

# THE CANCER LETTER

June 27, 2014

• www.cancerletter.com

• Vol. 40 No. 26



## ODAC Clarifies Standards for Maintenance In Ovarian Cancer; Nixes Olaparib in 11-2 Vote

*By Paul Goldberg and Tessa Vellek*

Some of the questions that landed the AstraZeneca drug Olaparib (lynparza) before the FDA Oncologic Drugs Advisory Committee were classic:

- How much progression-free survival is enough?
- Can you make use of post-hoc analysis to identify a cohort in which the drug appears to be most effective?

Two big questions in their own right, but in the case of Olaparib, these questions were even more important because of the setting. Olaparib is intended as maintenance for relapsed ovarian cancer, where the standard of care is no cancer drugs at all.

(Continued to page 2)

### Joint NCAB-BSA Meeting

## NCI Prepares for Intramural Program Review

NCI has received some relief from sequestration, and the budget cuts will be adjusted proportionally, Director Harold Varmus said at the joint meeting of the National Cancer Advisory Board and the Board of Scientific Advisors June 23.

(Continued to page 5)

### In Brief

## James Downing Named CEO of St. Jude

**JAMES DOWNING** was named CEO of **St. Jude Children's Research Hospital**, effective July 15. Downing most recently has served as deputy director, executive vice president and scientific director of the hospital.

(Continued to page 11)

Sekeres: "I was not convinced that these data would be confirmed in another trial"

... Page 4

Joint NCAB-BSA Meeting  
Varmus Discusses Launch Of Lung-MAP Trial

... Page 7

Groups Urge FDA to Take More Action Against Tobacco Products

... Page 10

### In Brief

Lynda Chin Named Fellow at MD Anderson Cancer Center

... Page 11

### FDA News

Lymphoseek Label Updated to Include Head and Neck SCC

... Page 12

## ODAC Votes 11-2 Against Olaparib Accelerated Approval

(Continued from page 1)

That being the case, the application posed two even more intriguing questions:

- How much toxicity is too much for a drug in a setting where the accepted alternative is not to treat?
- And—in ovarian cancer—is PFS an acceptable endpoint in the maintenance setting? One of the maintenance therapies on the market—Eli Lilly's Alimta (pemetrexed for injection)—was approved based on overall survival in the treatment of advanced nonsquamous non-small cell lung cancer.

Finally the question of accelerated approval loomed large.

ODAC was asked to decide on accelerated approval before the confirmatory trial was fully accrued. Would patients be willing to accept randomization to the standard of care—nothing—after a maintenance therapy becomes available?

The committee undid this Gordian Knot of questions by recommending against accelerated approval in an 11-2 vote at its hearing June 25. For the future, the group discussed the question of whether overall survival should be the preferred endpoint in the ovarian cancer maintenance trial, and if PFS is to be accepted, how great should improvement be? Opinions were voiced, but no vote was taken.

Olaparib is an oral inhibitor of polyadenosine 5'-diphosphoribose polymerases (PARP).

AstraZeneca sought an accelerated approval for a subset of patients: those with platinum-sensitive

relapsed ovarian cancer with germline BRCA (gBRCA) mutation, as detected by an FDA-approved test, who are in complete or partial response to platinum-based chemotherapy.

The application was based on the subgroup analysis from a single study, D0810C00019, or Study 19. The trial focused on a broader population, enrolling 265 patients with platinum-sensitive ovarian cancer who were responding to therapy.

Study 19 met its primary endpoint, and while the finding was statistically significant, the difference in PFS was modest—3.6 months.

However, the greatest PFS was observed in one group of patients: 96 women with deleterious germline BRCA mutation (gBRCAm)-associated, platinum-sensitive ovarian cancer. In that subset, median PFS for patients randomized to Olaparib was 11.2 months in the olaparib arm, vs. 4.1 months for placebo (HR=0.17).

“Olaparib has a positive benefit-risk in platinum-sensitive relapsed BRCA ovarian cancer,” said Robert Ozols, former chief clinical officer at Fox Chase Cancer Center, who testified for AstraZeneca at the ODAC hearing. “Olaparib extends maintenance period by a clinically meaningful time with acceptable toxicity. Olaparib is the first in class agent with a compelling biologic rationale for use in germline BRCA patients in maintenance therapy. Olaparib also demonstrates a safety profile that is supportive of maintenance therapy. Most importantly, the confirmatory study is underway to confirm the benefit risk.”

FDA reviewers and several committee members noted that retrospective identification of the subgroup where the drug appears especially efficacious has the potential to bias the results.

“The gBRCAm subgroup was retrospectively defined and does not reflect a random population,” said Geoffrey Kim, FDA medical officer and scientific liaison for gynecologic malignancies. “In addition, the subgroup population was relatively small, and this raises the question of how reliable the estimations of treatment effect are.”

Richard Pazdur, director of FDA Office of Hematology and Oncology Products, said the statistical problems with Study 19 are the main reason the agency brought the application to ODAC.

“This trial has problems,” Pazdur said of Study 19. “And that’s why we’re looking at it, and trying to have a further discussion about other evidence that can be brought in. Remember one of the central points here that we are bringing out is that this trial lost randomization because of the convenience sampling. The questions

**Editor & Publisher:** Paul Goldberg

**Associate Editor:** Conor Hale

**Reporter:** Matthew Bin Han Ong

**Interns:** Tessa Vellek and Will Craft

Editorial, Subscriptions and Customer Service:

202-362-1809 Fax: 202-379-1787

PO Box 9905, Washington DC 20016

General Information: [www.cancerletter.com](http://www.cancerletter.com)

Subscription \$405 per year worldwide. ISSN 0096-3917.

Published 46 times a year by The Cancer Letter Inc. Other than "fair use" as specified by U.S. copyright law, none of the content of this publication may be reproduced, stored in a retrieval system, or transmitted in any form (electronic, photocopying, or facsimile) without prior written permission of the publisher. Violators risk criminal penalties and damages. Founded Dec. 21, 1973, by Jerry D. Boyd.

© The Cancer Letter is a registered trademark.

that have come out are not to show so much that it has clinical benefit, but what is other supporting evidence one could have that could help us make these decisions?"

The agency has signed off on a confirmatory trial—SOLO-2—which is powered for PFS improvement. Nonetheless, the question of appropriateness of the PFS endpoint—as opposed to overall survival—was added to the list of questions literally at the last minute during the meeting.

Olaparib's toxicity added to ODAC's dilemma.

In Study 19, three patients receiving Olaparib (2.2 percent) were diagnosed with laboratory abnormalities that suggested MDS or AML. One patient with wild-type gBRCA status and primary peritoneal cancer was diagnosed with MDS while on Olaparib treatment at day 313.

There was one case of MDS on the placebo arm.

AstraZeneca reported that among the 2,618 patients who have been treated with Olaparib to date there were 21 cases of MDS and AML (0.8 percent). Of these, 16 patients have died, with 12 deaths attributed to MDS/AML as the primary or secondary cause.

"I have some pretty major concerns about potential rates of MDS and AML that were seen in patients enrolled in this study," said ODAC chair Mikkael Sekeres, associate professor of medicine at the Cleveland Clinic Taussig Cancer Institute. "Obviously, the development of MDS or AML is complicated in the therapy-related setting and can be the result of being treated with multiple prior therapies, or [attributed] to the therapy that we are discussing here today. Another issue with MDS and AML is one of under-diagnosis, and this is pretty well-recognized in the MDS and leukemia community."

FDA doesn't require statistical significance when it considers safety signals. The agency has to weight toxicity against efficacy.

"Nine percent of the patients discontinued therapy," said ODAC member Aman Buzdar, vice president of clinical research and professor of medicine at MD Anderson Cancer Center. "If the patients were on holiday, and if this was a break, they would not discontinue therapy. And two percent of patients actually died from complications directly from therapy."

Ursula Maturlonis, the principal investigator on Study 19, countered that Olaparib has mild side effects when compared to other cancer drugs.

"I have treated many patients with Olaparib, and my impression is that it is a very well tolerated drug," said Maturlonis, medical director and program leader of the Medical Gynecologic Oncology Program at

Dana-Farber Cancer Institute and associate professor at Harvard Medical School. "I do think patients have a little bit of nausea, but they are going to have a little bit of nausea, they are going to have a little bit of abdominal distention because of their ovarian cancer, because of their preceding therapies. They are just coming off the heels of platinum-based chemotherapy."

Sekeres focused on the tradeoffs posed by toxicity in a maintenance therapy.

"We are introducing the therapy that, compared to some other agents, has fewer toxicities, but is not without toxicity," Sekeres said. "So during those seven months of progression-free survival, some of these patients are spending 70 days with nausea or 113 days with abdominal distension or 40 days with constipation."

"We are looking for some patient-reported outcome to support a progression-free survival, to prove to us it's worth it to give patients side effects, when ordinarily they would not receive a drug, and therefore would not have drug-related side effects during that period."

SOLO-2, AstraZeneca's confirmatory trial, is similar in design to Study 19. Altogether, 264 patients will be recruited (2:1 Olaparib/placebo ratio). The study is powered to detect a statistically significant, but relatively small difference in PFS between study arms. The results of this trial are expected to be available at the end of 2015.

"The situation in which we would normally give accelerated approval, the confirmatory studies are basically very near completion, or they are exploring the drug in a slightly different setting," Pazdur said at the ODAC hearing. "In this situation, you have a duplication of this trial. So it poses a problem with informed consent, in a sense, to say to a patient, 'Well, you're going to have the potential to go on a placebo here and—by the way—this drug is FDA-approved, so the FDA has demonstrated and believes that it is safe and effective for this indication.' The patient is going to say, 'Look, I want to go on the drug.'"

ODAC member Brent Logan, professor of biostatistics at the Medical College of Wisconsin, said he didn't have confidence in the PFS advantage seen in Study 19.

---

### INSTITUTIONAL PLANS

allow everyone in your organization to read  
**The Cancer Letter and The Clinical Cancer Letter.**

Find subscription plans by clicking Join Now at:  
<http://www.cancerletter.com>

---

“We saw a 7.1 [month] improvement in PFS, but there are a number of issues in the design of the study that raise concerns about that particular selection of the most promising subgroup that tends to bias towards a larger treatment effect,” said Logan, explaining his nay vote. “You have the issue of retrospective tightening and the potential bias due to lost randomization, and the very small sample size, so the results are fairly sensitive to changes in just a couple patients. That produced a lot of uncertainty about the magnitude of the improvement in median PFS.”

Concern about the side effects in the maintenance setting prompted Sekeres to vote against approval.

“I was extremely concerned about the risk of secondary cancers in ovarian cancer patients who would otherwise receive no therapy at all,” he said. “I was also concerned that some of these secondary cancers had not been found yet, and thus were underreported. I was troubled about causing women months of nausea or gastrointestinal side effects during a period of time they would otherwise be spending away from hospitals or clinics, enjoying their lives. Finally, I was not convinced that these data would be confirmed in another trial.”

Edward Trimble, director of NCI Center for Global Health, one of the two board members who voted to recommend accelerated approval, said Olaparib delayed initiation of more toxic therapies, and therefore warranted an accelerated approval.

“As I reviewed the data, in my mind, this agent, which is being given to a very limited number of ovarian cancer patients, namely those who have platinum-sensitive disease and germ-cell mutations, showed that it prolonged the disease-free interval and protected those patients from going on intravenous cytotoxic chemotherapy.”

The other vote in support of the application was cast by Tito Fojo, program director of medical oncology at NCI.

“Like everyone, I was on the fence,” Fojo said. “I decided to vote yes because I didn’t think that it was that compelling that if harm was going to be done it was going to be so enormous. I was willing to take a chance on that while we wait for the final data.”

Temporary ODAC member William McGuire, medical director of Gynecologic Cancer Outreach at Inova Fairfax Hospital, said that he had wavered as well, but ended up voting no.

“I was very conflicted on this vote, but I voted no because I am concerned that there is no survival advantage seen,” McGuire said. “This is a group of patients that have generally good survival, patients with

platinum-sensitive disease, and I am most concerned about a possible signal that this drug may cause AML and MDS, which is a serious toxicity, and could actually lead to early death in a patient that would otherwise live for a longer period of time.”

Originally, FDA asked ODAC to comment on the magnitude of PFS that would provide convincing evidence of efficacy in the confirmatory study. However, before the committee turned to that question, FDA’s Pazdur amended it, asking whether overall survival should be the preferred endpoint.

“I support overall survival as an endpoint for the SOLO-2 trial,” said Sekeres. “I would accept PFS, along with the patient-reported outcome. It shows me that if they are not living longer, they are living better. In terms of duration, I’m not going to pretend to be an expert in PFS in ovarian cancer; I’m just not. I think we have a range of 3.6 months to 10 years—it’s probably somewhere in there.”

Biostatistician Logan agreed.

“I think survival outcome should be the preferred endpoint in these types of maintenance studies,” Logan said. “We are talking about an ongoing therapy with an ongoing exposure to toxicities and I think that’s difficult to weigh that kind of exposure against progression-free survival. Quality of life is certainly a reasonable alternative, but it’s difficult to show that kind of thing.”

Howard Fingert, the non-voting industry member of ODAC, said PFS should be acceptable.

“I want to bring back the concept of what is the practical reality of measurements,” said Fingert, senior medical director of Clinical Intelligence Millennium at the Takeda Oncology Company. “Most of this group has said no trial is perfect, but there is a practical reality in measuring PFS, either by investigative or by outside third party, that helps us understand the utility of a drug in a clinical protocol.

“So even though [PFS] is not perfect, I do think that this is an acceptable approach going forward that is part of the SOLO-2 trial and it’s why it is supported by academia and why I think the FDA, who accepted their protocol design, accepted their endpoint.”

Trimble concurred.

“Speaking in part on behalf of the Ovarian Cancer Trials Group, I am a strong supporter of PFS as a trial endpoint,” he said. “I think if we are thinking about quality of life, it’s not so much about the quality of life comparison between the Olaparib and placebo, it’s about the quality of life of patients who are receiving intravenous cytotoxic chemotherapy—which, giving all these drugs myself, is far worse than the relatively mild

side effects we saw reported for Olaparib.

“We can give people six months where they don’t have to go to the hospital for intravenous toxic chemotherapy if they have a maintenance drug, and I think that is definitely a significant clinical benefit. I think the six months that we saw in the trial we analyzed today is an appropriate magnitude of treatment effect on PFS.”

Sekeres, Logan, and Antoinette Wozniak, professor of the department of oncology at Wayne State University School of Medicine, rotated off the committee following the June 25 meeting.

### Joint NCAB-BSA Meeting

## **Varmus: Frederick National Lab Looking to Expand Beyond RAS**

(Continued from page 1)

“The FY 14 budget is not very dissimilar from last year’s budget,” Varmus said. “We had relief from sequestration. We have correspondingly reduced the level of cuts we have imposed on both competitive and non-competitive awards. We expect to be awarding roughly the same number of RPGs, research project grants, as we did in FY 13.”

In his remarks, Varmus said the institute is preparing for NIH-wide review of the intramural program, which is aimed at developing a 10-year campus-wide plan.

“The NCI has taken this charge quite seriously, and not trying to avoid simply delivering pablum about the traditional virtues of having an intramural program instead digging into a number of important questions,” Varmus said. “What kinds of new or continuing scientific initiatives deserve support, because they have special features of the intramural program, the Clinical Center and existing networks of investigators, and special facilities that make those programs particularly suitable for intramural research.

“We are all a little nervous about what will be said when NCI efforts to represent a very large fraction of the overall intramural program: 40 percent of the clinical center activity, the only epidemiological program of great size, and a very large intramural basic research program, run largely within the Center for Cancer Research.”

NCI’s spending on the intramural program is the highest at NIH (The Cancer Letter, [March 7](#)). Altogether, NIH institutes spend 11.1 percent on their intramural programs. At NCI, the budget authority for intramural research accounted for about \$869 million

in fiscal 2014, about 17 percent [of the institute’s overall spending](#).

Intramural research is separate from contracts. NCI’s largest contract involves running the Frederick National Laboratory for Cancer Research, which receives about \$300 million a year. This amount is expected to increase during the current fiscal year (The Cancer Letter, [Feb. 28](#)).

“We paid, over the last few years, special attention developing the Frederick National Lab with strong guidance from a new advisory committee, the Frederick National advisory committee,” Varmus said at the meeting.

“The national lab advisory committee at this point is looking for new projects that have the same level of appeal and importance as our RAS initiative, which is the keystone of the national lab at the moment. We will bring those candidate projects to the Board of Scientific Advisors for discussion as we did in the case of RAS. We try to do these projects with no change in the funding level for the national lab. And that was true for RAS. We closed some projects, and created this new initiative.

“Meanwhile a lot good things are happening on the RAS initiative, which has gotten publicity from me and others. Frank McCormick, who runs this, and is now spending a lot of time in Frederick, is shaping a really good team for the hub of the project at the Frederick National Lab... He’s also been discussing RAS projects with industry, it has a quite a large number of pharmaceutical companies that are now considering possibility of sharing pre-clinical and early clinical data on inhibitors of RAS signaling, so we can do for RAS what was done for HIV drug development.”

*Excerpted text of Varmus’s remarks follows. His full remarks are available on [The Cancer Letter website](#).*

We are looking for, hoping for, further relief for sequestration imposed in FY13 when NCI lost almost 6 percent of its budget.

We got halfway back in FY14, as you’ll remember. The president’s budget for FY15 asks for another 1 percent recovery. The Senate markup proposes yet another 1 percent, so that would be good, but it is not yet out of committee. So we are basically waiting to see what’s going to happen.

There’s been little action on the House side; the numbers are probably going to be lower, we don’t know exactly where they are going to end up. The proceedings of that committee have been slowed by a number of things, one of which is the fierce battle that [Rep. Jack] Kingston is under to try to win Republican primary to

run for the Senate in Georgia. That runoff doesn't start until late July, so we don't expect too much to happen until then.

Further in the wake of the fall of [Rep.] Eric Cantor [R-Va.], and with the prospect of a pretty intense election process in November, it's pretty unlikely that we'll have resolution of the appropriation battles until after the election, and possibly not even in the lame duck session. So we may be waiting until the new Congress assembles in January.

Not so different from what's happened in previous years, but if you try to manage a roughly \$5 billion budget like nice to know how much money you have. So despite the promises we have gotten from [Sen. Barbara] Mikulski [D-Md.] and others whose chair appropriation committees, I don't think we'll have a timely budget this year either.

We have had hearings on the appropriations this year. As has been the custom in recent years but not tradition over many years, there was only one witness who was allowed to deliver an opening statement—that was [NIH Director] Dr. [Francis] Collins. He certainly has the right to do that, but the institute directors sit mute until they are asked a question.

There were four at us at each hearing—the House and the Senate hearing. The questions, in general, were friendly.

There were follow-up questions also, and the consequences of the hearing are hard to know. It didn't get a whole lot of publicity. The members frequently spoke to the sorry state of NIH funding, but the consequences we care about would be an appropriation that is a healthy one.

There's been much talk on the Hill about trying to repair the damage that's been done over the last decade, in which we have lost about 25 percent of our spending power, and we are waiting to see whether any actual bills materialize and win support. But it's interesting to hear about.

I'm going to say a couple of things about a hearing that occurred before the Senate Special Committee on Aging, chaired by Sens. [Bill] Nelson [D-Fla.] and [Susan] Collins [R-Maine]. The hearing was on cancer in older populations, and I will tell you a little about it only because this was the first time in four years I have been asked to present testimony at a hearing.

That, in a sense, is partly a byproduct of being just an institute director rather than NIH director, but it's also a symptom of the fact that there isn't as much attention on Capitol Hill to the health of the nation, other than of course beating up the president on healthcare reform,

as there ought to be.

This hearing was designed to be an exercise in considering some of the efforts that we are making to combat cancer in the elderly. And I took the occasion to talk about several things, the demographics of cancer, and they collide with the demographics of the U.S. That is, we have a marked increase in individuals over age 65 in this country. Sixty-five is about the median age for cancer in the country.

There are effects of aging on the way we approach prevention, the way we approach screening and when screening should be done; and the way we approach therapeutics—who should be included in clinical trials and who should receive our best therapies. Cancer in the aging is affected by comorbidities.

I think there is an evolving sense in thinking about cancer in the elderly that we should pay more attention to physiological than chronological age. As I pass 65, I think most of you know happened some time ago, I'm particularly sensitive to this—I want the best therapy. I don't care what the number is behind my name.

There's general sympathy with that point of view.

We had quite an interesting group of witnesses. Valerie Harper, whom those of you who don't spend too much time watching daytime TV may not know as well as many in the normal human population know, is a star of stage and screen and a very gracious woman who has lung cancer that has metastasized to her brain, and she's been a great proponent of cancer research and cancer care, and spoke extremely elegantly about her desires to have NCI receive the money as the army.

Tom Sellers, who's head of the Moffitt Cancer Center was there; Mary Dempsey, who runs the cancer center in Maine that is devoted to sympathetic care for cancer patients; and remarkable young man named Chip Kennett, who was until recently a chief staffer for Sen. Rockefeller, who at the age 32 developed adenocarcinoma of the lung.

That gave him and me a chance to talk about some of the most remarkable changes that occurred in cancer care over the last few months. He had an ALK translocation, received an ALK inhibitor, went into remission, had recurrence, was treated with the second line ALK inhibitor, successfully temporarily. Then, when that failed, received at Hopkins one of these new checkpoint inhibitors and immunotherapy and had looked to be in robust health despite the fact we know he had widespread metastatic disease, but he gave a marvelous presentation, and gave me a chance to talk about things that happened in the last few years.

And we had six members of the Senate there, all

engaged in this topic and saying the nicest possible things about NIH and NCI. That engagement was particularly notable with respect to [Sens.] Elizabeth Warren [D-Mass.] and [Sheldon] Whitehouse [D] from Rhode Island as well as the chair and ranking member.

#### **“Relatively Minor Legislative Initiatives”**

There are many minor, what I would consider relatively minor, legislative initiatives underway.

There remains persistent interest in what is called recalcitrant cancers as a result of the legislation we’ve discussed here before. As I mentioned previously, we submitted a report and framework as requested on pancreatic ductile adenocarcinoma some months ago, which has been very well received by staff and members on the Hill.

I still get questions about it, and you will hear about an RFA we are conducting with NIDDK, the Diabetes and Digestive Kidney Disease Institute, to study the appearance of pancreatic cancer in patients who have been recently diagnosed with diabetes of certain types. And I’ll also mention the RFA initiative. Both represent follow-ons to some of the recommendations in our report on PDAC.

Jim will say a word or two about our report on small cell lung cancer, our second so called recalcitrant cancer, and Jim also recently briefed a large number of congressional staff on our approach to the cancers that the public considers the most deadly.

I would urge that all of us remember that our definitions of cancers are rapidly expanding beyond simple site of origin of cancer. We need to think about cell lineages, and genotype when talking about specific kinds of cancer.

I also find it less than optimal to talk about one cancer being more deadly cancer than another, when you have a cancer that’s not considered a deadly cancer and it’s killing you—that’s a deadly cancer, important to keep that in mind before we have internecine wars over these topics.

I think we are making headway on that trying to move beyond five year survival as the only metric to consider what I would think of as intractable clinical and scientific problems that deserve our greatest attention.

So that’s it for Congress.

---

#### **Advertise your meetings and recruitments**

In The Cancer Letter and The Clinical Cancer Letter  
Find more information at: [www.cancerletter.com](http://www.cancerletter.com)

---

#### **The Launch of Lung-MAP**

I want to now deal with assorted items in no special order, but I’m going to start temporally with an announcement made last week about a clinical trial called Lung-MAP, a multi-armed, genetically informed trial that will address the prospects for improving therapy of squamous cell cancer of the lung.

One important feature of this trial, apart from its deep dependence on genetic analysis of tumors, is the interesting way which it’s been organized with much of the management conducted at the Foundation for the NIH, with engagement by NCI, by the FDA, by Friends of Cancer Research, by several pharmaceutical companies, by Foundation Medicine and of course by the National Clinical Trials Network led by SWOG in this case.

Payment here is about one quarter from the NCI, about three quarters from industry. I have been very impressed by the collegial way which these many entities have worked together to develop this complex trial. It has five major arms, four with target-specific drugs, one with immunotherapy, and all arms controlled. This is one of the first so-called precision medicine trials.

No doubt all of you are familiar with IMPACT, a smaller trial started within the NCI intramural program several months ago, the ALCHEMIST trial which we described here before, as an attempt to assess use of targeted drugs as adjuvant therapies and early stage lung adenocarcinoma. The MATCH trial, a much more complex trial that will deal with advance cancers of all types, with over 10 companies already lined up to provide both approved and unapproved drugs in that trial and especially with respect to MATCH we hope to launch later in the year.

I want to express my gratitude to the many members of the NCTN working that out and to [NCAB member] Charles [Sawyers, chair of Memorial Sloan Kettering’s Human Oncology and Pathogenesis Program] who have been representing this group, helping us to plan this trial along with Jim and his colleagues, Jeff Abrams and others, in the Division of Cancer Therapy and Diagnostics.

All this is happening simultaneously with the reorganization and cooperative groups and the community-based trials and formation of NCTN and the National Community Oncology Research Programs with consolidation of some of the groups fades out for pre-existing organizations. This has all been complicated. We have also been creating the Early Therapeutics Clinical Trials Networks.

We’ll present all that to you in great detail at the

fall meeting of the NCAB, both in response to your requests for such an analysis, and also because there's a lot of interest things going on.

I would, in the meantime, point you all, if you haven't gone already, to a recent compilation of highly reliable information about the process, which this occurred and budgets for the various components of these groups. It's present under clinical trials on cancer.gov. We've put this together with some care. You will find there's accurate information you can depend on you will also find descriptions of precision trials that I have described including Lung-MAP.

In these clinical trials, there's heavy dependence on cancer genomics and informatics, which will be becoming important components of all our trials especially those that address precision medicine. There's been a lot of activity in this confluence of informatics and genomics and I'm just going to telegraph some of these things to you and if you want to hear more let me know and we can do it next time.

The Center for Cancer Genomics, now headed by Lou Staudt, who's back in the room, has initiated genomics data commons as well as continued the analysis of data being generated through the Cancer Genome Atlas Project and some projects being conducted jointly with International Consortium on Cancer Genomics.

Secondly, CBIIT, headed by Warren Kibbe, will announce recipients of cloud pilots, which we talked about here before. We are of course working with NIH more broadly in their initiative called Big Data to Knowledge, BD2K, a project now under the supervision of Phil Bourne, of UC San Diego, who has come here to be the chief—I don't know the official title is, but in charge of developing large scale informatics efforts on the NCI campus.

The NCI continues to be active in the organization I have described here before, the Global Alliance for Global Health, GA4GH, an organization which I believe will soon launch. Some of us have seen in the draft constitution. There are about 192 members to this group, institutional members, people who indicated an intention to join. This will be a big tent with lots of players, industry to smaller academic institutions, with many in between, including agencies such as NIH and institutes around the world.

The Global Alliance has initiated some pilot projects, the most interesting of which to my view is an attempt to compile all known information about BRCA 1 and 2 mutations, an effort led by Steve Chanock of DCEG and John Burns from the U.K., and I'm

optimistic this will illustrate the power of compiling information worldwide about an important genetic component of cancer, in a way that illustrates not just the virtues of compiling the information but detriments of keeping that information within the confines of a single company. You know who I mean.

In response to requests from you, including [BSA Chair] Todd [Golub], especially Todd, we're going to have a discussion of our future of cancer genomics at the NCI at our fall meeting. BSA perhaps will repeat it for the NCAB, unless you want to meet together again.

### **Grants and Intramural Program Review**

Couple of things about grants; everyone wants to know what's happening with grants.

The FY 14 budget is not very dissimilar from last year's budget. As I mentioned before, we had relief from sequestration. We have correspondingly reduced the level of cuts we have imposed on both competitive and non-competitive awards. We expect to be awarding roughly the same number of RPGs, research project grants, as we did in FY 13.

You will all remember from your previous visits to the website how those patterns of awards go in relation to percentile scores, but we think very similar kind of pattern will emerge this year. We won't have final data until the end of the fiscal year, and we will give a full report on that in the fall.

Couple of things about policies and mechanisms about grants. We discussed the interest the NCI has in altering the biosketch and other institutes agreed to do this and now this is a NIH-wide effort. If you read Sally Rockey's blog, she is deputy director for extramural research for NIH, she has announced the altered biosketch will soon become official business and will request that all applicants provide a written description of their five most important contributions to science.

Some of the details what will be involved are in her blog, and presumably will become official information very soon.

As we have discussed here before, the NIH has a NIH-wide interest in placing more emphasis on past accomplishments on the people we support, to decrease the complete emphasis on projects.

And that is manifest at the NCI by our outstanding investigator award, a seven-year award announced officially very soon, with the help of Dinah Singer putting some of the final brushes on this announcement and I know from discussions that many other institutes will be putting out very similar kinds awards, with some



difference in dollar amounts and other expectations and details how applications are crafted.

We are also hoping soon to have language in our notice of award that we expect all investigators who receive money from the NIH or the NCI to be willing to provide service on review groups, because still it remains a huge problem. Review is subpar, and one reason it's subpar is we don't have enough senior experienced people serving in study section, my personal opinion.

We had a group meet yesterday to talk about some of the new career awards we are talking about, and while none of these is resembling a finalized state, we're thinking awards that help propel trainees through the training process by beginning late in graduate work, working into post-doctoral period awards that would be designed for staff scientists, and awards that might facilitate the end of a glorious career by people who are in the late stages of their independent research career. We're going to have discussion on that later in the session.

Recommended by Dinah that I mention something about RFA that's been very successful and is terminating, that's RFA been reissued twice for the mouse models of human cancer consortium. A meeting was held last week to celebrate end of 15 years of support. This has been a successful program that's helped developed mouse modeling across the spectrum of activities. Just to show you some things do come to an end after one, two, three renewals, but I think good example of something that is clearly needed at the time. Perhaps has outlived its usefulness as a project which money should be retained for special awards.

### **Review of Intramural Program**

I mentioned to you before that the NIH in general is carrying out a review of the intramural program asked by Francis Collins to develop a prospectus for the next ten years, in part to see how we're doing, in times of financial stress and to show that NIH is paying careful attention to what is offered on the intramural campus.

The NCI has taken this charge quite seriously, and not trying to avoid simply delivering pablum about the traditional virtues of having an intramural program instead digging into a number of important questions. What kinds of new or continuing scientific initiatives deserve support, because they have special features of the intramural program, the clinical center and existing networks of investigators, and special facilities that make those programs particularly suitable

for intramural research.

How do we sustain the vitality of the clinical research center—at a time where growing fixed costs are growing in a budget which is declining, if anything—and how we make better use of one important component of the program, the population sciences that exist in DCEG, the Division of Cancer Epidemiology and Genetics.

And how do we exploit the progress we've made in enhancing diversity in the intramural program. These are featured elements of our report, which is still in stages of composition, but will be presented in detail at the fall meeting.

As that report goes forward to be hopefully not homogenized, but amalgamated into a larger report for the advisory committee to the director which will then, I don't know, will say something about the intramural program. We are all a little nervous about what will be said when NCI efforts to represent a very large fraction of the overall intramural program: 40 percent of the Clinical Center activity, the only epidemiological program of great size, and a very large intramural basic research program, run largely within the Center for Cancer Research.

Let me juxtaposition those with the Frederick National Lab, not part of the intramural program. It's part of our Federally Funded Research Development Contract, FFRDC.

It's housed in Frederick, Md., with a large part of intramural program mainly paid for by the Center for Cancer Research.

We paid, over the last few years, special attention developing the Frederick National Lab with strong guidance from a new advisory committee, the Frederick National advisory committee, which is now run by Joe Gray [associate director for translational research at the OHSU Knight Cancer Institute], a round of applause for Joe.

The national lab advisory committee at this point is looking for new projects that have the same level of appeal and importance as our RAS initiative, which is the keystone of the national lab at the moment. We will bring those candidate projects to the Board of Scientific Advisors for discussion as we did in the case of RAS.

We try to do these projects with no change in the funding level for the national lab. And that was true for RAS. We closed some projects, and created this new initiative.

Meanwhile, a lot good things are happening on the RAS initiative, which has gotten publicity from me and others. Frank McCormick [professor emeritus

at UCSF Helen Diller Family Comprehensive Cancer Center], who runs this, and is now spending a lot of time in Frederick, is shaping a really good team for the hub of the project at the Frederick National Lab. He's drawing in a lot of extramural investigators through the obvious social connections, webpages and other Internet-based devices but also by holding workshops, one on synthetic lethality, one on aspects of RAS signaling, and by announcing program announcements—one on synthetic lethality will soon be released.

He is also been discussing RAS projects with industry, it has a quite a large number of pharmaceutical companies that are now considering possibility of sharing pre-clinical and early clinical data on inhibitors of RAS signaling, so we can do for RAS what was done for HIV drug development.

And he is working with some of those companies and other donors, advocacy groups, for example, to create post-doctoral fellowships for people to work on RAS projects and act as emissaries who travel from lab to lab, doing collaborative work on RAS project. So this is very successful, and I hope with Joe's help will find some other areas that can be pursued with this model through the Frederick National Lab.

### **\$270 Million for AIDS Research**

Couple of words about Office of AIDS Research and budget.

As many of you know, about 5.5 percent of the NCI budget comes from DOAR, which is a kind of pseudo-institute. It has a budget, about 10 percent of the NIH budget, and allocates money to the institutes to carry out AIDS-related research.

Francis Collins asked for a review of that portfolio, especially in view of the success we have had in therapeutics and possibly in change the view of changing characteristics of the AIDS epidemic, worldwide and domestically. The committee that was put together to look at the portfolio has issued a report to the advisory committee to the director. We're still waiting for an interpretation of that report. It will have significant effect, 5.5 percent of the budget is \$270 million—that's not chicken feed.

And we have an advisory group in the NCI run by Robert Yarchoan that oversees efforts in dealing with HIV and AIDS. Our emphasis has been on co-morbidities, most obviously cancer, a variety of cancers, some AIDS-defining, others not AIDS-defining, but probably AIDS-related, with continued involvement with HIV therapeutics and a fairly strong

investment in HIV vaccines.

This is a possible topic for discussion that one of our future meetings—especially once Francis indicates how we will interpret the report that recently received from the special committee.

Final topic. I don't usually say too much about small business innovation research here, SBIR awards, but we've had a very energetic SBIR office headed by Michael Weingarten, and it's done number of interesting things over the years, but has received a fair amount of press attention last week with development of so called NIH ICORP program.

This is an effort to take grantees to receive phase I SBIR awards and teach them how to explore markets for their inventions and facilitate the transfer of what is learned on these small business awards to making a real product.

Several institutes at the NIH, in addition to NCI—Heart Lung and Blood Institute, The National Center for Advancing Translational Sciences, and the National Institute of Neurological Disease and Stroke—are all playing here, but we are the lead institute and Michael is guiding the charge, and we'll get a report from him eventually how things have worked.

## **Groups Urge FDA to Take Action Against Tobacco Products**

*By Tessa Vellek*

On the fifth anniversary of the landmark 2009 law granting the FDA authority over tobacco products, 10 leading public health and medical organizations called on the FDA and the Obama Administration to prioritize three actions to reduce tobacco use.

- Extend the FDA's jurisdiction to all tobacco products, with no exceptions, no later than April 25, 2015
- Issue the first-ever product standard governing the design and content of tobacco products, reducing toxicity, addictiveness, and appeal of cigarettes
- Require large, graphic cigarette warning labels covering the top 50 percent of the front and back of cigarette packs

This joint statement was issued June 19 by the American Academy of Pediatrics, American Cancer Society Cancer Action Network, American Heart Association, American Lung Association, Americans for Nonsmokers' Rights, Campaign for Tobacco-Free Kids, Legacy, National African American Tobacco Prevention Network, Smoking Cessation Leadership Center, and Tobacco Control Legal Consortium.

On June 22, 2009, President Barack Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which granted the FDA the authority to regulate the manufacturing, marketing, and sale of tobacco products. Five years later, these health groups are urging the FDA to go further with tobacco regulation.

“As the nation marks the 50th anniversary of the first surgeon general’s report and the fifth anniversary of the Family Smoking Prevention and Tobacco Control Act, our organizations call on the FDA and the Obama Administration to take action that can create a tobacco-free generation and end the tobacco epidemic for good,” they said in the statement.

The groups commended the FDA for the steps it has previously taken to reduce tobacco use, but pushed the FDA to take further action.

“It has restricted tobacco marketing, especially to children; ended the sale of candy- and fruit-flavored cigarettes that appealed to kids; cracked down on illegal tobacco sales to kids; banned misleading health claims about cigarettes such as ‘light’ and ‘low-tar;’ and launched a national media campaign to prevent youth tobacco use,” the statement read. “However, as the latest surgeon general’s report made clear, our nation’s tobacco epidemic calls for even bolder actions.”

### *In Brief*

## **Downing named CEO of St. Jude**

(Continued from page 1)

His primary focus as CEO will be to oversee an expansion of the hospital’s clinical, research and infrastructure programs.

He succeeds William Evans, retiring from the position after 10 years and returning full time to his long-standing pharmacogenomics research program at St. Jude.

Downing’s work as a genome sequencing pioneer, overseeing the Pediatric Cancer Genome Project, was recognized in 2012 by TIME magazine as one of the Top 100 new scientific discoveries.

Downing outlined his vision for St. Jude’s expansion, which includes: growing number of patients treated on the St. Jude campus; expanding the pediatric solid tumors treatment and research programs; expanding the International Outreach Program; incorporating genomic analyses into clinical work using the Pediatric Cancer Genome Project; growing the number of patients enrolled on the St. Jude LIFE long-term follow-up survivor study; and establishing a formalized patient advocacy consortium.

**LYNDA CHIN** was named a recipient of the Chancellor’s Health Fellowship by **MD Anderson Cancer Center**.

Chin, chair of the Department of Genomic Medicine, was recognized for development of a patient-centric oncology care delivery system initiated in late 2012. She is the wife of MD Anderson President Ronald DePinho.

During her one-year appointment as a fellow, she will coordinate the planning and development of a similar effort focusing on management of diabetes in South Texas. Chin will collaborate with faculty at The University of Texas Rio Grande Valley, including medical school dean Francisco Fernandez.

She plans to continue her roles as professor and chair of the Department of Genomic Medicine and scientific director of the Institute for Applied Cancer Science at MD Anderson.

Other current fellows are Jan Patterson, director of the Center for Patient Safety and Health Policy at UT Health Science Center at San Antonio, who is focusing on clinical effectiveness programs; and Stephen Linder of the School of Public Health at the UT Health Science Center at Houston, who is focusing on public health.

**THOMAS HANSEN**, chief executive officer of **Seattle Children’s**, will retire in 2015 as part of a long-planned leadership transition.

The hospital’s board of trustees plans to initiate a nationwide search for his replacement, beginning immediately with the appointment of a Search Committee.

Hansen, 66, who came to Seattle Children’s as CEO in 2005, said he plans to spend more time on research, particularly developing low-cost ventilators for premature infants born in low and middle income countries.

“I’ve celebrated the 100th anniversary of our organization; watched our research institute grow from less than 100,000 square feet with \$15 million in NIH funding to 330,000 square feet and nearly \$45 million in NIH funding; launched the new name and brand of Seattle Children’s; opened our first major outpatient expansion in Bellevue, and saw the completion of the beautiful new Building Hope expansion at the hospital; watched our foundation funding increase 66 percent; and so much more,” Hansen said.

---

**Follow us on Twitter: @TheCancerLetter**

---

**CORNELIA ULRICH** and **BRUCE EDGAR** will join the **Huntsman Cancer Institute** at the University of Utah as early as Sept. 1.

Ulrich currently serves as a director of the National Center for Tumor Diseases and department head at the German Cancer Research Center in Heidelberg, Germany. She will assume a leadership role, serving as HCI's new senior director of population sciences.

Her husband, Edgar, a professor and researcher at the German Cancer Research Center-Center for Molecular Biology Heidelberg Alliance, will head an HCI laboratory. The two have previously held faculty positions at the Fred Hutchinson Cancer Research Center.

"Dr. Ulrich and Dr. Edgar are a 'dynamic duo,' bringing with them an incredible breadth of knowledge and experience from the cancer research world. They are highly regarded researchers, both in the United States and in Europe, and we are indeed fortunate to have them join our ranks," said Mary Beckerle, HCI's CEO and director.

"Dr. Ulrich's studies into cancer prevention, especially in the realm of colon cancer, have brought major discoveries that have saved countless lives, and Dr. Edgar's work in cell cycle progression and proliferation have deepened our understanding of how normal cells become malignant."

Ulrich is an epidemiologist focused on how factors such as diet, exercise, and use of non-steroidal anti-inflammatory agents influence colorectal cancer risk, prevention, and prognosis. She is an elected member of the European Academy of Sciences and is currently a senior editor of the journal *Cancer Epidemiology, Biomarkers & Prevention*. In her new role, Ulrich will join the HCI Director's Cabinet, which oversees all clinical and research programs.

Edgar will join the faculty of the University of Utah as a professor in the Department of Oncological Sciences and an investigator in HCI's Nuclear Control of Cell Growth and Differentiation program. An expert in the molecular genetics of cell growth and cell cycle control using the *Drosophila* model system, he is a fellow of the American Association for the Advancement of Science and serves on the editorial board of the molecular biology journal *Cell*.

---

**Advertise your meetings and recruitments**

In *The Cancer Letter* and *The Clinical Cancer Letter*

Find more information at: [www.cancerletter.com](http://www.cancerletter.com)

---

## FDA Approvals

### **Lymphoseek Label Updated To Include Head and Neck SCC**

**FDA approved a new use for Lymphoseek** (technetium 99m tilmanocept) Injection, a radioactive diagnostic imaging agent, to determine the extent squamous cell carcinoma has spread in the body's head and neck region.

In 2013, Lymphoseek was approved to help identify lymph nodes closest to a primary tumor in patients with breast cancer or melanoma. It can now be used to guide testing of lymph nodes closest to a primary tumor for cancer, in patients with cancer of the head and neck.

Lymphoseek's safety and effectiveness were established in a clinical trial of 85 patients with squamous cell carcinoma of the lip, oral cavity, and skin. All patients were injected with Lymphoseek. Surgeons subsequently removed suspected lymph nodes—those identified by Lymphoseek and those based upon tumor location and surgical practice—for pathologic examination. Results showed that Lymphoseek-guided sentinel lymph node biopsy accurately determined if the cancer had spread through the lymphatic system.

Lymphoseek is marketed by Navidea Biopharmaceuticals Inc.

**FDA approved Aloxi (palonosetron HCl) injection** for the prevention of nausea and vomiting due to chemotherapy in children as young as one month to less than 17 years old, including highly emetogenic cancer chemotherapy.

This is the first approval of a product for acute chemotherapy-induced nausea and vomiting prevention in patients aged one month to six months.

The approval was based on a randomized, double-blind, non-inferiority pivotal trial comparing single-dose intravenous Aloxi 20 mcg/kg given 30 minutes prior to chemotherapy to a standard of care IV ondansetron regimen of 0.15 mg/kg given 30 minutes prior to chemotherapy followed by infusions four and eight hours after the first dose of ondansetron.

Within the first 24 hours after chemotherapy, complete response, defined as no vomiting, no retching and no antiemesis rescue medication, was achieved in 59.4 percent of patients who received Aloxi 20 mcg/kg versus 58.6 percent of those who received the ondansetron regimen, meet its primary endpoint.

Treatment-emergent adverse events were comparable across both arms, with the most frequently reported in the palonosetron group being headaches. While this study demonstrated that pediatric patients require a higher palonosetron dose than adults to prevent CINV, the safety profile was consistent with the established profile in adults. Aloxi is sponsored by Eisai Inc. and Helsinn Group.

**FDA granted Fast Track status for DNX-2401**, a replication-competent adenovirus for patients with recurrent glioblastoma, developed by DNatrix Inc.

Fast Track status facilitates development of new products for serious or life-threatening conditions which demonstrate the potential to address unmet medical needs, with the goal of getting important new products to patients earlier.

Oncolytic virus therapy is based on the concept of using live viruses to selectively infect and replicate in cancer cells, with minimal destruction of normal tissue. Replication amplifies the input dose of the oncolytic virus and helps spread the agent to adjacent tumor cells.

DNX-2401, a conditionally replication-competent adenovirus, is being developed for the treatment of several cancer indications, including patients with recurrent glioblastoma.

In a phase I dose-escalating monotherapy study conducted with DNX-2401 at MD Anderson Cancer Center for patients with recurrent malignant glioma, efficacy results have been extremely promising, with

evidence of total tumor destruction and long-term survival in several patients. A second phase I trial evaluating DNX-2401 in combination with the drug Temozolomide is currently underway at the Clinica Universidad de Navarra in Pamplona, Spain for patients with recurrent glioblastoma.

**FDA granted Orphan Drug Designation to mocetinostat**, as a treatment for myelodysplastic syndrome, developed by Mirati Therapeutics Inc.

Mocetinostat is being evaluated in phase II clinical studies in combination with Vidaza as a treatment for intermediate and high-risk MDS, as well as a single agent treatment in patients with diffuse large B-cell lymphoma and bladder cancer targeting specific genetic mutations in histone acetylation that increase the likelihood of response in tumor cells.

The FDA's Office of Orphan Drug Products grants orphan status to support development of medicines for underserved patient populations or rare disorders that affect fewer than 200,000 people in the U.S.

Mocetinostat is an oral, spectrum-selective HDAC inhibitor. Thirteen clinical trials have been completed, which enrolled over 400 patients with a variety of hematologic malignancies and solid tumors. Mirati also plans to initiate phase II studies of mocetinostat as a single agent in patients with mutations in histone acetyl transferases in bladder cancer and DLBCL.

## **Try The Cancer Letter Now**

### **Because the truth is a good read**

Over the past 40 years, The Cancer Letter has broken many stories on cancer research and drug development.

The Cancer Letter has won many awards for investigative journalism.

The Cancer Letter gives you information you need, coverage you can't get anyplace else. We promise a page-turner. Week after week.

Give The Cancer Letter a try.  
You will benefit from our  
experience and expertise.

[Click Here to Join Now.](#)

Check out our Public Section  
for a look inside each issue at:  
<http://www.cancerletter.com>

- ADVERTISEMENT -