoma and in addition to bevacizumab (Avastin) with or without chemotherapy in advanced solid tumors, as well as in a phase II study as monotherapy in PD-L1-positive locally advanced or metastatic NSCLC. **EBO**

Reference

1. Herbst RS, Gordon MS, Fine GD, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. *J Clin Oncol.* 2013;31(suppl; abstr 3000).

More Genetic Screening Needed for African-American Breast Cancer Patients

Lauren M. Green

One in 5 African-American women with breast cancer carries an abnormality in at least 1 gene associated with breast cancer susceptibility, according to results of a genomic profiling study by researchers at The University of Chicago, suggesting a need for increased genetic screening among a population group which previously has been understudied.

The research represents the first comprehensive examination of all known breast cancer susceptibility gene variations among African-American women, a group disproportionately affected by early onset and triple-negative breast cancer, a difference researchers have hypothesized may have a genetic component. However, prior studies have focused on *BRCA1/2* gene mutations rather than on all of the 18 inherited clearly damaging mutations currently known to be associated with an increased risk of breast cancer. Results of the study were announced at a press briefing during the 2013 ASCO Annual Meeting.

Overall breast cancer survival is worse among African-American women than it is for white women, and the gap continues to widen, noted the study's lead author, Jane E. Churpek, MD, assistant professor of medicine. "For those of us

here in Chicago, [this study] is particularly relevant, because we have one of the worst disparities in the country." The incidence of advanced breast cancer also is on the rise among young women, especially young African-American women, she added.

For the study, researchers analyzed DNA from 249 unrelated African-American women at The University of Chicago's Cancer Risk Clinic, using the targeted genomic capture and next-generation sequencing assay known as BROCA. This approach allows investigators to look at multiple genes at once and identify multiple types of mutations in those genes all at the same time, Churpek explained. The average age of the women included in the study was 43 years.

The researchers found that 22% of these patients (n = 56) inherited a clearly damaging mutation, 79% of which were *BRCA1* (n = 26) or *BRCA2* (n = 20). Investigators also found mutations in other genes with defined cancer risks, including *ATM* (n = 5), *CHEK2* (n = 3), *PALB2* (n = 3), and *PTEN* (n = 1). Almost all of the identified gene mutations were different, noted Churpek, which has important implications for genetic testing programs.

Jane E. Churpek, MD

"For some populations, we can use tests which look at only a few sites in a few genes, and we can identify the majority of mutations, but that technique will not work for this population with such great genetic diversity."

The researchers also looked at how these mutations were distributed according to personal and tumor characteristics. Damaging mutations were carried by 30% of women with a family history of breast or ovarian cancer, 30% of those with triple-negative breast cancer, and 27% of women who were young (aged ≤45 years) at diagnosis. Churpek added that even among those patients with no family history of breast or ovarian cancer, over 10% still carried a mutation, which, she stressed, "reminds us that family history is not the only criterion that we should think of."

"This work highlights the critical role of improved awareness and access to genetic counseling and testing services for *all* women, especially African-American women, who have unfortunately not utilized these services well in the past," said Churpek.

Demonstrating the cost-effectiveness and efficiency of next-generation sequencing assays—which allow for the comprehensive screening of multiple genes from multiple people in 1 test in a single visit—represents another important aspect of the study, added Churpek.

"These tools will allow us to identify who's at risk before they develop cancer, so we can begin to focus on prevention and eventually impact public health," she concluded. **EBO**

Reference

1. Churpek JE, Walsh T, Zheng Y, et al. Inherited mutations in breast cancer genes in African American breast cancer patients revealed by targeted genomic capture and next-generation sequencing. *J Clin Oncol*. 2013;31(suppl; abstr CRA1501).

More Evidence for 10 Years of Tamoxifen in ER+ Breast Cancer

Anita T. Shaffer

A British study has confirmed that 10 years of adjuvant tamoxifen substantially reduces late breast cancer recurrence and mortality among women with estrogen receptor (ER)-positive disease, supplying what investigators believe is the final piece of evidence supporting long-term use of the endocrine therapy.

The randomized, phase III aTTom study helps settle the question of whether 10 years of tamoxifen provides a benefit versus the more standard 5 years, said lead author Richard G. Gray, MA, MSc, discussing the findings at the 2013 ASCO Annual Meeting. The research was featured at a press conference and during the plenary session.

"There has been quite a remarkable improvement in the benefits of tamoxifen," said Gray, a professor of Medical Statistics at the University of Oxford in the United Kingdom, during his presentation. "What is really impressive is the effect on breast cancer mortality."

Gray said prior research has shown that 5 years of tamoxifen reduces breast cancer recurrence and mortality by approximately one-third over a 10- to 15-year period following diagnosis.

The benefits of longer treatment emerge later on, with reductions in recurrence starting to unfold after year 7 and reductions in mortality becoming evident after year 9, Gray indicated. He said the continued use of tamoxifen resulted in an additional 24% reduction in mortality after year 10.

"So, 10 years of tamoxifen compared to no tamoxifen reduces breast cancer mortality by a third in the first decade and a half in the second decade," he said.

The results of the aTTom study mirror those of the international ATLAS trial, which Gray presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium last December. Together, the study results "provide proof beyond reasonable doubt" about the benefits of continuing tamoxifen treatment, Gray said.

In the aTTom trial, 6953 women with breast cancer who had been taking tamoxifen for 5 years were randomized to continue receiving tamoxifen for another 5 years or stop taking the drug.

With follow-up of more than 10 years, there were 580 recurrences among women who had taken tamoxifen for 10 years, compared with 672 recurrences in the shorter-term treatment arm (*P* = .003).

Moreover, there were 392 breast cancer deaths after recurrence among participants who had taken the drug for a decade, compared with 443 deaths among those in the 5-year arm (*P* = .05).

Richard G. Gray, MA, MSc

When the results of the aTTom study and the ATLAS trial, which included 6846 women, are combined, the statistical significance of the benefits of longer tamoxifen administration are enhanced, with improvement in recurrence rates (*P* <.0001), breast cancer mortality (*P* = .002), and overall survival (*P* = .005), according to the aTTom abstract.

The disadvantages of taking tamoxifen for 10 years may include continuing menopausal symptoms such as night sweats and hot flashes, and rare adverse events such as an increased risk of endometrial cancer. In the aTTom trial, there were 102 cases and 37 deaths (1.1%) attributed to endometrial cancer in the 10-year tamoxifen arm, compared with 45 cases and 20 deaths (0.6%) in the 5-year group.

In the United States, the trial results likely will change the standard of care for women who are premenopausal at diagnosis to include 10 years of tamoxifen, said Sylvia Adams, MD, an associate professor at New York University School of Medicine who provided commentary on the study during the press conference. US women who are postmenopausal at diagnosis typically receive an aromatase inhibitor as adjuvant treatment but they may now consider incorporating extended tamoxifen into their treatment plan, Adams said. **EBO**

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THE AMERICAN JOURNAL OF MANAGED CARE

Predicting Treatment Outcomes in Older Adults With AML

Heidi D. Klepin, MD, MS

Older adults represent the majority of the more than 1.5 million people diagnosed with cancer each year. Unfortunately, significantly fewer older adults are enrolled on clinical trials, resulting in limited information regarding the risks and benefits of standard cancer therapies in the elderly.

While chemotherapy is offered increasingly as part of cancer treatment to older adults, it is known that chemotherapeutic side effects can increase significantly with age. These side effects may result in loss of independence and impaired quality of life. However, among older adults of the same chronologic age, an individual patient's ability to withstand the rigors of cancer treatment may differ widely. As a result, some older adults may tolerate and benefit from aggressive therapies similar to younger patients, while others may not.

Measurable patient characteristics that predict better tolerance have not been widely studied and are desperately needed in clinical practice to inform treatment decision-making and individualize care for each older adult. The field of geriatric oncology has developed in part to address this need. A major research focus within the field is to develop and test the utility of practical assessment strategies that predict tolerance and benefit to standard therapies.

Nowhere is the uncertainty regarding optional treatment for older adults more prominent than in the setting of acute myelogenous leukemia (AML). Due to the morbidity of the disease and intensity of treatment, AML represents one of the most dramatic examples of age-related outcome disparity in oncology. Older adults represent more than half of new cases of AML and experience significantly inferior outcomes with higher rates of treatment-associated morbidity and mortality and lower overall survival. However, clinical trials have shown repeatedly that selected older adults can tolerate intensive therapy and experience long-term survival when treated in a similar fashion to middle-aged adults. The difficulty is identifying those patients who are likely to benefit from intensive treatments at the time of diagnosis.

Treatment recommendations for older adults range widely and are often based to a larger extent on chronologic age. Research focused on identifying those older adults more likely to benefit from treatment has primarily focused on age-related alterations in tumor biology. Few studies have evaluated patient-specific characteristics

such as comorbid conditions, functional status, and cognitive status, all of which may be equally important in determining treatment tolerance.

To address this issue, we designed a study focused specifically on older adults with AML to test the utility of bedside geriatric assessment in predicting treatment outcomes. This study drew on the strengths of Wake Forest Baptist Health as a leukemia referral center, with robust geriatric and cancer research programs. In this observational study of 74 older adults who were treated intensively for their AML, we investigated the predictive value of a bedside geriatric assessment on overall survival. The geriatric assessment was composed of several brief questionnaires and physical performance tests, which were designed to measure physical function by self-report and objective evaluation, cognition, mood (depression and distress), and comorbidity.

We were particularly interested in the utility of objective physical function testing, which minimizes biases associated with self-report and allows for standardization of measurements. The physical performance measures used included the short physical performance battery (a brief 4-meter walk, repeated chair stands, and balance testing) and grip strength. The entire assessment was administered in approximately 30 to 40 minutes by a nurse prior to initiation of intensive chemotherapy.

The primary outcome of the study was overall survival. After adjusting for clinical and biological factors known to be associated with survival in older patients with AML, we found that both impairment on the cognition screen and impaired objectively measured physical performance were independently associated with worse survival in this cohort.

This is the first study to evaluate the role of cognition or physical performance in this setting. It is important to note that all patients enrolled on this study were already highly selected and deemed fit for intensive therapy by standard oncology assessment strategies. In this setting, assessments of cognition and physical performance were able to detect vulnerability that might otherwise be undetected and yet is clinically significant.

Multisite studies to validate the utility of geriatric assessment in the setting of therapy for AML are ongoing in the Alliance cooperative group. If validated, simple assessment measures of physical function and/or cognition may be used to help further individualize treatment decision making for older adults in clinical practice. Identifying characteristics that predict vulnerability to excessive toxicity may inform future clinical trial design by facilitating the development of treatment strategies specifically for vulnerable or frail older adults. Finally, this research may inform interventions to address vulnerability.

Building upon our observational study that showed the prognostic significance of lower physical performance at diagnosis, we have developed a physical activity intervention to minimize functional decline associated with intensive therapy. The goal of this work is to develop active strategies to prevent functional decline during treatment that will maximize treatment benefits and quality of life. **EBO**

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Optimal Paclitaxel Schedule Identified for Early-Stage Breast Cancer

Ben Leach

Low-dose weekly paclitaxel is as effective as and has fewer side effects than the standard biweekly schedule for patients with early-stage breast cancer, according to the results of a phase III study presented at the 2013 ASCO Annual Meeting.

G. Thomas Budd, MD

Paclitaxel is typically prescribed in either weekly or biweekly regimens. This is the first study to formally compare the 2 dosing schedules. The low-dose weekly administration of the chemotherapy agent paclitaxel resulted in equal disease-free survival (DFS) in patients with early-stage breast cancer when compared with biweekly administration of the drug, and although each dosing regimen resulted in a different set of side effects, the weekly dosing schedule appeared to offer a slightly more favorable side-effect profile.

"It's important to give these drugs in an optimal way," said G. Thomas Budd, MD, a medical oncologist at the Cleveland Clinic in Cleveland, Ohio, and lead author of the study. Budd noted that paclitaxel used to be given in higher doses every 3 weeks in the treatment of breast cancer until studies showed that the weekly and biweekly schedules in this study yielded superior results.

In this phase III trial, 3294 patients with node-positive or high-risk node-negative operable breast cancer first received treatment with one of 3 different regimens of doxorubicin and cyclophosphamide, after which they were randomized to receive either a low-dose regimen of paclitaxel weekly for 12 weeks or a standard-dose regimen of paclitaxel every 2 weeks for 12 weeks with pegfilgrastim support.

As of April 2013, DFS was essentially the same with both schedules of paclitaxel (hazard ratio = 1.05; 95% confidence interval, 0.89-1.25).

"It appears from these data that either way of giving paclitaxel produces a similar outcome," Budd said. "An investigator and a patient or a doctor and a patient could choose either one of these schedules."

The rate of any grade 3/4 toxicity was similar across the 2 arms, occurring in 36% of patients receiving the biweekly regimen and 35% of patients receiving the weekly regimen. However, researchers found that the different dosing schedules were characterized by different types of side effects of different severities. Allergic reactions were more common in the biweekly dose (14%) compared with the lower dose (6%), as were symptoms of bone and muscle pain (11% vs 3%, respectively). Neurologic toxicity was also more frequent in the biweekly dose of paclitaxel compared with the low-dose regimen (17% vs 10%, respectively), but Budd noted that patients received 6 cycles of the biweekly regimen instead of the standard four cycles for the purposes of scientific comparison, which may have slightly affected the frequency of these side effects.

The rate of hematologic toxicity was higher in the weekly dose arm (17%) than the biweekly dose arm (6%), as was the rate of leukopenia (6% vs 1%, respectively) and neutrophils (11% vs 2%, respectively). However, the rate of neutropenic fever was low in both groups (0.4% vs 0.1%, respectively) and the difference was not statistically significant ($P = .29$). Budd explained that the higher rates of hematologic toxicity in the weekly schedule could have been a result of ascertainment bias, since patients had toxicities measured on a weekly basis rather than the biweekly basis of the other study arm.

"In this study, the weekly schedule seemed to be less toxic for most patients," Budd said. **EBO**

Reference

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Pazopanib Maintenance Therapy Delays Relapse of Advanced Ovarian Cancer

Beth Fand Incollingo

An oral targeted drug already approved by the US Food and Drug Administration for the treatment of kidney cancer and soft tissue sarcoma has been found to extend disease-free survival in women with advanced ovarian cancer, according to study results presented at the 2013 ASCO Annual Meeting.

The phase III, randomized, multicenter clinical trial (AGO-OVAR16) showed that pazopanib (Votrient), following initial successful chemotherapy, extended disease-free survival by an average of 5.6 months compared with a placebo in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC).

The goal of treatment with pazopanib would be to maintain the successful but typically short-lived response experienced by these patients after initial treatment, said the study's lead author, Andreas du Bois, MD, PhD, a professor of Gynecologic Oncology at Kliniken Essen Mitte in Essen, Germany. Since there is no test available to predict a patient's risk for relapse, a maintenance therapy such as this one would be used for most patients in this population, experts at the ASCO meeting noted.

If approved in this setting, pazopanib would be the first maintenance therapy for the treatment of ovarian cancer in the United States, although bevacizumab (Avastin) is registered for use concurrently with chemotherapy and subsequently as maintenance therapy in Europe.

"Our findings show that we finally have a drug that can maintain control over ovarian cancer growth achieved through initial treatments," du Bois said. "If pazopanib is approved for ovarian cancer, many patients will experience longer disease-free and chemotherapy-free periods. During this time, the patient keeps control over the disease instead of the disease having control over the patient's life."

Pazopanib is an oral, multikinase inhibitor of VEGFR-1, -2, -3, PDGFR-a (alpha) and -ß, and c-Kit that blocks several targets involved in tumor angiogenesis, which "plays a major role" in AEOC, du Bois said.

Ovarian cancer is the fifth-leading cause of cancer death among women in developed countries, and has the highest mortality risk among all gynecological tumors. At the time of diagnosis, 70% of patients already have advanced disease, which is associated with a cure rate of only 20% to 25%, according to ASCO.

While 70% to 85% of patients are free of their tumors after initial treatment with surgery and chemotherapy, three-fourths of them experience recurrences, and half of those recurrences take place within the first year, du Bois said. Such patients typically live 2 to 4 years from the time of diagnosis, and can receive up to 5 lines of treatment during the course of their disease, he said.

The study was designed to evaluate the efficacy, safety, and tolerability of pazopanib maintenance therapy in patients who had not progressed after first-line platinum-taxane chemotherapy for AEOC, with a primary end point of progression-free survival (PFS). Secondary end points included overall survival, safety, and quality of life.

In the study, 940 patients, most of whom had stage III/IV AEOC (91%), were randomized 1:1 to receive either pazopanib or placebo daily for 24 months. All patients had prior surgery and 5 or more rounds of chemotherapy that prevented the disease from worsening.

Patients in the pazopanib arm had a prolonged PFS vs placebo (HR = 0.766; 95% confidence interval, 0.64-0.91; *P* = .0021; median 17.9 vs 12.3 months, respectively). The first interim analysis for overall survival (189 patients) showed no difference between arms, but those data will not be considered mature until it includes 551 events, du Bois noted.

Andreas du Bois, MD, PhD

As compared with a placebo, pazopanib treatment was associated with a higher incidence of adverse events (AEs) and serious AEs (26% vs 11%), several of them class-specific, including elevated liver enzymes. The most common were hypertension, diarrhea, nausea, headache, fatigue, and neutropenia, du Bois said. Fatal AEs were reported in three patients on pazopanib and one patient on placebo.

An immediate goal for this research is to combine pazopanib with other targeted drugs and personalize therapy according to patient and tumor characteristics, according to an ASCO press release.

"Relapses remain all too common for women with advanced ovarian cancer. This large trial shows us that targeting multiple molecular cancer drivers can have a substantial impact on this cancer's ability to grow, giving our patients significantly longer time before relapse. This study offers a real-world example of how the precision medicine era of cancer research is paying off in areas where no alternate approved drugs exist," said Carol Aghajanian, MD, ASCO spokesperson and gynecologic cancers expert and chief of Gynecologic Medical Oncology Service at Memorial Sloan-Kettering Cancer Center in New York City.

While bevacizumab (Avastin) is approved in Europe as a maintenance therapy for these diseases, it was studied in combination with chemotherapy, and then as a continuation therapy, which "was not a pure maintenance therapy setting. We don't know which part of the bevacizumab trial [sparked] the efficacy," du Bois said. "This differs from the population we have, since ours had successful primary treatment and 85% had no residual tumors."

The study of pazopanib—along with previous unsuccessful attempts to combine it with chemotherapy in this population—suggests that the drug will be best used as maintenance therapy in this population, du Bois said.

Future studies, he said, should address the optimal sequencing of pazopanib and chemotherapy. **EBO**

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Studies Highlight Newly Approved and Novel Multiple Myeloma Treatments

Barbara L. Jones

Researchers highlighted the latest developments in the treatment of multiple myeloma at the 2013 ASCO Annual Meeting. Noteworthy abstracts included updated data on pomalidomide (Pomalyst), which the US Food and Drug Administration (FDA) recently approved, as well as research involving the promising novel agents daratumumab and elotuzumab.

New Standard of Care in Relapsed/Refractory MM

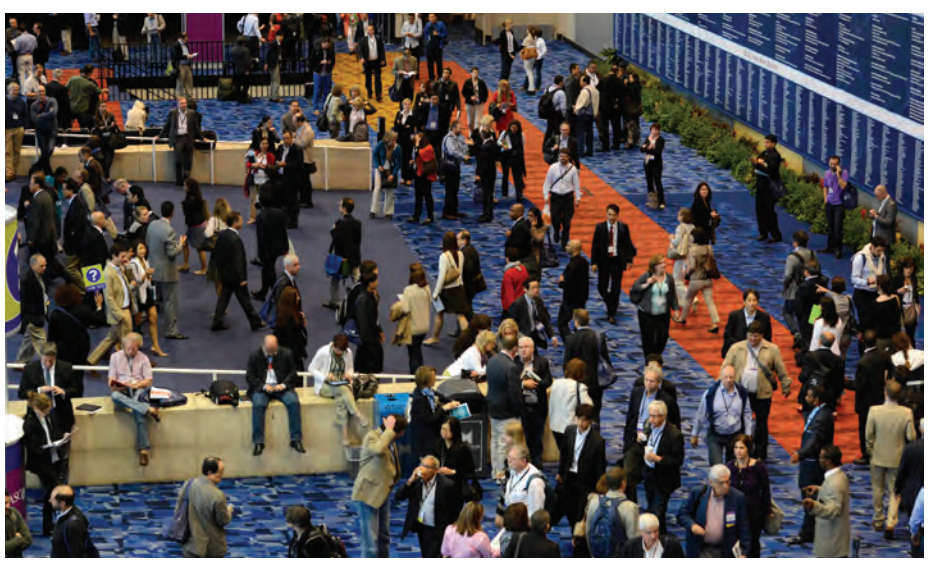
Pomalidomide plus low-dose dexamethasone "should become the standard of care for patients with relapsed/refractory multiple myeloma (MM) after treatment with lenalidomide and bortezomib," said Katja C. Weisel, MD, associate professor at University Hospital Tuebingen in Germany, reflecting the views of an international group of investigators taking part in the large MM-003 trial.[1]

The phase III MM-003 study enrolled 455 patients with relapsed or refractory MM. Eligible patients were refractory to their last prior therapy, had progressive disease during therapy or within 60 days, and had failed lenalidomide and bortezomib after two or more cycles of each therapy alone or in combination.

Patients were randomized 2:1 to a combination of pomalidomide plus low-dose dexamethasone (n = 302) or to high-dose dexamethasone (n = 153). At a median follow-up of 4 months, when the primary analysis was performed, patients receiving the combination of pomalidomide plus low-dose dexamethasone had significantly longer median progression-free survival (PFS), at 3.6 versus 1.8 months (hazard ratio [HR] = 0.45; *P* <.001) and overall survival (OS; not reached vs 7.8 months; HR = 0.53; *P* <.001) compared with patients receiving high-dose dexamethasone. The observed OS benefit included 29% of patients who received pomalidomide after experiencing progressive disease on high-dose dexamethasone.

Weisel reported data from an updated analysis after a median follow-up of 10 months. At this time, PFS and OS continued to favor treatment with pomalidomide plus low-dose dexamethasone, with median PFS of 4 versus 1.9 months (HR = 0.48; *P* <.001) and median OS of 12.7 versus 8.1 months (HR = 0.74; *P* = .028).

The investigator-assessed overall response rate for patients in the pomalidomide arm was 31% versus 10% in the high-dose dexamethasone arm (*P*



<.001), and 24% versus 3% for patients who were randomized 6 months or more after enrollment (*P* <.001).

The most frequent grade 3/4 adverse event for the pomalidomide combination was neutropenia (48%). Commenting on this rate of neutropenia, Weisel noted that there were only a few febrile complications.


Katja C. Weisel, MD

On February 8, 2013, the FDA approved oral pomalidomide for the treatment of patients with MM who have received at least 2 prior therapies, including lenalidomide and bortezomib, and who have had disease progression on or within 60 days of completion of the last therapy.

CD38 Monoclonal Antibody Yields "Unprecedented" Early-Stage Data

The investigational monoclonal antibody (mAb) daratumumab targets the CD38 molecule, which is highly expressed on the surface of multiple myeloma (MM) cells. Daratumumab has been shown to have broad-spectrum cytotoxic activity; it acts by mediating killing of CD38-expressing tumor cells via antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis.

In a phase I/II dose-escalation study reported by Henk Lokhorst, MD, PhD, from UMC Utrecht, The Netherlands, for an international group of researchers at ASCO 2013, the performance of daratumumab in patients with relapsed/refractory MM was described as "unprecedented for a single-agent mAb treatment of multiple myeloma."[2]

In early May, the FDA granted Breakthrough Therapy Designation for daratumumab for the treatment of patients with MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or for patients who are double-refractory to both classes of drugs.

Following on previously published safety and efficacy data, an international group of researchers reported finalized part 1 and preliminary safety data from an ongoing part 2 of the study, which enrolled patients 18 years and older with MM that was relapsed or refractory to at least 2 prior lines of therapy. Patients must also have been ineligible for transplant.


Sagar Lonial, MD

At the ≥4-mg/kg dosage (n = 12), daratumumab induced a marked reduction in paraprotein and bone marrow plasma cells in the group of heavily pretreated patients. In addition, in patients receiving the ≥4-mg/kg dosage, 5 partial responses and 3 minor responses were observed; 7 of these patients had a 50% to 100% concomitant reduction in bone marrow plasma cells. Median PFS in the ≥4-mg/kg dosage group was not reached by a data cutoff of 3.8 months.

No antidrug antibodies were detected among enrolled patients. The most common reported adverse events were infusionrelated and occurred predominantly during the first full infusion. A total of 44% of patients across all dosage groups had infusion-related events of grade 1 to 3. Other adverse events were anemia (n = 1), thrombocytopenia (n = 1), bronchospasm (n = 2), cytokine release (n = 1), and AST increase (n = 1).

Latest Results Promising for Elotuzumab Combo

The combination of the humanized anti-CS1 monoclonal antibody (mAb) elotuzumab plus lenalidomide/dexamethasone was generally well tolerated and resulted in a high objective response rate and encouraging PFS in patients with relapsed/refractory multiple myeloma (MM), according to Sagar Lonial, MD, Winship Cancer Institute of Emory University, Atlanta, Georgia, in an update of phase II and phase I/II long-term safety results.[3] Lonial reported these findings for a large international group of investigators at ASCO 2013.

Elotuzumab is a humanized anti-CS1 mAb that enhances natural killer-cell mediated, antibody-dependent cellular toxicity of CS1-expressing MM cells.

The study included a dose-finding phase I cohort (N = 28) and a phase II cohort (N = 73), with patients treated until disease progression, unacceptable toxicity, or death. (Data for patients treated with 1 or more [phase I] or 1 to 3 [phase II] prior therapies who received elotuzumab plus lenalidomide/dexamethasone were previously published [*J Clin Oncol*. 2012;30(16):1953-1959; *Blood*. 2012;120(21):Abstr 202].

The objective response rate in the phase II cohort (median age, 63 years) was 84%: 92% with 10 mg/kg (n = 36) and 76% with 20 mg/kg (n = 37). At a median follow-up of 20.8 months, median PFS was not reached for the 10-mg/kg group and was 18.6 months for the 20-mg/kg group.

The most common treatment-emergent grade ≥3 adverse events were lymphopenia (19%), neutropenia (18%), thrombocytopenia (16%), and anemia (14%). In general, grade 3/4 adverse events that were emergent after 18 months were consistent with those reported during the initial 18 months. **EBO**

Reference

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2. Lokhorst HM, Plesner T, Gimsing P, et al. Phase I/II dose-escalation study of daratumumab in patients with relapsed or refractory multiple myeloma. *J Clin Oncol*. 2013;31(suppl; abstr 8512).

3. Lonial S, Jagannath S, Moreau P, et al. Phase (Ph) I/II study of elotuzumab (Elo) plus lenalidomide/dexamethasone (Len/dex) in relapsed/refractory multiple myeloma (RRMM): updated ph II results and ph I/II long-term safety. *J Clin Oncol*. 2013;31(suppl; abstr 8542).

Bevacizumab Aids Survival in Cervical Cancer

Jason M. Broderick

Bevacizumab (Avastin) combined with either of 2 chemotherapy backbones improved overall survival (OS) by 3.7 months versus chemotherapy alone in patients with advanced cervical cancer, according to data from the phase III GOG 240 study. The likely practice-changing results were presented at a press briefing at the 2013 ASCO Annual Meeting.

"This is the first time that an overall survival benefit [with a targeted drug] has been shown in cervical cancer. This is a paradigm shift—patients live longer and feel better," said moderator and ASCO spokesperson Jyoti D. Patel, MD, an oncologist at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois.

The standard of care for newly diagnosed cervical cancer is cisplatin plus paclitaxel, and some patients are cured when treated with radiation plus cisplatin-based chemotherapy. However, the treatment options are highly limited for those patients whose disease progresses. These patients often become resistant to cisplatin, and "Unlike some other solid cancers, cervical cancer doesn't really respond to different chemotherapies…so we need some new therapeutic options," said lead GOG 240 study author Krishnansu S. Tewari, MD, a professor of Obstetrics and Gynecology at the University of California, Irvine, who presented the results at the ASCO press conference.

Researchers decided to test the anti-angiogenic VEGF inhibitor bevacizumab in this setting because "angiogenesis is very active in cervical cancer," according to Tewari.

In the 4-armed GOG 240 trial, 452 women with recurrent or metastatic cervical cancer were randomized to 1 of 2 chemotherapy regimens alone or combined with 15 mg/kg of bevacizumab. The chemotherapy regimens were cisplatin (50 mg/m^2) plus paclitaxel (135-175 mg/m^2) and topotecan (0.75 mg/m^2 days 1-3) plus paclitaxel (175 mg/m^2 day 1). Treatment was adminis-

tered on 21-day cycles until complete response, unacceptable toxicity, or disease progression.

The researchers included the non-cisplatin chemotherapy arm with their analysis because of the resistance concern with repeated cisplatin treatment. Topotecan plus paclitaxel was selected because a phase II trial in this population showed that the regimen is active in this population.

Patient characteristics in the four GOG 240 study arms were comparable with regard to age, histology, performance status, previous use of platinum as a radiosensitizer, and recurrent, persistent, or advanced disease.

Overall, there was a significant improvement with the primary endpoint of OS for patients receiving bevacizumab. At a median follow-up of 20.8 months, OS with bevacizumab plus chemotherapy was 17.0 months versus 13.3 months with chemotherapy alone (hazard ratio = 0.71; 95% CI, 0.54-0.94; *P* = .0035). The survival rate did not vary significantly between the two chemotherapy arms.

Response rates (level of tumor shrinkage) were better for patients receiving bevacizumab: 48% versus 36%, respectively (*P* = .00807). Tewari said bevacizumab also improved progression-free survival (PFS), but did not present the PFS data at the press briefing.

Krishnansu S. Tewari, MD

We feel [these results] are clinically meaning in a population of patients that doesn't respond to chemotherapy very well," said Tewari.

Regarding toxicities, higher rates of grade 3-4 bleeding (5% vs 1%), thrombosis/embolism (9% vs 2%), and gastrointestinal fistula (3% vs 0%) were reported with combination bevacizumab treatment versus chemotherapy alone.

Additionally, there were four fatal adverse events in both the bevacizumab and non-bevacizumab treatment groups.

Discussing the toxicity profile, Tewari said, "We found no new toxicities associated with bevacizumab. The toxicities were similar to what had been previously reported [with bevacizumab treatment] in other types of cancers."

GOG 240 also used patient-reported outcomes to compare quality of life between the treatment groups and found little variance. "The [QoL] assessment indicates that the survival gains associated with bevacizumab did not come at a decrease in quality of life," said Tewari.

Regarding the next steps for the GOG 240 study, Tewari said that the manuscript for the study has been written and will soon be submitted for review and publication.

He said that he does not know the specific timeline for when Genentech, which manufactures bevacizumab, might submit an application to the FDA for a cervical cancer indication for bevacizumab. He did note, however, that it is likely that Genentech will begin communicating with the FDA soon about the potential to expand the drug's indication. **EBO**

Reference

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For Partners of HPV-Positive Throat Cancer Patients, Good News in Studies

Lauren M. Green

Patients with human papilloma virus–positive oropharyngeal cancer (HPV-OPC) and their spouses may find some reassurance in a recent study by researchers at the Johns Hopkins Bloomberg School of Health. The study found that partners are no more likely to be infected by HPV than the general population, and their risk of contracting HPV-OPC remains low.

Findings of this pilot study—the first large study to examine oral HPV infection among patients with HPV-OPC and their partners—were announced in a press briefing at the 2013 ASCO Annual Meeting.

The majority of oropharyngeal cancers in the United States are now caused by HPV, and the incidence of HPV-related oropharyngeal cancer is increasing significantly, noted the study's lead author, Gypsyamber D'Souza, PhD, MPH, MS, associate professor of Epidemiology at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. "Some of the patients with this diagnosis worry about oral HPV transmission and the cancer risk to their partners or spouses."

To better understand this possible increased risk, D'Souza and colleagues enrolled a total of 166 patients with HPV-OPC; 94 of them had spouses or long-term partners who were also enrolled in the study. DNA samples were collected from both groups, following administration of a 30-second mouth rinse and gargle. Samples were obtained at the time of diagnosis and 1 year later.

Median age of the HPV-OPC patients was 56 years; 89% were male, 92% were white, non-Hispanic, and 94% had performed oral sex. Their partners were predominantly female (94%) and white, non-Hispanic (92%), with a median age of 53 years. Patients were significantly more likely to have had >10 oral sex partners over their lifetime (39%), versus their spouses/partners (11%).

Samples were analyzed for the presence of 36 subtypes of HPV DNA, among them, the most prevalent type found in the majority of HPV-OPC cancers—HPV16. DNA is considered the "gold standard" for determining presence of HPV in the tumor, D'Souza explained. She noted that for individuals without cancer, examining exfoliated oral cells from the rinse/gargle samples is the best available option for measuring oral HPV infection, since there is currently no validated, US Food and Drug Administration-approved test.

Researchers found that nearly two-thirds of the cases (65%) had HPV DNA in their oral exfoliated cells, and a little over half (54%) of these cases had HPV16, said D'Souza. After 1 year and completion of treatment, analysis of the oral rinse samples from the HPV-OPC cases demonstrated that a "vast majority of these cases no longer had any HPV16 DNA detectable," she added.

The prevalence of HPV among the long-term female partners of patients was 5%, which is comparable to the 4% prevalence among women in the general population, based on previously published data. HPV16 was found in just 2.3% of female partners and in none of the small number of male partners. In addition, no precancers or cancers were detected in the 60 partners/spouses who underwent a visual oral exam.

"These findings provide assurance that prevalence of oral HPV infection is not increased among partners [of patients with HPV-OPC], and their risk of HPV-OPC remains low," said D'Souza. "Couples who have been together for several years have likely shared whatever infections they have, and no changes in their physical intimacy are needed."

D'Souza concluded her presentation by noting that while oral HPV infection remains common, "many individuals who become infected are able to clear these infections and not get cancer."

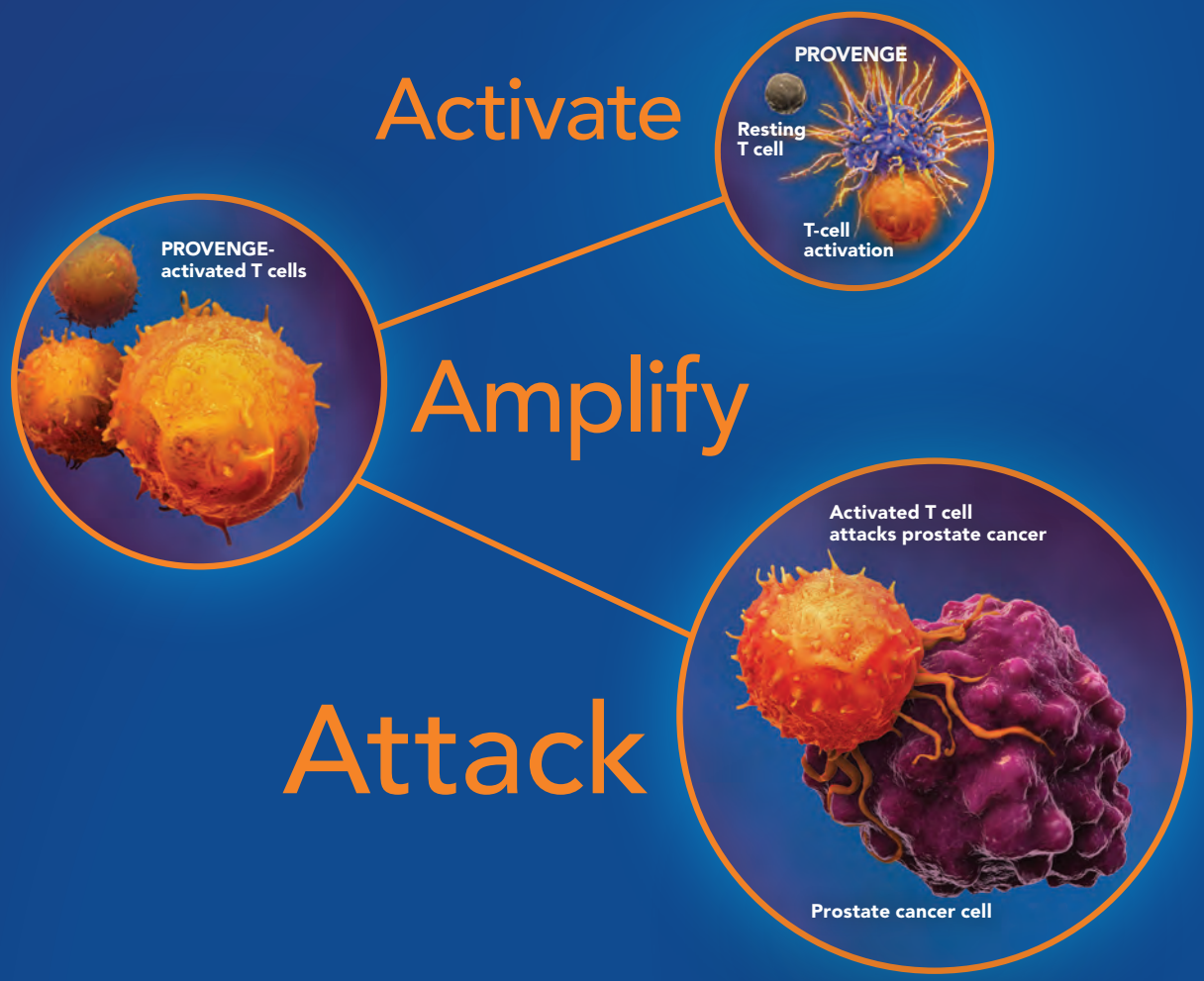
"HPV is responsible for thousands of cases of cancer of the oropharynx, cervix, and other sites every year," noted Gregory Masters, MD, ASCO spokesperson and moderator of the press briefing. "This study improves our understanding of HPV risk among the partners of patients with HPV-positive oropharyngeal cancers. I'm sure this news will provide long-awaited reassurance for patients, as well as their spouses and partners." **EBO**

Reference

1. D'Souza G, Gross ND, Pai SI, et al. Oral HPV infection in HPV-positive oropharyngeal cancer cases and their spouses. *J Clin Oncol.* 2013;31(suppl; abstr CRA6031).

In advanced prostate cancer

TREAT FIRST LINE WITH PROVENGE TO



EXTEND SURVIVAL

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

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

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

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

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

www.PROVENGE.com

PROVENGE®
(sipuleucel-T)

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

BRIEF SUMMARY – See full Prescribing Information for complete product information

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

(Table 1 continued on next page.)

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

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

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

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

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

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

Dendreon Corporation
Seattle, Washington 98101

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

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(sipuleucel-T)

Drug Shortages Persist in Wake of Surveys

Beth Fand Incollingo and Mary K. Caffrey

Headlines from the June meeting of the American Society of Clinical Oncologists (ASCO) in Chicago announced to the general public what oncologists and hematologists have known for more than 2 years: sporadic shortages of cancer drugs are forcing suboptimal treatment plans for patients, and government efforts have not filled the void.

Two months after 3 surveys were presented at the 49th Annual Meeting of ASCO, *Evidence-Based Oncology* asked both the US Food and Drug Administration (FDA) and Keerthi Gogineni, MD, MSHP, who presented one of the studies in Chicago, to offer updates on cancer drug shortages.

Gogineni, a medical oncologist in the Abramson Cancer Center and the Perelman School of Medicine in Philadelphia, was a co-author of the study conducted at the University of Pennsylvania.

While the FDA's Lisa Kubaska, PharmD, reports that the 2012 Food and Drug Safety and Innovation Act (FDASIA) is helping the agency identify shortages and find temporary solutions, such as importations of drugs, Gogineni states that some shortages remain, even though the FDA is "doing what it can."

"There are factors that contribute to drug shortages that the agency has limited control over," Gogineni said.

Kubaska and Gogineni agree the majority of shortages are due to quality control problems at several large manufacturing plants making drugs. Kubaska said preventing shortages is a "top priority," and that passage of FDASIA has enhanced the agency's ability to anticipate pending problems through an early notification system. But the FDA and physicians like Gogineni on the front lines view things differently.

Said Kubaska, "There has been 1 new shortage in 2013, Lomustine tablets, which was resolved through import of a drug with unapproved packaging until the approved package could be made available."

Gogineni said her own hospital "has had considerable difficulty acquiring this drug to treat patients with brain tumors. There is an ongoing attempt to obtain this drug by enabling NextSource Biotech to import the product but under a different trade name…Theoretically this should have made emergency supplies of the drug easier to obtain by July 2013, but practically speaking, this has not been the case."

What the Surveys Found

In the Penn study,[1] 94% of 214 oncologists and hematologists said their patients' treatment had been affected by drug shortages between March and September of 2012. Of those doctors reporting shortages, 83% said they had been unable to provide standard chemotherapy at some point during that time period, and 13% reported that patient enrollment or continuing participation in clinical trials had been compromised due to drug unavailability.

Two-thirds of the respondents work in community oncology settings.

A separate pair of surveys conducted by ASCO reported that members of the organization noticed only a slight easing of drug shortages between October 2012 and April 2013, but during the same period became increasingly concerned about the limited availability of treatments critical to supportive cancer care, such as antiemetics, pain medications, and basic IV fluids and electrolytes.

In the University of Pennsylvania survey, respondents said that the drugs most commonly in shortage were leucovorin, liposomal doxorubicin, 5-fluorouracil, bleomycin, and cytarabine. (According to Kubaska, the FDA arranged to have the first 2 temporarily imported to address the shortage.) These drugs are commonly used in the treatment of various forms of cancer, including gastrointestinal, blood, breast, ovarian, and testicular cancers. Cytarabine is particularly critical for curing certain forms of acute leukemia, ASCO stated.

Researchers noted that doctors adapted to such shortages in different ways, including switching treatment regimens (78% of doctors), substituting alternate drugs partway through therapy (77%), delaying treatment (43%), choosing among patients to determine which should receive the available supply of the chemotherapeutic agent (37%), omitting doses (29%), reducing doses (20%), and referring patients to another practice where drugs in shortage were available (17%). Most providers (70%) said they had no institutional guideline or committee to help make the difficult treatment modification decisions.

"We were surprised by the large number of cancer doctors that had to make changes in the way they care for patients due to drug shortages," Gogineni said in Chicago. "Unfortunately, cancer drug shortages will likely be a persistent issue. Doctors are adapting to this new reality as best as they can, but more uniform guidance is needed to ensure that modifications are made in the most educated and ethical way."

The research was supported, in part, by a Pfizer Medical and Academic Partnership Research Fellowship in Bioethics.

ASCO's 2012 and 2013 surveys of its members asked whether, in the previous 6 months, legislative and regulatory efforts to address drug shortages had been effective. A total of 390 and 462 doctors, respectively, responded.

Although the results from the second survey suggested that chemotherapy drug shortages may have eased very slightly, the changes were small, and practices were still faced with the need for drug substitutions. Moreover, respondents expressed growing concern over the shortage of supportive care drugs.

Keerthi Gogineni, MD, MSHP

In the more recent survey, 59% of responding physicians were aware of ongoing drug shortages in their own or colleagues' practices, versus 70% in the earlier survey.

Also in the 2013 survey, more than 40% of doctors said that drug shortages had not been resolved. Seventeen percent said the shortages were worse than in the fall of 2012, 16% responded that they were the same, and 9% that some shortages had improved while others had worsened.

Need for Substitutions Persists

"Quality cancer care also means providing patients with the right treatments at the right times, and we're learning today that cancer drug shortages are still interfering with that mission," said ASCO spokesperson Andrew D. Seidman, MD, an oncologist at Memorial Sloan-Kettering Cancer Center in New York City. "This ongoing crisis must not be forgotten—it demands urgent solutions from regulators, policy makers, and manufacturers today."

According to ASCO, generic drugs, especially common chemotherapies, have been most affected by shortages. In oncology, there are often no replacements for the standard agents that have been shown to improve survival, the organization reported, and when there are substitutes available, they are sometimes brandname drugs, which can be several-hundred-fold more expensive. This cost burden is shared by patients and institutions, as brandname drugs typically have higher copayments and out-of-pocket costs, ASCO stated.

In many cases, ASCO said, there is also a lack of clinical trial evidence to determine the appropriate dose for the substitute drug. In addition, according to a survey taken by the Institute for Safe Medication Practices,[2] mistakes are sometimes made in the formulations or strengths of drugs given as alternatives for medications in short supply.

Drug shortages have also spawned borrowing and hoarding among medical institutions, the sale of counterfeit drugs, and a gray market for medications in limited supply, experts have said.

"ASCO believes that there are likely numerous causes of drug shortages and will continue to call on Congress to convene a blue ribbon panel that includes providers, manufacturers, suppliers, FDA, and patients to develop comprehensive legislation to resolve these critical shortages," said ASCO Chief Medical Officer Richard L. Schilsky, MD. "The Government Accountability Office is also conducting a comprehensive investigation of the causes of the shortages, and we will be eager to learn its assessment when the report is published early next year."

Many Factors Behind Shortages

At last year's annual meeting of ASCO, Rear Admiral Sandra Kweder, MD, deputy director of the FDA's Office of New Drugs, blamed the shortages on manufacturing and quality problems and the plant closures that often result. Most shortages have involved sterile injectable drugs, she said, and as of last June, more than half of those were "due to product quality issues such as particulates, microbial contamination, impurities, and stability changes resulting in crystallization."

Shortages may also occur due to industry consolidation, increases in demand, and a lack of access to pharmaceutical ingredients, she said.

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Another option in short-acting G-CSF therapy

» FDA and EMA approved

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Indication

Tbo-filgrastim is a leukocyte growth factor indicated for reduction in 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.

Important Safety Information

Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue tbo-filgrastim and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving tbo-filgrastim.

Acute respiratory distress syndrome (ARDS) can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving tbo-filgrastim for ARDS. Discontinue tbo-filgrastim in patients with ARDS.

Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue tbo-filgrastim in patients with serious allergic reactions. Do not administer tbo-filgrastim to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

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 tbo-filgrastim in patients with sickle cell disease. Discontinue tbo-filgrastim in patients undergoing a sickle cell crisis.

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

The most common treatment-emergent adverse reaction that occurred in patients treated with tbo-filgrastim 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 Prescribing Information on adjacent page.

TEVA Oncology

Why does one plant shutdown prove so disruptive? In late July, Gogineni told *EBO* that there are a combination of underlying reasons. "There is little redundancy in the system," she said, and there is "a marked increase in new sterile injectable product applications without a concomitant increase in manufacturing capacity (which) has led firms to divert production to more expensive, branded agents."

The FDA, Gogineni explained, is authorized to address quality issues, but its ability to boost manufacturing capacity is quite limited—it can expedite reviews of "new" manufacturers. "It can take years for a manufacturer to increase capacity. There are few penalties for failing to supply critical drugs, and no incentive for companies to invest in 'excess' capacity. This is not something the FDA would have control over," she said.

Alongside the financial incentives to produce new drugs, Hagop Kantarjian, MD, a professor and chair of the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston, has blamed the shortages on the extremely low price of generics, which he said can't be raised to meet demand due to a Medicare physician reimbursement formula.

Under the recent government sequestration that slashed the budgets of many federal agencies, including the FDA, that formula became even more likely to hold down the prices of generic drugs, a dynamic that could further contribute to drug shortages, Schilsky said at the June 3rd press briefing.

The FDASIA, which became effective in October 2012, requires drug manufacturers to alert the FDA 6 months in advance about anticipated market withdrawals or drug-supply interruptions. The aim is to give the FDA time to step in with tactics such as helping to arrange for other companies to pick up the slack.

In the 6 months that followed the passage of the FDASIA, there was a 6-fold increase in early notifications from manufacturers, Commissioner Margaret Hamburg, MD, wrote on the FDA's website. In that 6 months, the FDA prevented 128 drug shortages and saw fewer occur—42 reported between January and May 2012, compared with 90 new shortages reported during that period in 2011, she stated.

"This data is a testament to how the FDA exercises flexibility and discretion in much of our work on drug shortages and the importance of strong collaboration and constant communication with industry, health professionals, and patients," Hamburg wrote.

Schilsky added that he is hopeful about another tenet of the FDASIA, which requires generic drug makers to contribute money intended to bolster the FDA's resources, so it can review generic drug applications more quickly and conduct swifter inspections of generic drug manufacturing facilities when questions about safety come up.

Based on anecdotal evidence, Schilsky said, he believes that similar shortages are ongoing in many European countries. **EBO**

References

1. Emanuel Z, Shuman K, Chinn D, Gogineni K. Impact of oncology drug shortages. Presented at: 49th Annual Meeting of the American Society of Clinical Oncology; May 31-June 4, 2013; Chicago, Illinois. Abstract CRA6510.

2. A shortage of everything except errors: harm associated with drug shortages. Institute for Safe Medication Practices website. http://www.ismp.org/newsletters/acutecare/showarticle.asp?id=20. Published April 19, 2012. Accessed June 3, 2013.

Inaugural "Giants of Cancer Care" Announced

Oncology Luminaries Selected by Peers for Prestigious National Honor

OncLive, a sister news portal to *Evidence-Based Oncology*, on July 26, 2013, unveiled the inaugural class of "Giants of Cancer Care." An advisory panel of eminent oncologists chose 12 honorees to be recognized for their remarkable achievements in research and/or clinical practice. The Giants of Cancer Care awards recognize and celebrate individuals who have achieved landmark success within the field of oncology.

The inaugural class of "Giants" was announced at a reception during the 14th International Lung Cancer Congress, hosted by Physicians' Education Resource, LLC, an affiliate of MJH Associates, the parent company of OncLive. Each of the winners will be individually profiled in a special edition of *OncologyLive* and prominently featured on OncLive.com.

MJH Associates Chairman and CEO Mike Hennessy said, "We're proud to honor these exemplary members of the oncology profession. These 'Giants' have dedicated their lives to improving the quality and quantity of life for cancer patients. Our enormous gratitude is the foundation of this program."

In evaluating criteria for selection to the inaugural class of Giants, the Advisory Panel considered "pioneers," characterized by individuals who have amassed a large body of work and have already accomplished their most notable contributions to oncology; and separately, "innovators," those who recently (within the past 10-15 years) have made a significant contribution to patient care, clinical trials, or translational research.

For more information, visit us online at giants.onclive.com. **EBO**

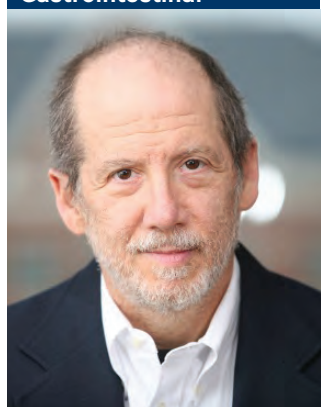
Giants OF Cancer Care™

Breast

Bernard Fisher, MD
University of Pittsburgh

Pioneer in our understanding of the biology and treatment of breast cancer

Gastrointestinal



Bert Vogelstein, MD
Johns Hopkins Medicine

Pioneer who discovered the molecular basis of colorectal cancer

Genetics

Elizabeth H. Blackburn, PhD
University of California, San Francisco

Innovator and Nobel Prize winner for her discoveries of the genetic composition and function of telomeres

Genitourinary

Lawrence H. Einhorn, MD
Indiana University

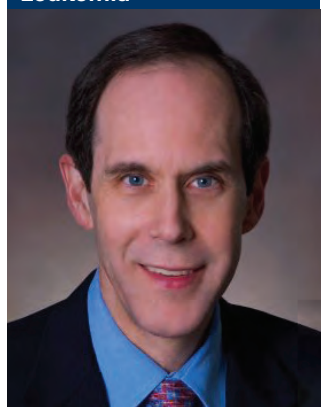
Pioneered the development of life-saving treatment for testicular cancer

Head & Neck

Everett E. Vokes, MD
University of Chicago

Innovator of concomitant chemoradiation therapy and curative treatment approaches for head and neck cancers

Leukemia



Brian J. Druker, MD
Oregon Health & Science University

Innovator of targeted therapies for chronic myeloid leukemia

Lung

Thomas J. Lynch, Jr, MD
Yale Cancer Center

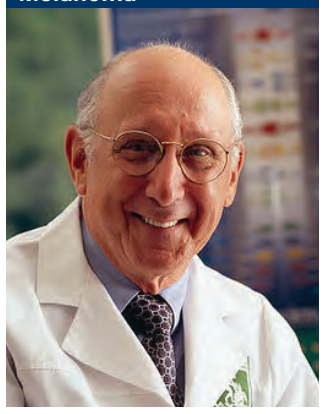
Pioneered the use of molecular testing for EGFR mutations in lung cancer

Lymphoma

Vincent T. DeVita, Jr, MD
Yale Cancer Center

Innovator of combination chemotherapy regimens for large-cell lymphomas

Melanoma



Steven A. Rosenberg, MD
National Cancer Institute

Pioneered the use of adoptive immunotherapy in melanoma

Myeloma

Robert A. Kyle, MD
Mayo Clinic

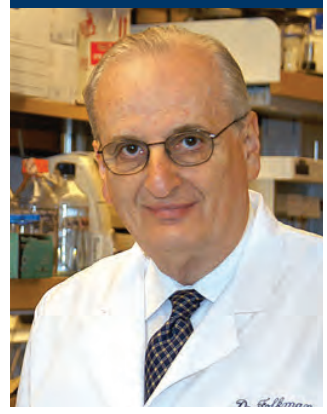
Pioneer and respected leader in myeloma research, treatment, and education

Prostate

Charles L. Sawyers, MD
Memorial Sloan-Kettering Cancer Center

Innovator of novel androgen-receptor inhibitor for treatment of advanced prostate cancer

Scientific Advances



Judah Folkman, MD (deceased)
Massachusetts General Hospital

Father of angiogenesis

Patient-Centered Oncology Care:

REAL-WORLD PERSPECTIVES

November 14-15, 2013

The Royal Sonesta Harbor Court | Baltimore

Join the nation's top oncology and managed care professionals as they discuss real-world opportunities and challenges facing payers, clinicians, patients, and other allied healthcare professionals in the ever-changing oncology landscape.

AGENDA

Keynote Session: How Does Oncology Fit Into the New ACO World?

Patient-Centered Oncology Care: Real-World Perspectives
- Oncology Practice in the Era of PCMHs and ACOs: Square Pegs or Round Holes?
- Where Do Major Cancer Centers Fit In: Focus on the Impact of Clinical Studies in Accountable Care
- Evaluating Episodes of Care in Oncology: The Impact of Payment Reform on Data Collection and Reporting
- Making the Pegs Fit: Implementation Case Studies

The Role of Companion Diagnostics in Targeted Treatments
- Where Do They Fit In? A Focus on OncoType DX
- Clinical Utility vs Cost vs Quality: Quantifying the Value of Personalization
- Diagnostic Preview: A Look Into the Future (Abstract Presentation)

Patient-Centered Oncology Care
- The Role of Consumerism in Deliverability of Care
- Implications of Healthcare Reform: "No" Will Be Heard
- End-of-Life Care: A Delicate Balance of Cost and Quality

Pharma/Payer Collaboration: A Focus on the Future (Panel Discussion)
- Where Does HEOR Fit in the Oncology Model? What Data Do Payers Want? If Pharma Provides, Will They Use It?
- Value-Based Pricing: The Role of Outcomes Data in Pricing Models
- The Impact of CER on Clinical Trial Design in Oncology

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Bruce Feinberg, DO
Cardinal Health Specialty Solutions

Cliff Goodman, PhD
The Lewin Group

Jeff Dunn, PhD
VRx

Kirby Eng, RPh
CVS Caremark

John Fox, MD, MHA
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Michael Chernew, PhD
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A. Mark Fendrick, MD
University of Michigan

Scott Ramsey, MD, PhD
Fred Hutchinson Cancer Research Center

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United Healthcare

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