THE CANCER LETTER

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AACR 2016

Biden Asks for Guidance in Leading Moonshot

By Conor Hale

"There is more brain power in this room than exists in many countries," said Vice President Joe Biden, addressing over 4,000 members of the American Association for Cancer Research, during a speech that turned personal at times, as he laid out several suggestions for accelerating progress.

As head of the federal government's cancer moonshot task force, the vice president listed recommendations he has received for reaching the initiative's goal, not a cure, but completion of a decade's worth of cancer research in five years. Recommendations include increasing research budgets across the federal government, making it easier to share data, removing paywalls around published research, and incentivizing verification of study results.

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Comparison with AstraZeneca Drug Hard to Ignore as ODAC Votes Down NSCLC Application from Clovis

By Paul Goldberg

A phase III trial will be needed to determine approvability of the Clovis Oncology Inc. agent rociletinib for the treatment of non-small cell lung cancer, the FDA Oncologic Drugs Advisory Committee recommended.

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Guest Editorial

30 Years after Chernobyl: Lessons Learned

By Robert Peter Gale

April 26 marks the 30th anniversary of the Chernobyl nuclear power facility accident in the former Soviet Union. Soon after the accident, I received a call from the Soviet ambassador to the U.S. on behalf of Mikhail Gorbachev asking me to come immediately to Moscow.

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Biden Talks Cancer Politics At AACR Annual Meeting

(Continued from page 1)

"Toward that end, last year, the 2016 budget, and working with Congress, we were able to increase funding by $2 billion for the National Institutes of Health. The largest increase in a decade," Biden said at the association's annual meeting April 20 in New Orleans.

The vice president told stories of how much encouragement he has received for initiative, both in Washington and internationally, and noted bipartisan support for making progress.

"Everywhere I go, when I talk about what is possible, it becomes clearer and clearer that there are areas of consensus among all of you. I had a very well-educated, bright grandfather… he would say, 'Joey, there are three kinds of politics: there's church politics, as in Roman Catholic; there's labor politics, as in unions; and there's politics. And they're difficult in that order.'

"I respectfully suggest that what I've learned of late is that there are four kinds of politics: cancer politics, church politics, union politics, and politics. And they're difficult in that order."

Biden said the White House is requesting another $800 million to support research activities across multiple federal departments as part of the anticancer effort.

"The president signed essentially what is an executive order giving me control over all the federal agencies and departments, from Veterans Affairs to the Department of Energy, because of their computing capacity. Departments you wouldn't think—well, you would—but most people wouldn't think had anything to do with a moonshot to end cancer as we know it."

Biden noted his admiration of researchers who stay committed to a daunting process of applying for federal grants, saying that researchers should be spending more time on science and less time preparing applications.

"We want to let scientists do science. There's an old cliché that too often grants are given for what you've already done, rather than what you're doing. You know," he said. "For example, the Prostate Cancer Foundation grant application, for those of you who engaged with prostate cancer research, is limited to 10 pages. You get an answer in 30 days. Why is it that it takes multiple submissions and more than a year to get an answer from us?

"It seems to me, we slow down our best young minds, by making them spend years and years in the lab before they can get their own grants. And when they do, they spend a third of their time writing a grant that takes months to be approved and awarded. It's like asking Derek Jeter to take several years off to sell bonds to build Yankee Stadium.

"I'm not joking when I say your dedication absolutely awes me. I really mean it. I really mean it. You've got really, really, really care. You've got to really want to save lives."

Biden said a researcher's publication history shouldn't determine whether he or she receive a grant, it should be the work they do, and that the results should be made publicly available as soon as possible:

"What you propose and how it helps patients, seems to me should be the basis of whether you continue to get the grant. And scores of your colleagues, scores, said make publications more readily available," he said. "Right now you work for years to come up with a significant breakthrough, and if you do, you get to publish a paper in one of the top journals. For anyone to get access to that publication they have to pay hundreds to thousands of dollars to subscribe to a single journal, and here's the kicker: the journal owns the data for a year. Your outfit does this."

After the research is done, the results need to be verified, Biden said.

"Verification is the core of science; even a lawyer like me knows that," he said. "And the way we verify is to replicate. That's how we know if a breakthrough actually works.

"Replicating published studies is not a rewarding career move…so why don't we give grants to people who replicate published studies to verify outcomes? We should incentivize verification.

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"All the characteristics of this system started years and years ago. It's the environment we all grew up in, studied in, worked in. And yes this system has produced enormous successes, but this is not the system, in my view, that will get us to our goal faster."

The vice president, along with his wife, Jill Biden, spoke of their family's personal fight with cancer, and the death of their son, Beau, last year.

"Jill and I didn't choose to become experts about cancer, but like everyone who has a family member that faces cancer, you tend to become—as my mother would say, a little bit of knowledge is a dangerous thing—you tend to learn as much as you can about the cancer your beloved family member is fighting, and that's what we did when our Beau was diagnosed.

"People said to me, why would you take on that job? I know government. I understood all aspects of it. I couldn't not after 42 years. I felt completely confident taking on an almost trillion-dollar spending program.

"But this is bigger, and I know so much less. Sometimes I find myself going to bed overwhelmed by—how can I meet my responsibility? I need your help. I need honest evaluations of the kind of changes that can be made."

This week, coinciding with the AACR's annual meeting, NCI launched an online platform for the research community and the public to submit ideas on national cancer moonshot efforts, at CancerResearchIdeas.cancer.gov. Submissions will be considered by the task force's blue ribbon panel.

Ideas can be submitted under the following categories: cancer clinical trials; data sharing; dissemination and population sciences; immunotherapy, combination therapy, and immunoprevention; pediatric cancer; tumor evolution and progression; and others. The ideas will be considered by the task force's working groups, and the panel plans to report its findings to the National Cancer Advisory Board later this summer.

"You are the very best we have," Biden said during his address.

"We need you badly to give me some guidance on how to make your job—not easier—but more likely to meet your ends."

A transcript of the vice president's remarks follows. An AACR webcast of his speech is available here.

The president, me, the whole White House, everyone that I work with in government, in both parties—if they were here, they'd be standing clapping for you. For all of you.

Dr. [Jose] Baselga, thank you for allowing me to be here, it's great to see you again. And thank you for leading the way supporting young investigators like Sophia [Lunt, of Michigan State University], and all the other cancer researchers.

Dr. [Douglas Lowy], I think, wasn't sure if it was a good thing or a bad thing, when he heard that I was in charge of the moonshot. He said oh my God what's this guy going to do?

I have a bad habit of never doubting that I mean what I say, and sometimes though I say all that I mean. Dr. Lowy is one of our great assets in the federal government, and I mean that sincerely, and I want to thank him for all the great work he's doing as head of the National Cancer Institute. Go ahead and clap for him, he deserves it.

It's an honor for Jill and me to be here today, and we wish we could ask each of you how you decided to devote your lives to cancer research. It's a life that you chose and it's obviously not an easy one.

Jill and I didn't choose to become experts about cancer, but like everyone who has a family member that faces cancer, you tend to become—as my mother would say, a little bit of knowledge is a dangerous thing—you tend to learn as much as you can about the cancer your beloved family member is fighting, and that's what we did when our Beau was diagnosed.

We had access to the best doctors in the world, and the more we talked to them, the more we understood that we are on the cusp of a real inflection point in the fight against cancer. I thought I was relatively well-informed, but I really didn't fully understand that immunotherapy was sort of a discipline "out there," ten years ago. I didn't fully understand that only in the last four to five years there has been increased interdisciplinary cooperation. Only recently have various disciplines been able to work together. As recently as five years ago, oncologists weren't working with immunologists, virologists, geneticists, chemical engineers, or biological engineers.

That's all changed. You've given humanity a sense of hope, and, I might add, expectation.

That's why when I announced my decision to not seek the nomination for president, and the president came out with me in the Rose Garden while I made that announcement, it was almost a wistful thought of mine; it wasn't a proposal, or a prepared initiative. I said I believe that we need a moonshot in this country to cure cancer. I said it is personal, and it's personal to so many, but I believe we can do this because there are so many breakthroughs just beyond the horizon in science and in medicine.

The things that are just about to happen, I believe

we can make them real if we make an absolute national commitment to end cancer as we know it. I went on to say that Democrats and Republicans share this passion to silence this disease. And I said if I could do anything, I would have wanted to be the president that ended cancer as we know it, because I think it's possible.

In a bitterly divided government—I served in the Senate a long, long time; I have been in federal government for a long time as a senator or a vice president—I have never quite seen a political situation as dysfunctional as today.

Some of you may know I have a reputation of being able to get along with both sides of the aisle, because I have enormous respect for the House and the Senate—but this may be the one subject, and one of the reasons I picked it, where there's absolute, unlimited, bipartisan support. One of the reasons why I thought it was so important, to do what we've undertaken, is that if we can accomplish the goal that we've set, it will give new hope and expectations to Americans about so much more we can do, in the physical sciences as well.

I was with President Xi [Jinping], I spent more time with him than any other leader in the world. And I was in Chengdu, China, with him and he asked me can I define America for him, because he and I had dinner with two interpreters. And I said yes I can, mister president, in one word: possibilities. We're all about possibilities.

Yet, right now in America, we're not nearly as optimistic as I think we should be. I'm not talking about Democrat or Republican, I'm talking about how well-positioned America is to lead the world in the 21st century. And all the enormous breakthroughs in the various sciences that are literally around the corner.

But I want to be clear: My job and my commitment is to bring together all the human, financial and knowledge resources that we have in the world to seize this moment. To make a quantum leap. To make decades worth of progress in five years.

As a consequence, without telling me, as you can probably tell by that video, the president announced in the State of the Union that I'm going to lead this moonshot effort. I heard it for the first time as the rest of the Congress heard it.

I was pleased, but I must tell you, in all my years on the national stage, I was overwhelmed by the response the announcement in the State of the Union generated, not just nationally, but globally. Worldwide.

The president signed essentially what is an executive order giving me control over all the federal agencies and departments, from Veterans Affairs to the Department of Energy, because of their computing capacity. Departments you wouldn't think—well, you would—but most people wouldn't think had anything to do with a moonshot to end cancer as we know it.

I realized the first thing I had to do was coordinate the federal government's efforts with the private sector. And I made a commitment that I will, as I gain this information and knowledge, I will eliminate the barriers that get in your way—that get in the way of science, research and development. And I know I had to touch all parts of the community in the fight against cancer. To learn from all of you, how we can proceed; how we can break down silos; how we can accommodate more rapidly the efforts you're making.

I've literally traveled the world thus far, visiting nearly a dozen cancer centers here in the United States, and more to go, discussing this issue with foreign governments, working our memoranda of understanding with other countries.

I was recently in the Middle East, because allegedly I have some expertise in foreign policy. I was meeting with [the crown prince of Abu Dhabi, Sheikh Mohammed bin Zayed Al Nahyan]. We sat down to discuss ISIS and the threats that are immediately apparent. And with his team, the first thing he said at our dinner was: "The first thing I want to talk to you is about cancer. How can we cooperate? Can we work out a memorandum of understanding on how our two countries can be engaged in your effort?"

We just had a nuclear security summit with 50 heads of state. As we sat around the East Room with long tables, with a space in the middle—with the president sitting by the fireplace and me sitting with my back to the main hallway that you see when he has a press conference. The president started off with the 50 heads of state and said, "Before we begin, a lot of you asked me about Joe's effort"—and then he named four countries, and said [he is] prepared to work out a memorandum of understanding with them on how we could jointly proceed.

I went to Israel, met with Shimon Peres, Bibi Netanyahu, and President [Reuven] Rivlin. The first thing they wanted to talk about was cancer, the database they have going back to 1961, and how they can be engaged.

We've heard from thousands of survivors. I've met over 250 leading oncologists and researchers at the world's leading institutions, and many of you are here today. I met with dozens of philanthropists who have invested billions of dollars, their own dollars, to engage in this fight. I met coalitions of cancer organizations that are attempting to aggregate cancer tissue genomics,

patient medical records, family histories and lifestyles in order to be able to take advantage of the supercomputing capability we have today to find answers that would otherwise take you a decade or more to find. Why does one immunotherapy work in one patient and then in a patient with apparently the same cancer, it will not work. That's what you're Project GENIE is all about. And then there's ORIEN, CancerLinQ, the Parker institute, and the QUILT coalition.

And quite frankly, as your leaders will tell you, when I met with the heads of each of those groups, it raises a question for me. Why is all this being done separately?

Why is so much money being spent when, if it's aggregated, everyone acknowledges the answers would come more quickly?

Today we have supercomputers that are able to do a thousand-billion computations per second. The first person who wanted to see me after this moonshot was announced was Secretary [of Energy] Ernie Moniz, one of the brightest guys anybody'll meet. When he told me that, in our national labs, we're on the verge of a supercomputer capability of a billion-billion calculations per second. Toward that end, I met with Eric Lander [of MIT], a lot of you know Eric, one of the most innovative guys I ever met in my life, pulling together data technology firms that are attempting to convert data into machine readable formats with the goal of making it all more accessible for you researchers.

Everywhere I go, when I talk about what is possible, it becomes clearer and clearer that there are areas of consensus among all of you. Some of you heard me say this before, I had a very well-educated, bright grandfather, an old Irishman from Scranton named Ambrose Finnegan, an old newspaperman, he would say, 'Joey, there are three kinds of politics: there's church politics, as in Roman Catholic; there's labor politics, as in unions; and there's politics. And they're difficult in that order.'

I respectfully suggest that what I've learned of late is that there are four kinds of politics: cancer politics, church politics, union politics, and politics. And they're difficult in that order. And as Barry Goldwater said as I was a kid running for the U.S. Senate, in your heart you know I'm right.

But advances in new immunotherapies suggest that this treatment approach is poised to become a part of a nation's anticancer strategy. Big data, and the computing power to get it, can provide significant insights into how genomics, family medical history, lifestyles, and genetic changes can trigger cancers.

There's a growing recognition of the need for more team science and increased collaboration among the private sector, academia, patient foundations and the government. And everywhere I go, there's an acknowledgement that we need new approaches to clinical trials as combination therapies become the norm for cancer treatments.

I'll be in meetings with some of the leading folks, some of who are in the audience, and I'll raise this, and after it's all over, one will pull me aside and say, I hope you push this, because it's hard for me institutionally to do some of this.

There's so much I could talk about today, but I want to focus on how to realign, if you believe it needs to be realigned, incentives in cancer research.

To be able to move more rapidly and better enable you to serve the very purpose you got engaged with in the first place: patients. I know this organization—I think it is 106 years old? 105? The American Association of Cancer Research has been working in this field for a long time. You've done incredible work. And you've focused on more support for physicians, for PhD's in associated fields and biomedical sciences, for more support for innovative research and stable funding.

The president and I agree with your objectives. Toward that end, last year, the 2016 budget, and working with Congress, we were able to increase funding by $2 billion for the National Institutes of Health. The largest increase in a decade.

The last time we were this engaged, when my friend, and I played a small part with him, Arlen Specter doubled funding for NIH. Included in that was about roughly $200,000 increase funding for the National Cancer Institute, and it's all in the budget for 2017, which I think we'll be able to pass.

We've asked for another $800 million, all of it this time, for the fight against cancer. If we succeed it will be spread across several government agencies that have a part to play in the fight against cancer: $75 million will go to the Food and Drug Administration, to fund a virtual oncology center of excellence. It will enable the Department of Veterans Affairs to take advantage of big data. And over $600 million will go to the NCI for research priorities such as enhanced cancer detection technologies, cancer vaccine development, cancer immunotherapy and combination therapies, genomic analysis in tumors and surrounding cells, enhanced data sharing, and pediatric cancer research. And if we do this well, we will be able to continue every year, for the foreseeable future to be able to fund a minimum of that amount of money every year. I think we can do it.

I believe we can do it.

We all know it takes more money, we also know there are other things we have to do. As I've traveled around the country and around the world since October, I'm constantly importuned by leaders in the field saying we have to realign research incentives. What behaviors would we want to encourage and reward? Because, believe it or not, I've come to understand just how difficult it is to qualify for a grant.

The more outside the box, which may be the answer to some cancers, the less likely you are to get funding. You've forgotten more about how difficult it is—you've still made enormous progress under the existing system—but let me suggest a few things that I have heard from multiple sources that may be able to further streamline the incentive process, and make progress for the 16 million folks a year who die of cancer.

Sharing data. The way the system is now set up, researchers are not incentivized to share their data. When I talked about this five months ago, the editor of the New England Journal of Medicine, in a lead editorial, which she later didn't get a lot of support for, said the following. She said that data sharing could breed data parasites. And she went on to say why it wasn't a good idea. But every expert I've spoken to has said there's a need to share this data to order to move the process more rapidly.

Involving patients earlier in clinical trial designs and focus. Clinical trial recruitment is a huge problem. Patients either don't know about the trials, or they're not consulted about how the trials are designed and targeted—and I don't think it's any wonder even if they know the trial is available, that they're hesitant to sign up. Only 4 percent of all the patients with cancer are involved with a trial.

We want to let scientists do science. There's an old cliché that too often grants are given for what you've already done, rather than what you're doing. You know.

For example, the Prostate Cancer Foundation grant application, for those of you who engaged with prostate cancer research, is limited to 10 pages. You get an answer in 30 days. Why is it that it takes multiple submissions and more than a year to get an answer from us?

It seems to me, we slow down our best young minds, by making them spend years and years in the lab before they can get their own grants. And when they do, they spend a third of their time writing a grant that takes months to be approved and awarded. It's like asking Derek Jeter to take several years off to sell bonds to build Yankee Stadium.

I'm not joking when I say your dedication absolutely awes me. I really mean it. I really mean it. You've got really, really, really care. You've got to really want to save lives.

The fourth thing we can do is measure progress by improving patient outcomes, not just publications. What you propose and how it helps patients, seems to me should be the basis of whether you continue to get the grant. And scores of your colleagues, scores, said make publications more readily available.

Right now you work for years to come up with a significant breakthrough, and if you do, you get to publish a paper in one of the top journals. For anyone to get access to that publication they have to pay hundreds to thousands of dollars to subscribe to a single journal, and here's the kicker: the journal owns the data for a year. Your outfit does this.

And by the way, the taxpayers fund $5 billion in cancer research every year. But once it's published, nearly all of that taxpayer-funded research sits behind walls. Tell me how this is moving the process along more rapidly.

There was an op-ed in Wired magazine this week by Ryan Merkley, CEO of Creative Commons. He said, and I quote, "Imagine if instead we said we will no longer conceal cancer secrets in paywalled journals with restricted databases, and instead make all that we know open to everyone so that the world can join the global campaign to end cancer in our lifetimes." It's a pretty good question. There are probably reasons why it shouldn't be answered the way I think it should, and I want to hear from you, I hope—because I have not made these recommendations yet.

But it seems to me that this matters. His question matters. Not all vital research is published behind paywalls.

For example, we have a model interest in open-source code NASA research that was used to unblur the images of the Hubble telescope. It was available to everyone immediately. Nobody argued about national security, nobody argued—immediately.

And guess what happened—and you may be in the audience—cancer research repurposed it for breast cancer screening. Imagine if that code was behind a paywall for a minimum of a year. Non-profits are already doing this. The Gates Foundation is already funding a billion-dollars-worth of research every year. And their policies are crystal clear: the results have to be free and open to anyone from the minute they are published.

The sixth recommendation I've received is reward

the work of verification.

Verification is the core of science; even a lawyer like me knows that. And the way we verify is to replicate. That's how we know if a breakthrough actually works.

Replicating published studies is not a rewarding career move. Very few people get grants to replicate studies. So why don't we give grants to people who replicate published studies to verify outcomes? We should incentivize verification. Over a 10-year period, Amgen scientists tried to replicate 53 landmark studies in cancer biology. Only six were able to be verified.

All the characteristics of this system started years and years ago. It's the environment we all grew up in, studied in, worked in. And yes this system has produced enormous successes, but this is not the system, in my view, that will get us to our goal faster.

One of the goals of the federal cancer task force is to achieve in 10 years of progress in preventing and treating cancer in five years. That requires a redesign, according to most of the experts I've spoken to in the cancer research enterprise. We are committed, the president and I, to realigning government programs and spending to accelerate the work all of you great researchers are doing. Nobody knows better than you that lives depend on it. We believe in you. We really do. So do the patients.

When my son received what we all knew was a death sentence, at one of the great cancer hospitals in the world, that he has stage IV glioblastoma—we knew it was a virtual death sentence. But our whole family, and he, my son, a highly decorated major veteran, an attorney general of the state of Delaware—we had hope, so much because of what you're doing and the progress you're making.

He was basically a trial of one; anti-PD1 and a virus injected into the tumor in his brain. I was recently at Duke, a different virus injected. I met a beautiful young woman, her mind, everything about her was beautiful, and who just finished nursing school after being diagnosed with stage IV glioblastoma. Same process, different virus. She's cured. That's what every single patient and parents of patients think about. What you do.

So the question I'd ask you to contemplate, because I'd like you to communicate with us, is does it require realigning incentives, changing behavior to take advantage of this inflection point. Does it require sharing more knowledge, treatments and understanding, with as many researchers as possible? Or does that slow the process up because there need to be other incentive motives as well that are totally legitimate.

I hope you all know it, it would be hard for you not to, but you're one of the most valuable resources this great country has, those of you sitting in this room.

So ask your institutions, your colleagues, your mentors, your administrators—how can we move your ideas faster together in the interest of patients? Every day, you know better than I that thousands of people are dying. Millions of people are desperately looking for hope—desperately looking for another day, another month, another year. I know you know this or you wouldn't be sacrificing all that you are.

I promise you, that I will—and I have the authority—to do everything in my power to put the federal government in a position where it is total value-added, and doesn't get in your way. You've got to tell me how. Many of you already have.

Put the federal government in collaboration with the private sector, academic institutions, philanthropists, investors—at your service, to serve your patients. I believe together we can design a new system, or adjust to a new system that better supports your efforts and saves lives sooner than otherwise would have been. Because I really do believe that we are on the cusp of breakthroughs that will save lives and benefit all of humanity.

We have to work together; we have to give you the ability to take chances. We have to help you do what you want to do, and why you got involved, to put patients first. I've been involved for 36 years in the Senate, and there's some very complicated matters relating to national security issues and the intelligence field. The enormous capabilities we have in science and technology to serve our national security interest. And I know—I know—that there's a generic benefit in collaboration.

So I ask you a rhetorical question: are we collaborating enough? What can we do, what can you do? You're already doing so very much.

I've taken on some big assignments in my career, including most recently, allocating $830 billion to be spent in 18 months. Every outside group has analyzed it; every outside agency points out less than two-tenths of 1 percent was waste, fraud, or abuse.

People said to me, why would you take on that job? I know government. I understood all aspects of it. I couldn't not after 42 years. I felt completely confident taking on an almost trillion-dollar spending program.

But this is bigger, and I know so much less. Sometimes I find myself going to bed overwhelmed by—how can I meet my responsibility? I need your help. I need honest evaluations of the kind of changes

that can be made.

Because I'm absolutely confident there is more brain power in this room than exists in many countries. You are the very best we have.

We need you badly to give me some guidance on how to make your job—not easier—but more likely to meet your ends.

I want to thank you for all you do from the bottom of my heart. May God bless you all, and may God protect our troops. Thank you.

AACR 2016 - In Brief

Nancy Davidson Begins Term As AACR President; Weinberg Gets Lifetime Achievement Award

NANCY DAVIDSON was inaugurated as president of the **American Association for Cancer Research** for 2016-2017 at the association's annual meeting in New Orleans.

Davidson is the director of the University of Pittsburgh Cancer Institute. She also serves as associate vice chancellor for cancer research; the Hillman professor of oncology; a distinguished professor of medicine and pharmacology and chemical biology; and a professor in the Clinical and Translational Science Institute at the University of Pittsburgh School of Medicine. Her research focuses on clinical and translational breast cancer research and cancer biology and treatment.

José Baselga, physician-in-chief and chief medical officer at Memorial Sloan Kettering Cancer Center in New York, now serves as AACR past president.

Davidson is known for her studies involving the role of hormones and the estrogen receptor in breast carcinogenesis that have defined the molecular mechanisms driving the disease as well as for her efforts to establish novel therapeutic approaches for patients who fail to respond to common treatment modalities. She has led clinical trials involving chemotherapy and endocrine-related therapies for treating premenopausal breast cancer and optimal chemotherapy for early breast cancer.

Davidson has been actively involved in the AACR since 1988 and was elected to the AACR board of directors. She is an editorial board member of Cancer Prevention Research and has served on numerous other boards and committees, including: the AACR Distinguished Lectureship in Breast Cancer Research Award Committee; chair of the Nominating Committee; the AACR Outstanding Investigator Award for Breast Cancer Research Committee; the Continuing Medical Education Committee; chair of the Breast Cancer Research Foundation-AACR Grants for Translational Breast Cancer Research Scientific Review Committee; the Dorothy P. Landon-AACR Prize for Translational Cancer Research Committee; chair of the Research Grant Review Committee; member of the Stand Up To Cancer Innovative Research Grants Scientific Review Committee; the Scientific Program Committee for the AACR International Conference on Frontiers in Cancer Prevention Research; and the AACR Award for Lifetime Achievement in Cancer Research Committee.

She has received the AACR-Women in Cancer Research Charlotte Friend Memorial Lectureship and is an elected member of the National Academy of Medicine, the Association of American Physicians, and the American College of Physicians.

Davidson is also a past president and former board member of the American Society of Clinical Oncology and is a member of the scientific advisory boards of many foundations and cancer centers.

Prior to joining the University of Pittsburgh in 2009, Davidson was professor of oncology at Johns Hopkins University School of Medicine in Baltimore and director of the Breast Cancer Program at Johns Hopkins Oncology Center. Early in her career, she was a research assistant professor of pharmacology at the Uniformed Services University of Health Sciences.

ROBERT WEINBERG was honored for his contributions to cancer research and cancer biology with the 13th annual **AACR Award for Lifetime Achievement in Cancer Research**.

Weinberg is a founding member of the Whitehead Institute for Biomedical Research; the Daniel K. Ludwig professor for cancer research in the Department of Biology at the Massachusetts Institute of Technology; and director of the Ludwig Center for Molecular Oncology at MIT.

Weinberg is known for his discovery of the first human oncogene, RAS, and the cloning of the first tumor suppressor gene, Rb. His groundbreaking observations were critical in establishing the concept that cancer arises as a result of genetic mutations.

More recently, Weinberg's research has focused on understanding the molecular mechanisms that regulate carcinoma invasion and metastasis, delineating the connection between epithelial-mesenchymal-transition and the metastatic spread of cancer.

Weinberg has been honored with numerous awards throughout his esteemed career, including induction into the inaugural class of the Fellows of the AACR Academy, the Inaugural Breakthrough Prize in Life Sciences, the Otto Warburg Medal, the Wolf Prize in Medicine, the Pezcoller-AACR International Award for Cancer Research, the Landon-AACR Prize for Basic Cancer Research, the Keio Medical Science Prize, the National Medal of Science from the National Science Foundation, the AACR-G.H.A. Clowes Memorial Award, and the Canada Gairdner International Award.

He is an elected member of the National Academy of Medicine and the National Academy of Sciences, an elected foreign member of the Royal Swedish Academy of Sciences, and an elected fellow of the American Academy of Sciences.

ROBERT LANGER received the **AACR-Irving Weinstein Foundation Distinguished Lectureship**. Langer is the David H. Koch institute professor at the Massachusetts Institute of Technology.

He was recognized for his research at the interface of biotechnology and materials science, which has led to the development of drug-delivery systems and breakthroughs in the fields of tissue engineering and regenerative medicine. He has authored more than 1,250 articles and holds nearly 1,050 patents.

"Dr. Langer is a world-renowned scientist whose exceptional work has revolutionized science, biotechnology, and clinical medicine," said Margaret Foti, CEO of the AACR. "His pioneering research has had a far-reaching impact on understanding of numerous diseases and medical conditions, including cancer. Dr. Langer's insights over the years have spurred innovative thinking on the part of scientists in physics, mathematics, and related fields, as well as cancer research and physician-scientists around the world, and he is greatly deserving of this award."

Langer's list of honors includes the U.S. National Medal of Science and National Medical of Technology and Innovation, the Charles Stark Draper Prize, the Millennium Prize, the Priestly Medal from the American Chemical Society, the Wolf Prize in Chemistry, the 2014 Breakthrough Prize in Life Sciences, the Kyoto Prize, and the Canada Gairdner International Award.

He was elected to the National Academy of Medicine, the National Academy of Engineering, the National Academy of Sciences, and the National Academy of Inventors.

Additionally, he is serving as a co-chairperson of the AACR special conference, Engineering and Physical Sciences in Oncology, to be held in Boston, June 25-28.

WAUN KI HONG received the **Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research**.

Hong is a professor of medicine in the Department of Thoracic/Head and Neck Medical Oncology and the Samsung distinguished university chair in cancer medicine emeritus at MD Anderson Cancer Center.

His clinical trials demonstrated the effectiveness of larynx sparing treatment and helped established the BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) approach.

Hong served as president of the AACR from 2001 to 2002, and was elected to the inaugural class of Fellows of the AACR Academy in 2013. He was also one of the founding editors of Clinical Cancer Research.

Hong's work with the AACR began in 1982. He is currently a senior editor of Cancer Discovery, editorial board member of Cancer Prevention Research, co-chair of the Stand Up To Cancer-Farrah Fawcett Foundation Joint Scientific Advisory Committee, member of the SU2C-Cancer Research UK-Lustgarten Foundation JSAC, and has served on various other editorial boards and committees for the AACR.

In addition, Hong has served on the NCI Board of Scientific Advisors, the National Cancer Advisory Board, the American Society of Clinical Oncology board of directors, and the subspecialty board of medical oncology for the American Board of Internal Medicine.

Hong has received awards including the AACR-Cancer Research and Prevention Foundation Award, AACR-Joseph H. Burchenal Award, AACR-Richard and Hinda Rosenthal Foundation Award, American Cancer Society Medal of Honor in Clinical Research, and David A. Karnofsky Memorial Award. He is an elected fellow of the American Association for the Advancement of Science.

MARY "DICEY" JACKSON SCROGGINS received the **Distinguished Public Service Award** for her advocacy on behalf of cancer patients and for her many years of service and commitment to the AACR.

Following her diagnosis with stage I ovarian cancer in 1996, Scroggins co-founded In My Sister's

Care, an organization focused on eliminating health disparities and on improving gynecologic cancer awareness and care for medically underserved women. She also served as director of The Pathways Project.

Scroggins has served as a volunteer leader at three separate AACR Cancer Health Disparities conferences and participating in the AACR congressional briefing on cancer disparities in 2013. She has also participated in and has served as a mentor for the AACR Scientist↔Survivor Program and served for eight years as an AACR/ASCO Methods in Clinical Cancer Research Workshop faculty member.

Scroggins also recently joined the editorial advisory board of the AACR magazine Cancer Today. In addition, she served as a member of the judging panel for the inaugural AACR June L. Biedler Prize for Cancer Journalism.

THE WOMEN'S HEALTH INITIATIVE, a nationwide, federally funded research program coordinated by Fred Hutchinson Cancer Research Center, received the 10th annual **AACR Team Science Award**.

Biostatisticians Ross Prentice and Garnet Anderson, leaders of the WHI Clinical Coordinating Center, accepted the award on behalf of the WHI program. Other members include Bette Caan, Rowan Chlebowski, Rebecca Jackson, Charles Kooperberg, JoAnn Manson, Electra Paskett, Jacques Rossouw, Sally Shumaker, Marcia Stefanick, Cynthia Ann Thomson, and Jean Wactawski-Wende.

Launched in 1992 with a $625 million contract from NIH, the WHI is one of the largest U.S. studies of its kind and the largest, most ethnically and geographically diverse study of older women. It initially consisted of three randomized clinical trials and an observational study that together involved more than 161,000 postmenopausal women at 40 U.S. research centers.

The clinical trials tested the effects of postmenopausal hormone therapy, dietary changes, and calcium and vitamin D supplements on heart disease, fractures, and breast and colorectal cancer. Those studies ended between 2002 and 2005. Since then, more than 115,000 WHI participants have continued providing health information that is being used to investigate a variety of key women's health questions. More than 80,000 of these women, ages 67 to 101, remain in active follow-up nationwide. Many of these women are also participating in two new trials: one is testing whether cocoa extract and multivitamins can help reduce the risk of cardiovascular disease and cancer; the other is testing the effect of physical activity on heart disease prevention.

The WHI is known for its 2002 findings that combination hormone therapy significantly increased the risk of heart disease, stroke and breast cancer. Researchers estimate that because of the decrease in hormone therapy use following the WHI publication, there have been 15,000 to 20,000 fewer cases of breast cancer each year in the United States.

SIR RICHARD PETO received the **AACR-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention**. Peto is a professor of medical statistics and epidemiology at the University of Oxford.

Peto delivered his award lecture titled "Halving Premature Death." This award recognizes outstanding research accomplishments in cancer epidemiology, biomarkers, and prevention.

JOHN BYRD received the **Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research**. Byrd is director of the Division of Hematology at the Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

Byrd delivered his award lecture "Targeting BTK in CLL: A New Treatment Paradigm."

RONALD LEVY received the **AACR-CRI Lloyd J. Old Award in Cancer Immunology.**

Levy is the Robert K. and Helen K. Summy Professor of Medicine at Stanford University. He delivered his award lecture "Immunotherapy Comes of Age Improving Efficacy and Reducing Toxicity."

JAMES BRADNER received the **AACR Award for Outstanding Achievement in Chemistry in Cancer Research.**

This award is presented for chemistry research which has led to important contributions to the fields of basic cancer research, translational cancer research, cancer diagnosis, the prevention of cancer, or the treatment of patients with cancer.

Bradner is president of the Novartis Institutes for BioMedical Research. He delivered his award lecture "Chemical Biology of BET Bromodomains."

VISHVA DIXIT received the **G.H.A. Clowes**

Memorial Award, which recognizes outstanding recent accomplishments in basic cancer research. Dixit is vice president of research at Genentech.

Dixit delivered his award lecture titled "Ubiquitin Mediated Regulation of Transcription Factor Stability."

WORTA MCCASKILL-STEVENS received the **AACR-Minorities in Cancer Research Jane Cooke Wright Memorial Lectureship.**

This lectureship recognizes a scientist who has made contributions to the field of cancer research and who has, through leadership or by example, furthered the advancement of minority investigators in cancer research.

McCaskill-Stevens is director of the NCI Community Oncology Research Program and chief of the NCI Community Oncology and Prevention Trials Research Group. She delivered her award lecture "Community Clinical Trials: A Path to Leveling the Cancer Research Playing Field."

FRANZISKA MICHOR received the **Award for Outstanding Achievement in Cancer Research**.

This award recognizes a young investigator, not more than 40 years of age, on the basis of meritorious achievement in cancer research.

Michor is a professor of computational biology at Dana-Farber Cancer Institute. She delivered her award lecture "Biology and Dynamics of Cancer Evolution."

JOAN MASSAGUÉ received the **Pezcoller Foundation-AACR International Award for Cancer Research.**

Massagué is director of the Sloan Kettering Institute, the Alfred P. Sloan Chair, and director of the Metastasis Research Center at Memorial Sloan-Kettering Cancer Center.

Massagué delivered his award lecture "Latent Metastasis" at the annual meeting.

ANTONI RIBAS received the **Richard and Hinda Rosenthal Memorial Award.**

This award honors the recipient and provides incentive to investigators not more than 50 years of age who are engaged in the practice of medicine, for research that has made, or promises to soon make, a notable contribution to improved clinical care in the field of cancer.

Ribas is a professor of medicine, surgery and molecular and medical pharmacology at the University of California Los Angeles Medical Center. He delivered his award lecture "How Cancer Resists PD-1 Blockade."

ANGELIKA AMON was honored with the **AACR-Women in Cancer Research Charlotte Friend Memorial Lectureship.**

The WICR Friend Lectureship is presented to a scientist who has made meritorious contributions to the field of cancer research and who has, through leadership or by example, furthered the advancement of women in science.

Amon is the Kathleen and Curt Marble Professor of Cancer Research at the MIT Koch Institute for Integrative Cancer Research. Amon delivered her award lecture titled "Effects of Aneuploidy on Cell Physiology and its Role in Tumorigenesis."

WILLIAM KAELIN JR. was honored with the **Princess Takamatsu Memorial Lectureship.**

This award recognizes an individual scientist whose work has had or may have a far-reaching impact on the detection, diagnosis, treatment, or prevention of cancer, and who embodies the dedication of the princess to multinational collaborations.

Kaelin is an investigator for the Howard Hughes Medical Institute, and a professor of medicine at Dana Farber Cancer Institute. He delivered the award lecture "New Cancer Treatment Strategies Emerging From Studies of the VHL and IDH Proteins."

ODAC Votes Down NSCLC Application from Clovis

(Continued from page 1)

At a meeting April 12, ODAC in effect voted against granting an accelerated approval of rociletinib for the treatment of patients with mutant epidermal growth factor receptor non-small cell lung cancer who have been previously treated with an EGFR-targeted therapy and have the EGFR T790M mutation as detected by an FDA approved test.

The question posed to the committee was whether the results of a randomized trial would be needed for FDA to make a regulatory decision on this application. All but one of the committee members voted in the affirmative, amounting to a 12 to 1 vote against. The Clovis TIGER-3 phase III, randomized, controlled trial is expected to be completed in late 2018.

Arguably the most interesting question on the table concerned another drug—AstraZeneca's Tagrisso (osimertinib)—which has been granted an

accelerated approval for the same indication. Since that agent's approval is accelerated, it doesn't raise the bar for competing drugs—such as rociletinib. Once Tagrisso's approval switches from accelerated to regular, newcomers would need to show that they provide a superior safety or efficacy profile.

Much of ODAC's discussion focused on cross-study comparisons, which, albeit inconclusive, suggest that the AstraZeneca drug has a better safety and efficacy profile. Such comparisons—which ODAC members readily admitted are informal and methodologically perilous—are becoming increasingly important in determining therapeutic choices as physicians and their patients choose between the plethora of recently-approved cancer drugs.

In the treatment of many cancers, this dilemma is made all the more profound by the absence of evidence establishing the sequence in which the new generation of drugs should be used.

Consider this comment by ODAC member Bruce Roth, professor of medicine at the Washington University School of Medicine:

"While we have the luxury of not considering the osimertinib data, if this was approved today, the same is not true of a practicing physician, and if you were going to prescribe the drug in a T790 patient, would you pick the drug that had a 59 percent response rate, and duration of response of 12.8 months, and a 2.7 percent incidence of QTc [corrected QT interval] prolongation beyond 60 millisecond—or would you pick the 30-percent response rate with the median duration of response of nine months, where you have to have a risk mitigation strategy for the QTc prolongation, and half your patients are going to be on the hyperglycemic agents as well?"

ODAC member Michael Menefee, assistant professor of medicine at the Mayo Clinic Jacksonville, said the situation isn't limited to lung cancer.

"I am seeing the scenario that Dr. Roth has mentioned in clinical practice with medullary thyroid cancer, where we have vandetanib and cabozantinib, two drugs that are similar and in the same space, and we don't know how best to use them, and it's not a good situation," Menefee said. "I would hope that studies would be better designed that will help the practitioners to know exactly how use the drug."

Wall Street engaged in similar analysis. Indeed, Clovis Oncology's stock price went off a cliff Nov. 13, 2015, when FDA granted an accelerated approval to the AstraZeneca drug. Prior to approval of this competing agent, Clovis shares were trading at $99.40. Within four days of approval of osimertinib, Clovis stock plunged to $26.80 per share.

Another drop occurred before the ODAC meeting. On April 7, Clovis was trading at just above $19 per share. Post-ODAC, it slipped to just above $14 per share. The company has been facing shareholders' suits since last November.

AstraZeneca's osimertinib isn't the only drug with an accelerated approval in a similar indication.

The other drug is Merck's Keytuda (pembrolizumab), which received an accelerated approval for the treatment of patients with metastatic NSCLC whose tumors express programmed death ligand 1 as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.

The dosage of Clovis's rociletinib also raised questions.

In its initial filings, Clovis proposed a recommended dose of rociletinib of 500 mg orally BID with food.

However, as ODAC neared, the company proposed changing the dose to 625 mg BID with food. This change is based on Clovis's interpretation of the objective response rate, as confirmed by the independent radiology review. The company said ORR was higher at the 625 mg dose.

FDA disagreed, proposing 500 mg orally BID with a meal as the recommended dose.

The agency said it was leaning toward the 500 mg dose because of the similar systemic exposures of rociletinib across the dose range of 500 mg to 1000 mg. Moreover, the exposure-response and exposure-toxicity analyses of the 500 and 625 mg doses indicate a similar ORR with overlapping confidence intervals for efficacy, and no major differences in safety.

This is important because the company's confirmatory trial proposes evaluating the 625 mg dose. A protocol change the company proposed a month before its date with ODAC would randomize patients 1:1:1 to receive rociletinib 500 mg, 625 mg, or chemotherapy, and increases the sample size from 600 to 900 patients. There would be no formal efficacy comparison of the two rociletinib arms.

"The key issues for this application are whether the activity of rociletinib as reflected by the [objective response rate] and [duration of response] are reasonably likely to predict clinical benefit and are superior to

Source: FDA

Table 1 Approved Therapies for NSCLC in the Second-Line Setting

Date	Product Indication	Studies and Approval Endpoints
DEC- 1999	**DOCETAXEL** Single agent for locally advanced or metastatic NSCLC after platinum therapy failure	1. Docetaxel (N=55) vs. BSC (N=49) • mOS 7.5 m (5.5, 12.8) vs 4.6 m (3.7, 6.1); HR 0.56 (0.35, 0.88); p=0.01 • ORR 5.5% (1.1, 15.1) vs N/A 2. Docetaxel (N=125) vs. Vinorelbine/Ifosfamide (N=123) • mOS 5.7 m (5.1, 7.1) vs. 5.6 m (4.4, 7.9); HR 0.82 (0.63, 1.06); p=0.13 • ORR 5.7% (2.3, 11.3) vs. 0.8% (0.0, 4.5)
FEB- 2004	**PEMETREXED** Single agent for locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	Pemetrexed (N=205) vs. Docetaxel (N=194) Non Squamous population • mOS 9.3 m (7.6, 9.6) vs 8.0 (6.3, 9.3); HR 0.78 (0.61, 1.0)
DEC-2014	**RAMUCIRUMAB** In combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving ramucirumab	Ramucirumab/Docetaxel (N=628) vs Placebo/Docetaxel (N=625) • mOS 10.5 m (0.95, 11.2) vs 9.1 (8.4, 10.0); HR 0.86 (0.75, 0.98) p = 0.024 • mPFS 4.5 m (4.2, 5.4) vs 3.0 m (2.8, 3.9) ; HR 0.76 (0.68, 0.86) p < 0.001 • ORR 23% (20, 26) vs. 14% (11, 17); p < 0.001
MAR-2015	**NIVOLUMAB** Metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving nivolumab	I. Nivolumab (N=135) vs. Docetaxel (N=137) Squamous NSCLC • mOS 9.2 m (7.3, 13.3) vs. 6.0 m (5.1, 7.3); HR 0.59 (0.44, 0.79) p=0.00025 • ORR 20% (14, 28) vs 9% (5, 15) II. Nivolumab (N=292) vs. Docetaxel (N=290) Non-Squamous NSCLC • mOS 12.2 m (9.7, 15.0) vs. 9.4 m (8.0, 10.7); HR 0.73 (0.60,0.89) p=0.0015 • ORR 19% (15, 24) vs 12% (9, 17)
NOV-2015	**OSIMERTINIB**[A] Treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.	Two multicenter, single-arm, open-label studies of patients with metastatic EGFR T790M mutation-positive NSCLC with pooled ORR (N=411) of 59% (95% CI 54, 64) by blinded independent central review. The median duration of response in 63 patients in Phase 1 with EGFR T790M NSCLC was 12.4 months.

[A] Accelerated approval therefore not considered available therapy per FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics, May 2014; BSC= best supportive care; mOS= median Overall Survival; ORR= objective response rate; mPFS= median Progression-free Survival

available therapy, if so, whether Clovis's proposed recommended dose of 625 mg BID is supported by the clinical and clinical pharmacology data, whether the risks (particularly with respect to QTc prolongation leading to Torsades de pointes) are acceptable in the intended population, and whether the dose modification strategy to mitigate the toxicities of rociletinib has been adequately characterized," the agency said in a briefing document.

It's worth noting that FDA wanted ODAC to vote on this application.

At the previous ODAC, nearly a year ago, FDA signaled that it may not always ask the committee to vote (The Cancer Letter, Feb. 19).

However, in this case the application was plagued by problems of establishing surrogacy as well as by pharmacological issues and it was unclear that the confirmatory trial is going to answer those questions. A decisive vote by outside advisors will give scientific gravitas to the agency's final decision.

By way of comparison, no confounding issues arose in connection with the application for accelerated approval of osimertinib. The agency didn't consult ODAC on the AstraZeneca drug.

Here are the safety and efficacy findings of the company's two non-randomized studies CO-1686-008 and CO-1686-019:

Clinical Pharmacology Summary

• There is high variability in systemic exposure to rociletinib and its major metabolites, M502 (which induces hyperglycemia) and M460 (which induces QTc prolongation).

• Exposure-response analyses indicate a plateau in ORR at exposures obtained with rociletinib at doses ranging from 500 mg BID to 1000 mg BID.

• The major metabolites of rociletinib, M502 and M460 are metabolized by N-acetyltransferase (NAT2). Patients who are classified as NAT2 slow acetylators based on NAT2 genotype have increased M502 and M460 exposures. In exposure-safety analyses, there is an increased risk for QTc prolongation and hyperglycemia with increasing exposure to M502 and M460, respectively.

Efficacy Summary

• In a pooled analysis of patients with metastatic EGFR T790M mutation positive NSCLC who have been previously treated with an EGFR-targeted therapy and who received rociletinib at doses of 500 mg, 625 mg, and 750 mg BID:

• The objective response rate per RECIST v1.1, as assessed by an IRC, is 30.2 percent (95% CI 25.2, 35.5).

• The median duration of response per RECIST v1.1, as assessed by an IRC is 8.9 months (95% CI: 7.2, 12.9).

Safety Summary

• The most common (≥ 30%) treatment emergent adverse events in patients who received rociletinib were hyperglycemia (58%), diarrhea (55%), nausea (52%), fatigue (44%), decreased appetite (36%), QT prolongation (33%), and vomiting (30%).

• The incidence of Grade 3 or 4 hyperglycemia was 34 percent

• The incidence of Grade 3 or 4 QT prolongation was 11 percent

• Serious adverse events observed in ≥ 2% of patients were hyperglycemia (9%), pneumonia (5%), pancreatitis (2%), nausea (2%), vomiting (2%), and diarrhea (2%).

• There were two sudden deaths. There were three cases of ventricular tachyarrhythmia and one case of Torsade de pointes.

• The incidence of dose reduction was 51 percent, dose interruption was 56 percent, and discontinuation of rociletinib for adverse reactions was 21 percent.

Explaining the Votes

ODAC members explained their rationale for voting to recommend waiting for more data before deciding on the Clovis drug.

Their comments follow:

Donald Mager, *associate professor of pharmaceutical sciences at the University at Buffalo:*

I voted Yes. I think it's quite clear from the discussion today that the high variability in exposures really makes no attempt at dose/response. I think the FDA has done a remarkable job at examining exposure/response relationship and that the dose that's proposed is really not supported by the data.

The lower bound of a single-point estimate in a single-arm non-randomized study really doesn't justify the dose that has been chosen. In my question earlier about drug risk management, I don't feel that they quite have it, given that we won't have NAT2 genotyping. We will have some drug monitoring.

Given the very tight relationship between some of the exposure in terms of the adverse events, I don't think a confirmatory trial will necessarily give us any information about about the dose. I think that's pretty well answered, but I think it will provide additional efficacy data that I think will be very useful in assessing the risk/benefit.

Eva Szabo, *chief of the Lung & Upper Aerodigestive Cancer Research Group at the NCI Division of Cancer Prevention:*

I voted Yes. The benefit-risk to me was not as clear as I would like it at this stage. There are multiple other drugs in this space currently, and so how this drug would be used currently was not clear to me, and there are some very definite risks associated with it, so I just thought we need some more information.

Michele Orsa, *(acting consumer representative) senior advisor to the executive director at Patient-Centered Outcomes Research Institute:*

I voted No, which is unusual for me, because I am a big fan of outcomes. I would like to see the results of the study.

I also voted very narrowly on the question. I think that 2018-2019 is a long time to wait, which is not to say that I would vote to approve it today. I think there are a lot of questions that have to be worked out.

I am not confident that the study, even when it's done, will give us a lot of the answers we are looking for. I was concerned that there is a population that could be benefiting from this in the meantime, and we need to do some more work to identify that group and consider accelerated approval for them.

William Douglas Figg, *senior investigator and head of the Clinical Pharmacology Program at the NCI Center for Cancer Research, and head of Molecular Pharmacology Section and deputy branch chief in the NCI Genitourinary Malignancies Branch:*

First, let me say that public testimony from the individuals who have received the drug or are receiving the drug was very compelling. With that said, I voted Yes.

I think that simply there are too many unanswered questions that need to be addressed. I am also concerned that the current phase 3 trial that is ongoing doesn't answer all the necessary question.

Grzegorz Nowakowski, *assistant professor of medicine at the Mayo Clinic Rochester:*

I voted Yes. The degree of benefit over the standard therapy was not clear from the data presented, and the quality of the data were not fully supporting it.

More so, I was concerned about the safety profile, with the cardiac toxicity and hyperglycemia. Also, the dose was not well defined. I think there is also an elephant in the room with osimertinib. Although it was granted an accelerated approval, it appears to be less toxic in this space.

Tito Fojo, *professor of medicine at Columbia University:*

I voted Yes. I do think that this is a drug that has activity. Yes, this is a drug whose toxicity could be manageable.

I would say that I am concerned when it comes to 2018 and the data come is, and with what you see you would realize that the company ought to go back to FDA and say, "You know, you were right: 500 mg is the same."

Why don't we just get rid of that third arm [in the proposed TIGER-3 confirmatory trial] and do a 600-patient trial, with 300 [patients] getting 500 [mg] against 300 [patients] with chemotherapy, and you will be done sooner.

Go forward with 500 [mg dose]. Worry about 625 [mg dose] later. Get it approved sooner at 500 [mg].

ODAC Chair **Deborah Armstrong**, *professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University School of Medicine:*

I voted Yes as well. I think we have discussed issues about toxicity, dosing and metabolism issues. But the requirement for accelerated accelerated approval to have superiority to current treatment I don't think has been shown by the data that we have at this time.

Bruce Roth, *professor of medicine at the Washington University School of Medicine:*

I agree with Deb. I don't think it met the criteria to be accepted as superior to existing therapy, and as Dr. Nowakowsky also said, while we have the luxury of not considering the osimertinib data, if this was approved today, the same is not true of a practicing physician, and if you were going to prescribe the drug in a T790 patient, would you pick the drug that had a 59 percent response rate, and duration of response of 12.8 months, and a 2.7 percent incidence of QTc prolongation beyond 60 millisecond, or would you pick the 30–percent response rate with the median duration of response of nine months, where you have to have a risk mitigation strategy for the QTc prolongation, and half your patients are going to be on the hyperglycemic agents as well?

For me, it did not meet the criteria for accelerated approval.

Michael Menefee, *assistant professor of medicine at Mayo Clinic Jacksonville:*

I voted Yes for many of the reasons that have been mentioned. I am seeing the scenario that Dr. Roth has mentioned in clinical practice with medullary thyroid cancer, where we have vandetanib and cabozantinib, two drugs that are similar and in the same space, and we don't know how best to use them, and its not a good situation. I would hope that studies would be better designed that will help the practitioners to know exactly how use the drug.

I share Dr. Figgs concern that trial TIGER-3, unfortunately, is not going to answer these questions in terms of how best to use this drug in clinical practice.

But I do think it's a good drug. It's clearly active, it's clearly helping some patients and a lot of the issues in terms of dosing and toxicity can be managed, but we need better study designs that will be useful for practitioners.

Brian Rini, *professor of medicine at the Cleveland Clinic Taussig Cancer Institute and Glickman Urological and Kidney Institute:*

I voted Yes. It's clearly an active drug. The response rate shows activity. For me, it didn't pass the standard of being clearly superior to standard therapy at present, noting all the limitations of cross-trial comparisons which are flawed, but which we have been doing all day long, because they are necessary.

And there wasn't objective evidence of clinical benefit, which was something that I struggled with, and I don't doubt that there was—again, we heard it from the anecdotes that were mentioned.

But we weren't presented any data of quality of life, of narcotic use, of symptom control, of something that would convince us that the response rate, whatever the estimate ends up being ends up being, is beneficial to patients.

With regards to dose, I hear that this is a hugely complex issue. I think the major problem—I think this is a problem not just for Clovis study, but for all of us who develop drugs—is we don't really individualize the dose.

We prepare a standard dose based on a small number of patients and them we try to shoehorn people into that dose and for some its probably too low and for others its too high, and we just hope for the best.

We prepare an average dose based on a number of patients and for some its probably too low and for some its too high and we just sort of hope for the best as we develop all these drugs. And it's really not a smart way to do it.

Having said that, I think the comments about

that phase 3 [trial] are highly pertinent. I would either pick one dose and pick 625 [mg] or 500 [mg], and adequately test it, or power the study for each of the doses.

And it's not just from the regulatory standpoint, but you want to be able to use your drug at the end of the day, when it ultimately gets approved. So you want data to say that the balance of risk is more favorable with one over the other. Otherwise you will end up with some underpowered data that won't really be informative, and I think it's a shame to waste all those resources.

Arun Rajan, *associate research physician in the NCI Thoracic and GI Oncology Branch:*

I voted Yes. I do believe, like all physicians in the room, that we should have multiple options at our disposal. And clearly we heard from patients and physicians that this drug does benefit patients clinically. But having said that, I think the risk/benefit ratio is informed by other options that are available, and had there been no options for T790M in NSCLC, maybe I would have voted differently.

So I think there are unanswered questions. There is an ongoing study. I really hope the sponsor can work with the FDA to try to amend the ongoing study to address some of these questions so two ears from we are not in the same position where some of these questions have to be debated. But I think the main crux for answering yes is that there is an alternative that at least on the face of it appears to be safer and has a higher response rate.

Bernard Cole, *professor in the Department of Mathematics and Statistics at the University of Vermont:*

I voted Yes largely for the same reasons that have been mentioned around the table. As a biostatistician member of the committee, I focused my attention primarily on the statistical evidence. Of course, here we are trying to make two bridges.

The first is the bridge from the singe-arm study to a benefit, and the second is the bridge from surrogate endpoint to a clinically meaningful outcome, such as PFS, or overall survival advantage, and unfortunately the statistical evidence along these lines is rather weak, and we we are simply not able to make that bridge.

I was very moved by the statements from the audience, and the patients who have undergone the therapy, and I am very hopeful that the phase 3 study will show benefit that is provable.

Guest Editorial

Lessons from Chernobyl, Thirty Years Later

(Continued from page 1)

The world (but not Soviet citizens) had been following the spread of a radioactive cloud over Europe for several days and I offered the Soviet government access to advanced medical technologies I knew they lacked. I arrived to find about 205 of the most seriously-affected victims had been flown to Hospital 6 in Moscow connected to the Institute for Biophysics.

I was able to quickly assemble a team of experts from the U.S. (Richard Champlin and Paul Terasaki) and Israel (Yair Reisner) and, together with a superb group of Soviet physicians including Angelina Guskova, Alexander Baranov and Andrei Vorobiov, used diverse technologies including molecularly-cloned haematopoietc growth factors and transplants to treat the nuclear worker and firefighters exposed to high doses of radiation (1). Twenty-nine died despite our efforts, mostly of thermal and chemical damage. Fortunately, we were able to rescue the other 176. This was also the first chance to treat humans (including ourselves) with molecularly-cloned myeloid growth factors (but that's another story [2]).

Most physicians are more interested in the long-term including radiation-related cancer and cardio-vascular disease. Fortunately, we are now in a reasonable position to comment what has happened over these 30 years and what may happen over the next several decades. Some of these data and predictions can inform our calculus on two related issues: nuclear energy and nuclear weapons.

The health impact of the Chernobyl accident was in some ways enormous and in others minor for expected and unexpected reasons. Despite extraordinary claims by people and organizations with either complex political and/or social agendas or limited scientific knowledge (often both) claiming thousands of deaths and injuries the direct long-term health effects from radiation exposures are small. The most startling and unexpected outcome was the rapid development of about 7000 excess thyroid cancers in children and young adults, cancers which resulted from drinking milk contaminated with radioactive iodine-131 in a population with background iodine deficiency (endemic goiter). Also, infrastructure limitations prevented us from rapidly distributing non-radioactive iodine tablets which would have blocked uptake of iodine-131 and from quarantining

contaminated foods. (None of these conditions apply to the Fukushima nuclear power facility accident where I expect few if any thyroid cancers.) Fortunately, thyroid cancer in children is largely curable: there were fewer than 20 deaths. There is also a suggested increase in chronic lymphocytic leukaemia amongst the more than 100,000 personnel involved in mitigating the accident (called *liquidators* in Russian). However, I think these data shaky and more likely to reflect surveillance biases. Increases in more common cancers, like breast lung and colon cancer can be anticipated if one takes the relatively small radiation doses received by most of the surrounding population and multiples the risk by millions of people. Whether such a calculation is appropriate is controversial. Also, seeing no convincing increase in solid cancers yet is not surprising given the more than 30 years it took for most radiation-related cancers to develop in the A-bomb exposed population. The absence of a detectable increase in acute leukaemias or chronic myeloid leukaemia after Chernobyl is encouraging as these leukaemias were markedly-increased in the decade after the A-bomb explosions. If we use conventional cancer risk-estimators one might expect about 12,000 excess cancers from Chernobyl over the next 40 years about 4000 of which will be fatal. This is only about a 1 percent increase in the proportion of exposed persons expected to die from cancer were there no accident. (Our baseline lifetime cancer risks are rather high, about 50 percent in persons born after 1960.) This is not surprising given that only 10 percent of cancers in the A-bomb survivors were caused by exposure to radiation at substantially higher doses. Whether these level of detection with the current epidemiological techniques; we have no specific markers of radiation-induced cancers. Moreover, the increased cancer risks resulting from smoking tobacco (25-fold) and drinking alcohol (20,000 deaths per year in the U.S. [4]) far exceed those resulting from Chernobyl-related radiation exposures. There are increasing data radiation causes an increased risk of death from cardio-vascular diseases but typically at much higher doses than the Chernobyl population such that no radiation-induced increase is expected. Other good news: there are no convincing data of a deleterious impact of Chernobyl-related radiation on reproduction or genetic or birth abnormalities. The bottom line is that the average Ukrainian, Russian and Byelorussian is far more likely to be killed driving to a local store to buy cigarettes or alcohol than by radiation released by the Chernobyl accident. The same is for the chances of dying from environmental pollution from burning coal and oil in Kiev, Moscow and Minsk in winter than from radiation released from Chernobyl.

In contrast, environmental, social and economic impacts of Chernobyl are enormous. Plants and animals in areas contaminated by radionuclides released by the Chernobyl accident were severely affected. Genetic abnormalities were detected in many species and trees died. Although these problems are resolving because of radioactive decay and mitigation interventions, some will persist for more than 100 years because of the long half-lives of isotopes like cesium-137. About 300,000 persons were relocated because of the accident. The quality-of-life of many of these people is severely compromised by inappropriate concerns for their health (most received radiation doses unlikely to adversely affect them), unemployment and social dependency. The cost of the accident, including loss of agricultural land, employment and opportunities likely exceeds 250-400 billion USD.

Do these extraordinary data mean we should abandon nuclear energy? I think not. In considering any potential energy source we must compare costs, risks and opportunities. Fossil fuels are expensive, limited resources. Furthermore, their use entails substantial health risks: some obvious, some less so. Examples include not only lives lost mining, transporting and processing these fuels but also environmental pollution, global warming and thinning of the atmospheric ozone layer. The latter is expected to increase radiation doses to the earth's population resulting in more cancers, especially melanoma. A less obvious cost are lives lost in geopolitical actions directed at protecting our energy sources. And the enormous bill for Chernobyl seems smaller daily as we spend billions in Iraq and Afghanistan. Perhaps most sinister is the possibility that defense of fossil fuels could lead us to a nuclear conflict which would release more radiation and cost more lives than a nuclear power facility accident. The recent treaty with Iran was a close call; the story is not over. In sum, the health and environmental consequences and costs of a fossil fuel-orientated society, including nuclear risks, may exceed those of wisely and safely using nuclear energy. We should continue to support evolving technologies to make nuclear energy safer and cheaper and reduce our addiction to fossil fuels. Japan after Fukushima is a good example. Closing Japan's nuclear power facilities and importing oil has increased its carbon footprint 500 percent and adversely affected its economy.

Finally, there is a lesson here about nuclear

weapons. The demise of the Soviet Union has increased rather than decreased the global nuclear threat. Also, the nature of the risk has changed. Consider terrorists using a conventional weapon intentionally contaminated with radioactive materials or sabotaging a nuclear power facility. Belgians have become acutely aware of these risks. Prevention is, of course, better than cure but our data and experiences from Chernobyl indicate the public's fear of the radiation consequences of such events is exaggerated. These are weapons of *mass distraction*, not *mass destruction* to quote my UCLA colleague Bennett Ramberg. Education about what radiation can and cannot do to us is one step we can take to reduce the potential impact of nuclear terrorism.

The author is a physician/scientist who led the international medical response team at Chernobyl and teaches at Imperial College London. He and Eric Lax are authors of Radiation: What You Need to Know, published by A. Knopff. Full disclosure: he and Eric get $0.05 if you buy a copy.

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Academy of Arts and Sciences Elects 213 New Members

The American Academy of Arts and Sciences elected 213 new members, including some of the world's most accomplished scholars, scientists, writers, artists, as well as civic, business, and philanthropic leaders.

Members of the 2016 class include winners of the Pulitzer Prize and the Wolf Prize; MacArthur and Guggenheim Fellowships; the Fields Medal; the Grammy Award and the National Book Award.

The new class will be inducted at a ceremony Oct. 8 in Cambridge, Mass.

The full list, organized by class and section, is available here.

Members of the 2016 class working in the biological sciences, including foreign honorary members, are:

Biochemistry, Biophysics and Molecular Biology

- Richard Ebright, Rutgers University
- Lila Gierasch, University of Massachusetts
- Robert Glaeser, University of California, Berkeley and the Lawrence Berkeley National Laboratory
- Adrian Krainer, Cold Spring Harbor Laboratory
- Lawrence Loeb, University of Washington
- Eva Nogales, University of California, Berkeley

Cellular & Developmental Biology, Microbiology, and Immunology

- Keith Burridge, University of North Carolina at Chapel Hill
- Mark Hochstrasser, Yale University
- Michael Lichten, National Cancer Institute
- Joachim Messing, Rutgers University
- Carl Nathan, Weill Cornell Medical College
- Anne Villeneuve, Stanford University
- Carl-Henrik Heldin, Ludwig Institute for Cancer Research/Uppsala University
- Christof Niehrs, Institute of Molecular Biology

Neurosciences, Cognitive Sciences, and Behavioral Biology

- Michael Brainard, University of California, San Francisco
- John Gabrieli, Massachusetts Institute of Technology
- Alex Kolodkin, Johns Hopkins University

School of Medicine

• Kelsey Martin, University of California, Los Angeles

• Bruce Rosen, Harvard Medical School/ Massachusetts General Hospital

• John Rubenstein, University of California, San Francisco

• Tamar Flash, Weizmann Institute of Science

• Nancy Ip, Hong Kong University of Science and Technology

Evolutionary and Population Biology, and Ecology

• Farooq Azam, University of California, San Diego

• Andrew Clark, Cornell University

• Douglas Emlen, University of Montana

• Joel Grant Kingsolver, University of North Carolina at Chapel Hill

• Mark Alan McPeek, Dartmouth College

• Sarah Otto, University of British Columbia

• Ary Hoffmann, University of Melbourne

Medical Sciences, Clinical Medicine, and Public Health

• John Michael Carethers, University of Michigan Medical School

• James Downing, St. Jude Children's Research Hospital

• Gary Gilliland, Fred Hutchinson Cancer Research Center

• Beatrice Hahn, University of Pennsylvania Perelman School of Medicine

• Warren Leonard, National Institutes of Health

• Ralph Weissleder, Harvard Medical School/ Massachusetts General Hospital

Intersection and Interclass Candidates

• Benjamin Cravatt, The Scripps Research Institute

• Larry Jacoby, Washington University in St. Louis

• Jay Keasling, University of California, Berkeley/ LBNL

• Steven Jacobsen, University of California, Los Angeles

• Yang Shi, Harvard Medical School/ Boston Children's Hospital

• Karen Vousden, Beatson Institute for Cancer Research, Glasgow, U.K.

BSA Approves Plan to Expand SEER Infrastructure, Funding, and Research Support Capacity

By Conor Hale

The NCI Board of Scientific Advisors approved a proposal to expand the infrastructure and capacity of the SEER program, including introducing registries designed specifically to support cancer research projects, an increase of the program's overall budget, and moving toward a more advanced, uniform data management system.

The new structure of the surveillance program would create core registries, selected through a competition of the U.S. central cancer registries, which would then collect the most comprehensive data to be used for SEER statistics and public use.

These core registries would be the equivalent of the current SEER program, said Lynne Penberthy, associate director of the NCI Surveillance Research Program, during her presentation of the proposal to the board March 29.

"What we're proposing is as follows: a full and open competition that will enable any central cancer registry in the U.S. to apply, from the entire pool of central cancer registries," Penberthy said. "I'd like to point out that it doesn't necessarily have to be a state cancer registry. It could be a group of counties that have a defined population, [or] a metropolitan region—we currently have the Detroit metropolitan region and Seattle—so it could be a different definition of a central cancer registry than you might think about."

"From that pool of central cancer registries, we will identify the SEER expanded infrastructure. The first set of registries would be the core registries."

Separate from the core registries would be registries designated for research support, which would only be eligible to compete for special projects, such as a SEER-linked virtual tissue repository or virtual pooled registry, Penberthy said. These research support registries would receive less funding, and no support for core data collection.

The research support registries would have to transition to SEER*DMS, the data management system that would provide support for all core cancer registry functions, including importing data, editing, linkage, consolidation, and reporting. The centrally designed system will make it easier to share the data received from hospitals, pathology laboratories, radiology facilities, physician offices and other

facilities, according to NCI, and would automate certain tasks previously done manually—employing natural language processing and machine learning to help capture the relevant results more efficiently.

The ten-year proposal takes aim at the main challenges facing the SEER program; challenges that affect all of cancer surveillance, Penberthy said.

"The first is a complexity of cancer care. As you're well aware, new treatment and new treatment modalities have increasingly been identified, and not only are there new modalities, but there is also ongoing treatment. Many cancer patients have treatment from the time of diagnosis through their death; they receive multiple cycles, and that's very difficult for registries to be able to capture accurately," she said.

The surveillance program also needs to focus on outcomes other than survival—such as recurrence, disease progression, and patient-reported data, Penberthy said.

"The expansion of data characterizing each cancer with precision medicine—with the complex molecular and genetic characterization of each cancer case—has really identified the need for us to capture new data sources, and require new methods such as novel linkages and automation."

The SEER program will also have to keep pace with the dispersion of cancer diagnosis and treatment across multiple providers and locations: "When SEER started in 1973, everybody received their diagnosis and treatment in a hospital. That's no longer the case," Penberthy said.

The proposal would increase SEER's budget to $46.2 million a year for the next decade, a boost of about 10 percent. Over the past eight years, the program has seen an average annual increase of about 1.3 percent.

The proposal also plans to form a virtual pooled registry, which will help consolidate duplicated cases within the SEER program and other registries, Penberthy said.

"It will give us a more accurate assessment of multiple primary cancer incidents," she said. "Currently, if you have a cancer diagnosed, for example, in North Carolina, then you move to New Mexico and have a second cancer, there is no way that we know that you as an individual have more than one cancer. So I think that our estimate of multiple primary cancer incidents is very underreported, and this is an opportunity for us to get a better handle on that."

SEER currently covers about 30 percent of the U.S. population, and receives over 450,000 reported incident cases annually. BSA member Kevin Shannon, professor in the Department of Pediatrics at the UCSF Helen Diller Family Comprehensive Cancer Center, asked if the program could save money by going with a more focused approach.

"This is the broad-and-shallow versus narrow-and-deep question," Shannon said. "Clearly, SEER is now trying to go narrow and deep, and collect more detailed and in-depth information, which I think is really important. The question that occurred to me is, do we need to continue to survey 35 percent of the population, or can we get the equal bang for the buck and survey 25 percent of the population?"

"I think to our eye, in fact, we may want to survey more people rather than fewer people—with an understanding that, as we wish to predict outcomes for individual people based on multiple characteristics of their disease in broader context, more granular detail at the individual patient level about large swaths of the population may be beneficial," said BSA member Ethan Basch, director of the Cancer Outcomes Research Program at the University of North Carolina at Chapel Hill.

"In addition for many of the analyses that make use of SEER data, by the time one cones down to the particular research question, the population that's available for those analyses is actually vastly smaller than the overall population. But I can't really speak to 25 percent versus 35."

Penberthy added: "It's 30 percent of the population, but we have oversampled specific subgroups of the population to make sure that we can get adequate rates for Hispanic, Asian American, Asian-Pacific islander, etc. So it's 30 percent, but it has significant numbers of subpopulations, and that's sort of where we get that percent of the population."

BSA member James Lacey asked if there was an estimate of "proportion of the budget being spent today on the types of manual tasks that could be replaced" by computer automation.

"Everything is done manually currently," Penberthy said. "So I think there's a tradeoff between what we collect using some of the automated systems—[natural language processing] and machine learning doing these linkages—that will save us money, so we can add detail without necessarily increasing the cost."

Commenting on the plans to include more complex data in the registries, BSA member Mary Smith, co-founder of the Research Advocacy Network, said: "I'd just like to enforce the need of counting cancer patients who have been diagnosed with recurrence and

are living with metastatic disease. Cancer patients don't die of early stage disease, they die of metastatic disease. And yet we don't know right now how many patients are living with metastatic disease. And we don't know if that prevalence is changing. So are we winning or are we losing? So thank you for including that."

Three More RFAs Approved

The BSA also approved three RFAs: a U.S. and Russian research collaboration, research to optimize screening processes in diverse populations, and a network of 13 centers to discover and develop molecular cancer targets.

The bilateral research collaboration, in cooperation with the U.S. Department of State and the Russian Basic Research Foundation, is a new RFA that plans to issue 10 R21 awards over three years, at up to $100,000 per year for direct costs. The awardees would be chosen after receiving high scores from both countries' agencies following a simultaneous review process. The research program also plans to set aside 10 percent of its funds to support intramural research collaborations.

The awards would focus on 12 main topics—with 10 proposed by the Russian Basic Research Foundation: immunotherapy and the tumor microenvironment; targeted delivery of anticancer drugs; precision medicine for cancer; bio-imaging of cancer; biomedical applications of nanoparticles; brain tumor biology; epigenetics, proteomics and metabolomics; effect of cancer therapy on brain tumors; biomarkers; and the fundamental and clinical aspects of tumor angiogenesis.

Additionally, the U.S. proposed the topics of radiation epidemiology and physical sciences and engineering in cancer biology. In October 2015, an NCI delegation visited the Russian Basic Research Foundation in Moscow to negotiate the initial list of collaboration topics.

The BSA renewed the RFA for the NCI's PROSPR program, which promotes coordinated, multidisciplinary research to evaluate and improve the cancer screening processes for breast, colon and cervical cancer. First funded in 2011, PROSPR includes research sites across the country capturing large and diverse populations, and is jointly sponsored by the NCI Division of Cancer Control and Population Sciences and the Division of Cancer Prevention.

"It's clear that mortality can be reduced by cancer screening," said Stephen Taplin, deputy associate director of the Healthcare Delivery Research Program, in presenting the proposal to the board. "We know for breast, colon, and now lung cancer—we have three different cancers, all of which have been shown through randomized control trials, that there is a mortality reduction: about 15 percent for breast, about 13 to 21 percent for colon, and about 19 percent for lung."

"For cervical cancer screening, we don't have randomized control trials, we have large Nordic populations, where screening was introduced and then withdrawn and reintroduced—and when it was present, mortality reductions appeared, and invasive cervical cancer rates dropped. So no one is willing to put that through another randomized trial, it's very clear that from those population studies, cervical cancer screening works. But screening is a process, and not a test."

The PROSPR reissuance would place a greater emphasis on disparities; expand the data available for screening studies, by increasing longitudinal follow up and adding lung cancer screening; and evaluate the quality of the screening process. The program would set aside $12 million annually for four research centers, with one cancer type per center. It would also set aside $1.5 million for a coordinating center for data aggregation and oversight of quality measurements across centers.

The Cancer Target Discovery and Development Network works to validate discoveries from large-scale genomic initiatives and advance them toward precision medicine through data sharing and the work of the 13 participating centers.

"The network helps researchers go from "large multidimensional genomic data to target validation, small molecule modulators, and therapy," said Daniela Gerhard, of the NCI Office of Cancer Genomics, in presenting the proposal. "To date, there are 132 publications and more are coming. Twenty of them have already been cited more than 40 times."

The network maintains data portals that allow the centers to collaborate before posting the data publicly, and currently incorporates genomic data from projects such as The Cancer Genome Atlas and the Cancer Genome Characterization Initiative, among others. The RFA's renewal proposal would also integrate new data from the ALCHEMIST and NCI-MATCH trials.

The proposal would also hold a competition for $12 million in U01 cooperative agreement grants for a total of 12 centers. "There are no presumptions for the current centers," Gerhard said. "It's going to be an open competition. The goal is to establish the best network possible."

Cell Therapy Production, Patient Accrual Suspended at Rosenberg's Lab at NCI

By Paul Goldberg

NIH has suspended the facilities that produce investigational compounds for an NCI laboratory engaged in cell therapy production and a National Institute of Mental Health facility producing positron emission tomography materials.

As a result, no new new patients will be enrolled in affected trials until the issues are resolved, NIH said in a press release.

"There is no evidence that any patients have been harmed, but a rigorous clinical review will be undertaken," the statement reads.

The cell therapy lab is that of Steven Rosenberg, chief of the NCI Surgery Branch and one of the pioneers of immunotherapy.

"The NCI supports the NIH effort to improve our facilities to minimize potential risk to patients. Although it is not ideal to temporarily pause studies to improve the facility, we believe that these renovations will further minimize risk and patients will benefit," William Dahut, acting scientific director for Clinical Research in the NCI Center for Cancer Research, said in a statement. "We hope to complete the needed renovations in our labs as soon as possible. We look forward to enrolling new patients in the very near future."

Kite Pharma Inc., a Santa Monica, Calif., company involved in a Cooperative Research and Development Agreement with NCI said that "the cell therapy manufacturing facilities at the National Cancer Institute are undergoing a voluntary internal review by the National Institutes of Health in connection with the NIH's review of all NCI facilities involving sterile material."

The company said patients enrolled in NCI trials will continue to receive therapy, "but no new patients will be enrolled until the review is complete." The company said NCI's trial of a fully human anti-CD19 chimeric antigen receptor-based product candidate is not affected by the review.

Last year, serious problems identified in the NIH Clinical Center Pharmaceutical Development Section, prompting NIH to launch an investigation. This involved hiring two companies specializing in quality assurance for manufacturing and compounding to evaluate all of its facilities producing sterile or infused products for administration to research participants.

Preliminary findings by these companies—Working Buildings and Clinical IQ—"identified facilities not in compliance with quality and safety standards, and not suitable for the production of sterile or infused products," NIH said.

In a related development, last December the NIH director formed a working group of his Advisory Committee to the Director to evaluate and make recommendations about ways to enhance organization, financing and management of the Clinical Center and its affiliated labs and production facilities.

The working group delivered its report to the ACD April 21.

After the report was accepted, Collins issued the following statement:

The Clinical Center on the National Institutes of Health campus in Bethesda, Maryland, has made historic contributions to medical research. Many breakthroughs have occurred and many lives have been saved in this largest hospital in the world dedicated to clinical research. But, above all else, the hospital has an obligation to ensure that its processes for patient safety and quality of care are world class. Therefore, it was deeply disturbing to me when I learned last May of serious deficiencies in the hospital Pharmaceutical Development Section identified by the U.S. Food and Drug Administration. Fortunately, there was no evidence then, and there is no evidence to this date, that any patients were harmed by these problems, but it was incumbent on NIH to act swiftly.

While the immediate deficiencies identified by FDA have since been addressed, it became clear to me while addressing these issues that a broader review of hospital operations was needed by outside experts in hospital management and administration, patient safety, and clinical laboratory quality and safety regulations. I established a working group of my Advisory Committee to the Director (ACD) made up of such experts to evaluate and make recommendations about ways to enhance the overall organization, financing, and management of the Clinical Center and its affiliated labs and production facilities. Today, the ACD has delivered a set of strong recommendations based on the working group's findings that aim to improve the Clinical Center by fortifying a culture and practice of safety and quality; strengthening leadership for clinical care quality, oversight and compliance; and addressing sterile processing of all injectable products to ensure quality controls are at the highest standards.

I want to personally thank the members of the

working group. These renowned leaders in hospital and research administration and management have provided their time, knowledge, and expertise to help develop a plan that will establish and sustain world class standards at the Clinical Center.

In response to these recommendations, I am taking the following immediate actions:

• Establishing a hospital board and appointing Laura Forese, M.D., as chairperson. Dr. Forese, who is a member of the working group, currently serves as executive vice president and chief operating officer at New York-Presbyterian. The hospital board will be composed primarily of external advisors, replacing the current NIH Advisory Board for Clinical Research. The scope of the new board will be to advise on the Clinical Center's performance, including management, finances and quality; requirements for hospital leadership and gaps in expertise; and policies and organizational approaches that promote quality and patient safety.

• Establishing a Clinical Practice Committee of senior clinical and laboratory experts, with a charge to carry out continuous surveillance of all clinical activities in the Center and suggest strategies for improvement.

• Announcing the selection of Kathryn Zoon, Ph.D., as interim director of the newly established NIH Office of Research Support and Compliance to improve the agency's ability to maintain the highest levels of compliance with research regulations and standards. Dr. Zoon was previously the scientific director for the Division of Intramural Research at the National Institute of Allergy and Infectious Diseases. From 1992 to 2002, she was the director of the FDA's Center for Biologics Evaluation and Research (CBER).

• Making changes to performance plans for clinical staff by adding patient safety elements that are consistent across all NIH Institutes and Centers. This will enhance accountability and ensure that staff is meeting uniform hospital standards for patient care.

• Hiring Working Buildings and Clinical IQ, two companies specializing in quality assurance for manufacturing and compounding, to conduct assessments of all facilities that produce sterile or infused products for administration to research participants at NIH to ensure compliance with Current Good Manufacturing Practices and other regulations. This work is already well under way.

In addition to these immediate actions, NIH will implement other recommendations provided today by the ACD over the course of this year. Meanwhile, patients who come to the Clinical Center can be confident that they will continue to be cared for by highly dedicated medical professionals. Continuous improvement is an essential part of hospital management, and this is an opportunity to strengthen our patient safety framework. These changes and improvements will help ensure that the Clinical Center will reinforce its commitment to patient safety and compassionate care, while continuing its record of extraordinary scientific accomplishments.

Drugs and Targets

FDA Approves Gilotrif Tablets For Squamous Cell Lung Cancer

FDA approved Gilotrif (afatinib) tablets for the treatment of patients with advanced squamous cell carcinoma of the lung whose disease has progressed after treatment with platinum-based chemotherapy.

The U.S. approval follows the recent marketing authorization of Gilotrif in this patient population by the European Commission. Gilotrif, an oral, once-daily EGFR-directed therapy developed by Boehringer Ingelheim, is currently approved in the U.S. for the first-line treatment of specific types of EGFR mutation-positive NSCLC.

The sNDA was based on results of the head-to-head LUX-Lung 8 trial in patients with SqCC of the lung whose tumors progressed after first-line chemotherapy. Gilotrif, compared to erlotinib, demonstrated: significant delay in progression of lung cancer, reducing the risk of cancer progression by 18 percent; significant improvement in overall survival, reducing the risk of death by 19 percent; and a significantly improved disease control rate, at 51 vs 40 percent (p=0.002).

The most common adverse reactions observed with Gilotrif were diarrhea, rash or acne, stomatitis, decreased appetite, and nausea.

The University of Chicago and AbbVie entered into a five-year collaboration in oncology.

Initially, both organizations will work together to advance research in several areas of oncology, which could include, among others, breast, lung, prostate, colorectal and hematological cancer. Research projects are chosen by a joint steering committee, comprised of representatives from each organization. AbbVie also gains an option for an exclusive license to certain University of Chicago discoveries made under the agreement.

As part of the agreement, AbbVie will provide

funding for the collaboration that may be used for purposes including preclinical research, clinical trials and possible future programs at the University resulting from this partnership.

University of Chicago physicians and scientists will be able to participate in AbbVie-sponsored clinical trials, access new therapies developed by AbbVie for use in preclinical research funded under the collaboration, as well as work closely with AbbVie's research and development teams.

As part of the agreement, researchers from the University of Chicago and AbbVie will participate in an annual symposium that brings together scientists from both institutions to discuss research and evaluate potential new projects.