THE CANCER LETTER

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Vol. 39 No. 20
May 17, 2013

Turmoil in Texas

CPRIT Likely to Get Funding For Two Years; DePinho Announces Austerity Measures

By Paul Goldberg

The Cancer Prevention and Research Institute of Texas will likely receive funding for the next two years, provided state legislators are satisfied with plans to overhaul the institute that channels nearly $300 million a year to uses that include research.

Legislators earlier this week said they placed $594 million into CPRIT appropriations for the next two years.

Appropriation appears to be contingent on passage of legislation that would address the problems that came to light during the past year, resulting in multiple firings, resignations and investigations.

The House and Senate bills define and address conflicts and appearances thereof.

(Continued to page 2)

Guest Editorial

As ACS Turns 100, Society President Calls For Tools to Finish the Fight Against Cancer

By Vincent T. DeVita, Jr.

For more than 50 years, I've had the privilege of working at some of the finest institutions with some of the brightest people of our time, all dedicated to furthering cancer research. My career has taken me from universities such as the University of Michigan and George Washington, to the National Cancer Institute, Memorial Sloan-Kettering, and today to Yale—its cancer center and the university.

I've worked during a remarkable time in the history of the fight against cancer; a time that has given us greater advances—and more lives saved—than we ever thought possible. It's a time that has taught us much of what we need to know, and has already given us many of the tools we need to one day finish the fight.

(Continued to page 4)

In Brief

Sparano Named Vice Chair of ECOG-ACRIN

JOSEPH SPARANO was named vice chair of the **ECOG-ACRIN Cancer Research Group**.

Sparano is professor of medicine and professor of obstetrics, gynecology, and women's health at the Albert Einstein College of Medicine, and associate chairman of the Department of Oncology at Montefiore Medical Center.

(Continued to page 14)

Turmoil in Texas
Belt-Tightening at MD Anderson for 2014
. . . Page 3

Drug Approval
ODAC Unanimously Rejects Melblez, Citing Lower Survival
. . . Page 8

FDA Approves Xofigo For Prostate Cancer
. . . Page 10

Sequestration
$1.71 Billion Cut To NIH Budget Will Reduce Number of RPGs
. . . Page 11

Outcomes Research
PCORI Awards $88.6 Million To 51 Research Studies
. . . Page 12

Obituary
Barbara Brenner, 61
BCA Executive Director
. . . Page 15

CPRIT Appropriation Contingent On Addressing Recent Problems

(Continued from page 1)

The House bill, which cleared the committee but not yet presented to the entire chamber, calls for ousting the 11-member oversight committee. A new board would then be appointed by the governor, lieutenant governor and House speaker.

A version of the bill approved by the Senate that seeks to define conflicts of interest and calls for appointment of a compliance officer, whose job would be to ensure that grant proposals comply with "rules before being submitted to the oversight committee for approval and that everyone involved in CPRIT "complies with "all laws and rules governing the peer review process and conflicts of interest."

CPRIT's troubles began when the institute bypassed its peer review procedures when considering an application for a $20 million biotechnology incubator that was to be co-directed by MD Anderson scientist Lynda Chin, the wife of that institution's president Ronald DePinho (The Cancer Letter, May 25, 2012).

That deviation from peer review standard prompted the resignation of CPRIT's chief scientific officer, Alfred Gilman, who was followed out the door by a vast majority of scientists who reviewed grant applications for the institute. The scandal continued to expand and ultimately included revelations that CPRIT had failed to conduct formal peer review of an $11 million commercialization grant awarded to Dallas-based Peloton Therapeutics Inc.

The Senate bill prohibits CPRIT employees from occupying an office in a facility owned by an entity receiving or applying to receive money from the institute. (Gilman's office space was rented by CPRIT from UT Southwestern. It was a condition of Gilman's employment by CPRIT that he be allowed to retain his office in an academic/biomedical environment.)

If the institute is indeed funded, its current CSO, Margaret Kripke, formerly of MD Anderson, would face the challenge of putting together the peer review mechanisms that disintegrated after Gilman resigned in protest (The Cancer Letter, Dec. 14, 2012).

To keep the CPRIT missions—and its constituencies—from clashing, CPRIT would annually set priorities for each grant program and each category of funded research.

If approved by the full House, the legislation will return to the Senate for agreement with House amendments.

In a recent opinion piece for the Austin American-Statesman, John Mendelsohn, director of the MD Anderson Cancer Center's Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy and former president of MD Anderson, said CPRIT has learned from its mistakes.

"Like almost any new and innovative organization working to gain traction in pursuit of its mission, CPRIT stumbled along the way," wrote Mendelsohn, who lobbied the legislature to form the $3 billion institute in 2007.

"The organization learned important lessons from these administrative missteps, and it can emerge stronger," Mendelsohn wrote. "Among the tough—but valuable—lessons CPRIT learned was that, as a state agency entrusted with spending tax dollars wisely and responsibly, its guidelines and policies and all of its actions must be totally transparent and beyond reproach.

"In recent weeks it appears that CPRIT is moving in the right direction. The new CPRIT leadership has taken important steps to restore public and legislative confidence by implementing new procedures and safeguards. In addition, Texas lawmakers are pursuing a host of reforms to this vital program.

"I am encouraged that the state's top elected leaders have authorized CPRIT to move forward on 25 awards to bring additional renowned cancer researchers to Texas. These recruitment awards and a number of new research and prevention grants were approved by CPRIT last year but put on hold as CPRIT underwent review. I hope the remaining frozen grants for research and for

THE CANCER LETTER

® The Cancer Letter is a registered trademark.

Editor & Publisher: Paul Goldberg
Associate Editor: Conor Hale
Reporter: Matthew Bin Han Ong

Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $405 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Founded Dec. 21, 1973, by Jerry D. Boyd.

cancer prevention and early detection services, such as breast cancer screening, will be eligible for activation soon so that more Texans can be screened, diagnosed and better treated for cancer."

CPRIT remains under criminal investigation related to awards of commercialization grants.

Belt-Tightening at MD Anderson for FY2014

To cope with financial difficulties, MD Anderson Cancer Center will reduce hiring and postpone capital projects, the institution said in an email to all employees.

"What we're facing today is much like what you'd face with your own checkbook if you spent more than you were paid each month for several months, relying on gifts or investment income to keep going," said the email, cosigned by MD Anderson President Ronald DePinho and the institution's top executives.

The text of the email, dated May 15, follows:

Over the past several months, you've read and heard that our financial health isn't as strong as we'd expected it to be this year. For most of Fiscal Year 2013 (FY13), our operating expense has exceeded our operating revenue—meaning that we've spent more than we've made from providing our patient care services. What we're facing today is much like what you'd face with your own checkbook if you spent more than you were paid each month for several months, relying on gifts or investment income to keep going.

Our financial challenges are as complex as our organization. We're not in the same financial situation we experienced in 2009, but we must apply what we've learned in the past to slow our growth, control our expenses and prepare for what's ahead. We're faced with increasing external challenges, such as the Affordable Care Act implementation and continuing federal deficits. We're in a fortunate position compared with other institutions, but we must take steps now to stop this trend and get us moving in the right direction.

It's everyone's responsibility to monitor our resources, and every area in the institution will play a part in getting us back on track. For FY14, we've budgeted a 6% increase in new patients and we'll grow the number of clinical caregivers proportionately so that the level of clinical productivity per provider is consistent with FY13.

But that also means we must reduce our expenses. We've identified savings that will bring next year's operating expenses in line with operating revenue without compromising the highest level of patient care:

1. Slow down hiring. At the executive level, we're analyzing open positions and will closely review all position requests to ensure they are strategic and meet critical needs. We anticipate hiring additional faculty to support our projected clinical growth, but we cannot fill other open positions at the rate we have been. Additionally, we will not fill every vacancy that occurs, thus reducing our number of employees through attrition.

2. Reduce FY14 merit program. There will be no merit increases for administration or faculty. Merit increases for classified employees will be paid on schedule.

3. Continue FY14 incentive/Anderson Award goals. The Anderson Award is based on institutional financial goals and departmental-set goals. The departmental goals should continue as many are set to help us achieve professional development goals and institutional financial goals, which still are greatly needed. If we meet our goals, the incentive program awards will be distributed as planned.

4. Postpone specific capital projects. The Pavilion and West Side Diagnostic Imaging Center will proceed on schedule. The Rotary House renovations, Radiology Outpatient Center II, Zayed Phase II and the Clinical Research Building animal area renovation have been put on hold.

We hope these are temporary measures. This isn't the first time we've had to make some hard budget choices, and in the past, we've been able to make up for the changes when the budget improves.

If we have a great year and revenue grows quicker than anticipated while expenses are held in line, we'd of course do that again. We know this won't be easy, but we believe that by acting *before* external challenges force us into crisis, we can achieve smart savings and move MD Anderson forward.

It's going to take all of us to focus on safeguarding our resources, working more efficiently and continuing to provide the world's best cancer care for our patients and their families. We have much to be proud of at MD Anderson, and we thank you for all that you do every day for our patients and for the institution.

Ronald DePinho, M.D., President

Leon Leach, Ph.D., Executive Vice President

Thomas Burke, M.D., Executive Vice President and Physician-in-Chief

Thomas Buchholz, M.D., Provost and Executive Vice President ad interim

---

Follow us on Twitter: @TheCancerLetter

DePinho Says He Was Unaware Of Tivozanib Survival Data And Details of FDA Meeting During CNBC Appearance

In an email blast to MD Anderson employees, the institution's President Ronald DePinho said he was unaware of the details of the meeting between FDA officials and the company he co-founded, AVEO Pharmaceuticals Inc.

Last week, The Cancer Letter reported that On May 12, 2012, AVEO officials held a pre-NDA meeting with FDA, where agency officials told them that lower survival among patients who received the AVEO drug tivozanib made the application unapprovable (The Cancer Letter, May 10).

Yet, six days after the AVEO meeting with FDA, in an appearance on CNBC, DePinho, who was then a member of the company's board, touted the AVEO stock and tivozanib.

The Cancer Letter story was cited in a front-page story in the Houston Chronicle.

"You should know that when I made those comments, neither my wife Dr. Chin nor I had been informed of the company's recent interactions with the Food and Drug Administration, and I based my remarks on the public information leading up to the June 1 American Society of Clinical Oncology annual conference, where the agent received favorable comments from an impartial expert who reviewed the data of the study," DePinho wrote in an email to MD Anderson employees May 13.

A video of DePinho's appearance is available on the CNBC website.

The text of DePinho's email follows:

You may have read in the Houston Chronicle on Sunday about my prior position as an outside director of AVEO Pharmaceuticals, one of a number of positions I held before coming to MD Anderson.

As an institutional leader, it's been important for me to go above and beyond what's required and set the highest standard possible. For that reason, I began resigning from my corporate board positions before I arrived here, and completed that process last year. I have also divested many of my stock holdings and submitted plans to the UT System to establish a blind trust that, once approved, will manage any remaining ones.

The Chronicle story mentioned my appearance on CNBC on May 18, 2012, in which I remarked on AVEO. Discussing AVEO was not the purpose for the interview, and I was not anticipating any questions relating to AVEO. Regardless, commenting on the company was a poor decision on my part and I apologized for it shortly thereafter.

I absolutely should not have mentioned the company. But you should know that when I made those comments, neither my wife Dr. Chin nor I had been informed of the company's recent interactions with the Food and Drug Administration, and I based my remarks on the public information leading up to the June 1 American Society of Clinical Oncology annual conference, where the agent received favorable comments from an impartial expert who reviewed the data of the study.

It is a privilege and honor to serve as president of this remarkable and respected institution. If you have suggestions, comments or concerns, I welcome hearing from you.

Guest Editorial

DeVita: We Avert More Than 400 Cancer Deaths Per Day

(Continued from page 1)

For more than four decades of my career, I've been involved with the nation's largest voluntary health organization—the American Cancer Society. I am serving as volunteer president of the organization in the year it celebrates its 100th birthday.

Being around for half of that century allows me the perspective to look at how far we have come today, and how much further we can go tomorrow. And I believe tomorrow holds nearly limitless possibilities.

An Impenetrable Black Box

A century ago, cancer was a mystery, essentially an impenetrable black box. We knew the answers were in there, but we simply couldn't access them.

The American Cancer Society was founded in 1913, not so long after champagne and carriage

rides—anything to distract from the inevitable—were considered "treatment" for cancer patients.

Indeed, for the entire first half of the 20th century, surgery and radiotherapy were the only viable options for cancer treatment, and only a minority of patients could be cured by surgery alone. Surgery and radiotherapy failed because there was no effective treatment for cancer cells that escaped into the bloodstream.

In the years that followed, we saw advances that let us begin to peer inside the black box of cancer, and all along the way, the American Cancer Society was helping shine the light.

The ACS research program was founded in 1946 with $1 million raised by Mary Lasker and over the years has continued to provide a much needed partnership with the National Cancer Institute. The Society's research program today comprises a rigorous, world-class peer-review program that ensures the best research receives funding, as well as a world-class intramural research program that continuously works to find the causes of cancer and track progress against the diseases.

In the past 67 years, the ACS has funded more than $3.9 billion in cancer research, including 46 scientists who have gone on to win the Nobel Prize. Examples of the research supported in those early years read like a timeline of major events in cancer history:

• The lid of the black box was seriously pried open for the first time when a retired scientist at Rockefeller University showed that cellular information was transmitted not by proteins but by DNA. His work led directly to the important discovery of the structure of DNA by James Watson, funded by the American Cancer Society, and Francis Crick, in 1953. They would win the Nobel Prize in 1962 for their discovery.

• In 1961, Marshall Nirenberg, who had been funded by the ACS early in his career, led a team that broke the genetic code, establishing the central dogma of biology: that information was transmitted from DNA to RNA and resulted in the synthesis of proteins.

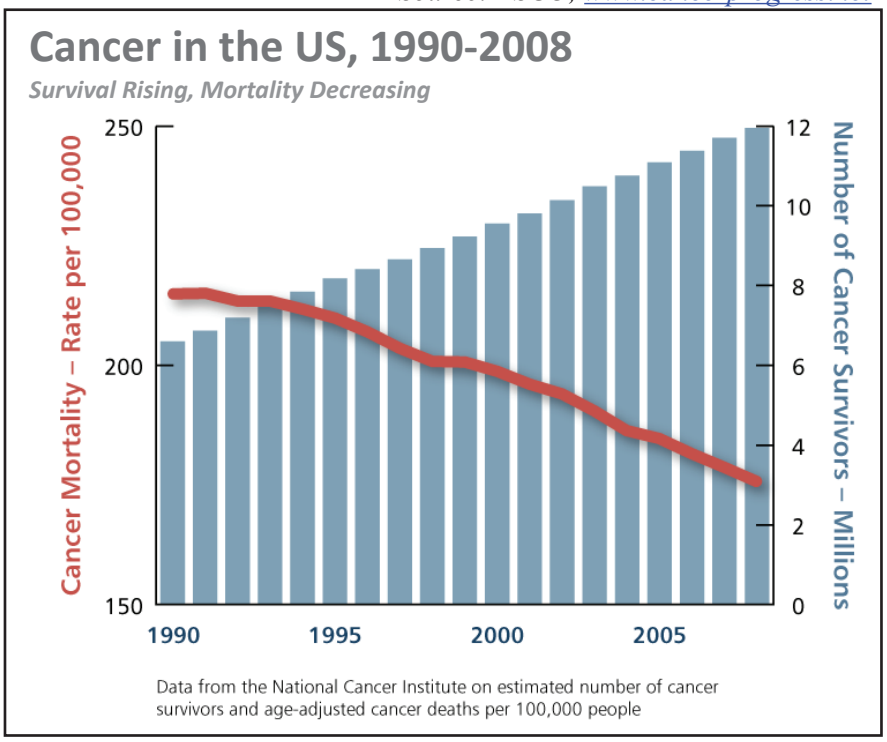
• In 1970, the discovery of reverse transcriptase by Howard Temin, Satoshi Mizutani, and David Baltimore, which showed that information could be transmitted the other way, from RNA to DNA, had a profound influence on medicine but most particularly on cancer medicine. The ACS funded Baltimore and Temin.

• In 1971, the passage of the National Cancer Act paved the way for profound discoveries in cancer. This was the beginning of the nation's "war on cancer." It led to federal funding for cancer research rising from $4.3 million in 1953 to an estimated $5.1 billion in 2012.

It was about this time that I first got involved with the American Cancer Society. Back then, experts projected that cancer incidence and mortality would continue to rise through the year 2000 and beyond.

I didn't believe it then—and today we know I was right.

Source: ASCO, www.cancerprogress.net



The Black Box Opens

Today, the black box is open. Inside is a translucent blueprint for tackling the challenges of cancer. We have the plans to build a future without cancer, and proof that the plans are sound.

But our job is not done. Not by a longshot. During World War II, when Great Britain was fighting alone, Winston Churchill sent a message to the United States in a radio broadcast with a now-famous quote: "Give us the tools and we'll finish the job," he said. Well, we did —and we all know what happened.

Today, I believe we have many of the tools we will need to finish the fight against cancer. Just take a look at some of our discoveries over the past century, thanks in no small part to the American Cancer Society.

Treatment:

• 1948: ACS-funded researcher Sidney Farber produces remission in childhood leukemia with an anti-folate drug, aminopterin—the first time leukemias responded to chemotherapy.

• 1967: A group of us at the NCI show that childhood leukemia and advanced Hodgkin disease in adults could be cured by combination chemotherapy. This work provides proof of principle that cancers could be cured by chemotherapy, the missing link in cancer treatment.

• 1968: ACS -funded researcher Bernard Fisher reported work that would revolutionize breast cancer treatment by showing that less radical surgery plus chemotherapy or radiation therapy is a better option than the Halstead mastectomy.

• 1978: Another breast cancer revolution comes with the approval of tamoxifen as a standard addition to surgery for women with certain forms of breast cancer. ACS-funded researcher V. Craig Jordan is integral to this work. More than 20 years later, the drug is also approved to reduce the risk of breast cancer following work by Bernard Fisher, also an ACS grantee.

• 2000: Former ACS grantee Brian Druker reports stunning success in treating chronic myelogenous leukemia with a molecularly targeted pill called imatinib (Gleevec). This work provided proof of principle that treatments targeting specific molecular abnormalities that are unique to certain cancers could convert them into manageable chronic illnesses. Since then, chemotherapy has become targeted therapy, and the literature has been dominated by the search for drugs to inhibit unique molecular targets, with recent success in the treatment of some very difficult-to-treat tumors, such as melanoma and lung cancer.

In the early 1990s came an achievement that once would have been thought impossible: cancer mortality rates began to decline. That decline continues today, and in 2013, we are celebrating a 20 percent drop in overall cancer mortality since its peak in the early 1990s.

To put that another way, we are averting more than 400 cancer deaths every day, with 1.2 million cancer deaths avoided since rates began to decline. As we like to say at the American Cancer Society, our research program has helped create many more birthdays.

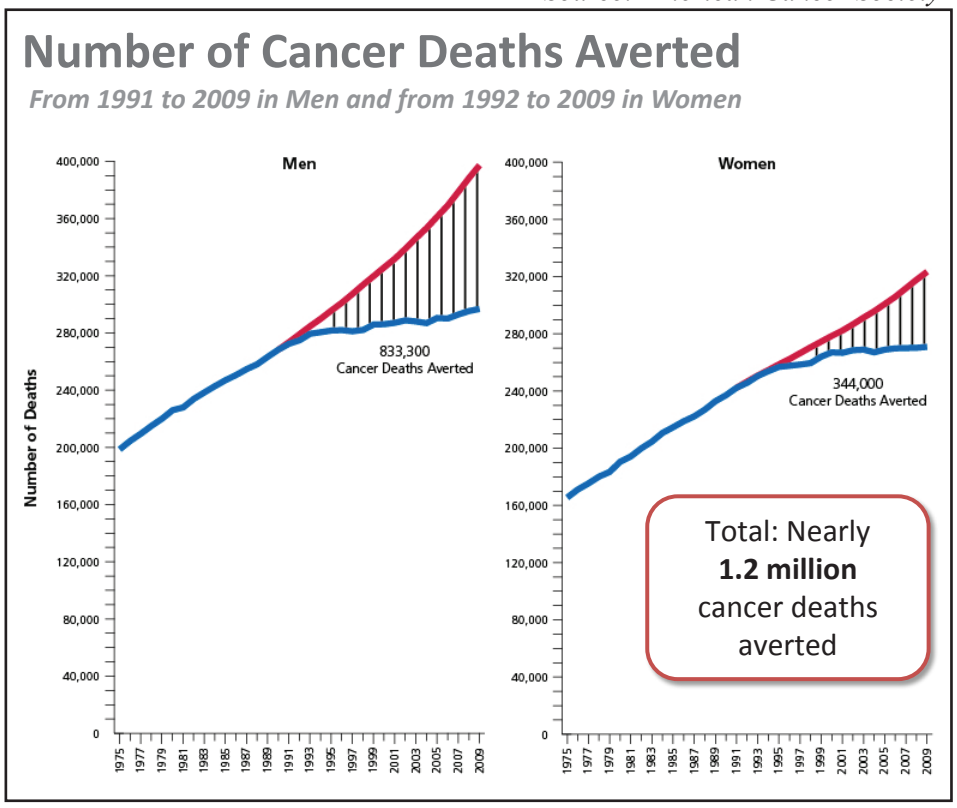
Prevention:

No matter how successful we become at treating cancer, it is always preferable to prevent cancer. But prevention has been an elusive goal.

Time has taught us four major pathways to success with prevention: the connection between viruses and cancer; methods of chemoprevention; the role of tobacco in cancer; and the increasingly important role that nutrition and physical activity, and their partner, obesity, play in cancer. At the same time, early detection, while proven effective for only a few cancer sites, has shown the potential to have a remarkable impact.

• 1948: The ACS crusades for acceptance of the Pap test, developed by George Papanicolaou. The

Source: American Cancer Society



widespread adoption of this simple test has resulted in a more than 70 percent decrease in death from cancer of the uterine cervix in the U.S.

• 1954: The ACS Hammond-Horn study confirms the link between smoking and lung cancer. The success of this study leads to the society's Cancer Prevention Study-I in 1959 and Cancer Prevention Study-II in 1982. These studies involved 2 million people and have resulted in more than 500 scientific studies and reports.

• 1973: The ACS invests more than $1 million to demonstrate that mammography can detect breast cancer early. Mammograms remain an important tool for catching breast cancer when it's most treatable.

• 2000: The FDA approves a vaccine to prevent HPV, early work for which was supported by the ACS, offering a potentially lifesaving advance in cervical and other cancers.

• 2003: The work of ACS epidemiologist Michael Thun and colleagues, using data from the ACS Cancer Prevention Study-II, shows that people who reported regular aspirin use had a 40 percent lower death rate from colon cancer.

• 2003: Groundbreaking research led by ACS epidemiologist Eugenia Calle links increased body weight with higher death rates for multiple cancer sites and with all cancers combined.

• 2010: The National Lung Screening Trial, a National Cancer Institute study supported by the ACS, shows heavy smokers screened with low-dose spiral CT had a 20 percent lower risk of lung cancer death compared to smokers who received chest X-ray.

Another advance with profound implications was the sequencing of the human genome in 2000. This one development has had perhaps the greatest impact on our blueprint for fighting cancer, because we now have the ability to "watch the wheels go 'round."

The human genome gives us the technology to pick out abnormalities of the cancer cell. And when you can pick out these abnormalities, you can target them. We now have proof of principle that when you target these specific abnormalities, it can work.

Recently, I wrote a piece for the New England Journal of Medicine that included this sentence: "Soon we'll be able to sequence the genome for $100 in two days and it will become a routine test." They politely said to me, "Would you mind taking that out, because it's a little far-fetched." Three months later, The Wall Street Journal reported there were two startup companies that had sequenced DNA in 48 hours for $1,000. The New England Journal put the sentence back in.

Clearly, genetic studies will soon be within the realm of a routine lab test, giving us the potential to target abnormalities we find with drug therapies. If the effects are anything like what we've seen in recent years with targeted therapy, our ability to prevent or treat cancers in the future will truly be impressive.

All told, these tools mean that when the volunteer leaders of the American Cancer Society get together at a Board of Directors meeting, we don't worry about if we can make progress; we worry about if we can make progress fast enough; if we can use these tools to their full extent. And while this is indeed a very real concern, it's a much different problem than the far more serious one we had not so long ago, as we watched incidence and mortality continue to rise.

Follow us on Twitter: @TheCancerLetter

Finishing the Job

The remarkable progress over the past century makes it possible to think of a world without cancer sometime in the next century and to see a world in which we are controlling this disease like never before.

Even more exciting is the fact that most of the declines we're seeing in cancer incidence and mortality are the result of implementation of existing tools to prevent, detect, and treat cancer.

Still largely untapped is the potentially enormous payoff from more recent investments; the clinical application of the fruits of the molecular revolution since the passage of the National Cancer Act.

I believe with what we've learned thus far, and what we will learn tomorrow if we redouble our efforts to support research, we will have the tools to finish the job—to finish the fight against cancer.

This is something the American Cancer Society also strongly believes—that together, we can make this cancer's last century.

As the ACS marks its 100th birthday of saving lives, we want to celebrate the progress we've made together with others who have made immeasurable contributions over the past century—the researchers, the institutions, the volunteers, the donors, and those who selflessly taken part in studies of cancer over the decades.

But far from resting on our laurels, we stand inspired by the vision of where we can go tomorrow, if we fight even harder and make even more noise. We're using this once-in-a-lifetime opportunity to inspire people to join us so that together we can make even more progress and finish the fight once and for all.

The American Cancer Society has done so much to help make this century of progress possible.

And now, we want to let everyone know that cancer's time is up. We want to put ourselves out of business.

I know that's a day we'd all like to see.

Looking back, the word "cancer" wasn't even spoken 100 years ago.

We lost almost every patient. Even 60 years ago, hope of survival was fairly bleak.

If there is one thing we've learned, it's that cancer thrives on silence and complacency and that progress comes when we speak out, when we make noise. We know that silence won't finish the fight—only action will.

As we enter this next century, we need to continue to make noise and to redouble our efforts to develop the tools we need to finish the fight.

The author is president of the American Cancer Society. He is the Amy and Joseph Perella Professor of Medicine, Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven, Yale School of Medicine, and Professor of Epidemiology and Public Health at Yale School of Medicine. In 1980, he was appointed by the President Jimmy Carter as Director of the National Cancer Institute and the National Cancer Program. DeVita has also served as Physician-In-Chief at Memorial Sloan-Kettering Cancer Center, and Professor of Medicine at Cornell University School of Medicine.

Drug Approval

ODAC Unanimously Rejects Melblez, Citing Lower Survival

By Matthew Bin Han Ong

The FDA Oncologic Drugs Advisory Committee May 2 voted 16:0 against an application for a device that administers chemotherapy regionally to patients with ocular melanoma with metastases to the liver.

Sponsored by Delcath Systems Inc., the combination Melblez Kit had a flaw reminiscent of renal cancer drug tivozanib—overall survival in the experimental arm was worse than survival in the control arm.

In fact, the agency grouped the two drugs in a single meeting in an effort to send a strong message that a deficit in overall survival is fatal to a new drug application. This holds true even when the deficit isn't statistically significant, when survival isn't a primary endpoint, and when the study produces an improvement in progression-free survival.

At the same meeting, ODAC voted 13:1 against approval of tivozanib, sponsored by AVEO Pharmaceuticals Inc. (The Cancer Letter, May 3).

This forcefully stated point doesn't signal any policy change on the part of the agency. The bar remains where it has been.

The only change worth noting is the agency's decision to accept the filings instead of issuing refuse to file letters. The RTFs, being confidential documents, have no didactic value. The meetings of ODAC, by contrast, are very public.

Melphalan—the chemotherapy drug in the Melblez Kit—was tested against investigator-determined best alternative care in an open-label, multicenter, randomized trial. Alas, overall survival pointed to a detrimental effect: 9.8 months for the experimental agent, and 10 months in the control arm.

On the positive side, the device yielded a statistically significant hepatic PFS advantage of seven months (HR=0.42, p=0.001), compared to 1.6 months in the BAC arm.

There was less of an effect in terms of overall PFS—three months.

"To start out, we have a terrible disease—nobody's denying that," said ODAC Chair Mikkael Sekeres, associate professor of medicine at the Department of Hematologic Oncology and Blood Disorders at the Cleveland Clinic Taussig Cancer Institute.

"These people are desperate for something; they don't have available therapies that work terribly well.

"We have an [overall PFS] advantage of three months in a limited patient dataset," Sekeres said. "But we also have a risk of causing significant, very significant harm or even death in almost 25 percent of these people immediately.

"Is that an acceptable-risk benefit analysis?

"I just can't imagine how I would sit down with a patient and try to walk them through this and say there is also a risk this may truncate your survival compared to other approaches."

Increased Risk of Death by Toxicity

The experimental arm in the trial suggested a 7 percent incidence of toxic death resulting from serious adverse events, including cerebral vascular events, myocardial infarction and acute renal failure.

"What is concerning about this device is that we're also seeing what is potentially a detriment in overall survival advantage of 35 percent," said Richard Pazdur, director of the agency's Office of Hematology and Oncology Products.

"As FDA has pointed out, when you add up the toxic death rate along with serious adverse events, it totals 24 percent of patients who either die as a result of this therapy, or who have very serious complications.

"And that would have to be part of anyone's consent process in embarking on this sort of therapy," Pazdur said.

There are no FDA-approved drugs for the treatment of unresectable, hepatic-dominant, metastatic ocular melanoma, which develops in up to 1,250 adults per year.

"The expected survival from the diagnosis of metastatic disease was estimated to be from 2 to 9 months; however, a recent report of a phase III trial conducted in patients with previously untreated metastatic ocular melanoma reported a median survival of approximately 14 months," said agency briefing documents for the committee.

The Melblez Kit was studied on efficacy and safety measures with 93 and 122 patients, respectively.

Hepatic PFS was the primary endpoint in the efficacy study, where patients randomized to BAC were allowed to cross over to receive Melblez Kit treatment at the time of hepatic disease progression.

"The issue about crossover confounding overall survival, I'd also like to comment about, because we see this frequently in many of the trials, especially where you don't have any therapy," Pazdur said.

"In general, what crossover will do would be to obliterate a survival advantage if one is there, because one either gets the therapy at the initiation of therapy or at the time of crossover, so you're comparing two different time points.

"It should not explain a detriment in overall survival," Pazdur said. "And this is bothersome because we are seeing a potential 30 percent increase in the risk of death here."

ODAC member Brent Logan mulled publicly on why overall survival isn't the appropriate primary endpoint for the trial, given the reasonably short median survival times of four to six months as well as the potential for a lot of toxicity.

"In terms of evaluating the survival data in this particular study, unfortunately, the design precludes a lot of that because of the allowance of crossover, so we are prevented from getting nice interpretable survival data to consider here," said Logan, associate professor of biostatistics in the Division of Biostatistics at the Medical College of Wisconsin.

"The limited data we do have is certainly concerning, trending toward an adverse affect of the PHP, especially as is mentioned—no surviving patients in the PHP arm but 14 percent surviving in the best available care group.

"And then finally, I think it is important, when you are looking at survival data, to make sure you are looking at the randomized comparisons and not to get bogged down by groups that are not randomized comparisons—for example, the crossover vs. no crossover survival comparisons," Logan said.

"Those are not randomized groups, there is a lot of selection bias and you don't want to be misled by those curves."

An advantage in progression-free survival must be put in the context of the toxicity of the therapy, Pazdur said.

"When one talks about hepatic progression-free

survival or overall progression-free survival, the risk-benefit analysis is paramount, because you are basically dealing with a radiographic endpoint," Pazdur said.

"We have dealt with many therapies that do not have good options. But this level of toxicity, where you have a 7 percent death rate, a 4 percent stroke rate, a 2 percent myocardial infarction rate, a 5 percent GI perforation rate, a 6 percent grade 3 to 4 hemorrhage rate, and 70 percent of the patients developing grade 4 neutropenia, is unprecedented.

"We have to put this into some sort of context, and I just want to make that comment that we have to be consistent in our regulatory decision making."

Intervention Worsens Quality of Life

Moments before the vote, ODAC member Aman Buzdar chastised the sponsors for the application in an impassioned speech about how it kills patients before the disease does.

"These are the patients who have very limited or no options," said Buzdar, vice president of clinical research and professor of medicine at the Department of Breast Medical Oncology at MD Anderson. "The option has to make the quality of life better.

"Over here, quality of life, if you measure by any yardstick, would be worse after the intervention than no intervention, because these patients have zero performance status at start.

"And subsequently, some died while you did therapy," Buzdar said. "They might have lived for another several months.

"In the end, you have reduced their lifespan by 35 percent across the board, even though it is not statistically significant.

"We all agree there is no option available, but the option, which we are offering to the patient is—we are making your quality of life much worse, and your risk is increased by 35 percent—dying before the natural disease does you in."

It goes back to the issue of overall survival, as is the case with tivozanib, Pazdur said.

"One of the precedents here, and I think this is to echo what Dr. Buzdar was saying, is 'do no harm,' and that's a basic premise of medicine," Pazdur said.

"We all hope for better therapies here, but our issue on the table is, are we actually harming people in an attempt to do good?"

ODAC chair Sekeres offers an answer after the vote:

"Patients with metastatic ocular melanoma have a terrible disease and very few treatment options, and this is an area we need to do much better in," Sekeres said.

"That being said, exposing them to a treatment that could kill them in the next month is not the right thing to do, and the risks of this procedure, of this treatment, far outweigh any potential benefit and may actually introduce harm."

FDA Approves Bayer's Xofigo For Late-Stage Prostate Cancer

FDA approved Xofigo to treat men with symptomatic metastatic castration-resistant prostate cancer that has spread to bones, but not to other organs. The drug is intended for men whose cancer has spread after receiving medical or surgical therapy to lower testosterone.

Xofigo (radium-223 dichloride) was reviewed through the agency's priority review program, and is being approved more than three months ahead of Aug. 14, the date the agency was scheduled to complete review of the drug application.

"Xofigo binds with minerals in the bone to deliver radiation directly to bone tumors, limiting the damage to the surrounding normal tissues," said Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "Xofigo is the second prostate cancer drug approved by the FDA in the past year that demonstrates an ability to extend the survival of men with metastatic prostate cancer."

In August 2012, FDA approved Xtandi to treat men with metastatic castration-resistant prostate cancer that has spread or recurred, even with medical or surgical therapy to minimize testosterone. Xtandi is approved for patients who have previously been treated the chemotherapy drug docetaxel.

Xofigo's safety and effectiveness were evaluated in a single clinical trial of 809 men with symptomatic castration-resistant prostate cancer that spread to bones but not to other organs. Patients were randomly assigned to receive Xofigo or a placebo plus best standard of care.

The study was designed to measure overall survival. Results from a pre-planned interim analysis showed men receiving Xofigo lived a median of 14 months compared to a median of 11.2 months for men receiving placebo. An exploratory updated analysis conducted later in the trial confirmed Xofigo's ability to extend overall survival.

The most common side effects reported during

clinical trials in men receiving Xofigo were nausea, diarrhea, vomiting and swelling of the leg, ankle or foot. The most common abnormalities detected during blood testing included low levels of red blood cells, lymphocytes, white blood cells and platelets.

Xofigo is marketed by Bayer Pharmaceuticals.

FDA approved the cobas EGFR Mutation Test, a companion diagnostic for the cancer drug Tarceva (erlotinib). This is the first FDA-approved companion diagnostic that detects epidermal growth factor receptor gene mutations, which are present in approximately 10 percent of non-small cell lung cancers.

The test is being **approved with an expanded use for Tarceva** as a first-line treatment for patients with NSCLC that has metastasized and who have certain mutations in the EGFR gene.

The safety and effectiveness of the cobas EGFR Mutation Test was established with clinical data showing that, on average, NSCLC patients with specific types of EGFR mutations (exon 19 deletions or exon 21 L858R substitution mutations) lived without their disease progressing for 10.4 months when they received Tarceva treatment, compared to 5.4 months for those who received a standard two-drug chemotherapy regimen. Investigators used tumor samples from the clinical trial to validate the test's use in this patient population.

The approval is Tarceva's fourth indication and the third use for lung cancer. The FDA approved Tarceva on April 16, 2010, for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Tarceva was originally approved in November 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

The cobas EGFR Mutation Test is manufactured by the Roche Molecular Systems. Tarceva is co-marketed by Genentech, a member of the Roche Group, and OSI Pharmaceuticals.

Sequestration

$1.71 Billion Cut to NIH Budget Will Reduce Number of RPGs

By Matthew Bin Han Ong

NIH will have $1.71 billion less to spend in fiscal 2013—a decrease of about 5 percent—and will award 703 fewer new and competing research grants.

The overall budget for NIH through the end of September will be reduced to $29.15 billion, a number the agency hasn't seen in seven years.

Exceeding previous sequestration estimates by as much as $224 million, the final cuts to the 2013 NIH budget are sizable, given that the agency has been losing up to 23 percent of its purchasing power over the last decade due to flat budgets and medical inflation (The Cancer Letter, March 22).

The total number of research project grants will drop by 1,357 to 34,902—of those, 8,283 are new and competing RPGs.

NIH will try to keep the average size of competing awards at 2012 levels, but will not adjust for inflation in future year commitments for all competing RPGs. However, adjustments for special needs, which include equipment and added personnel, will continue to be accommodated, according to a May 8 NIH notice.

Reductions to non-competing continuation awards cut by 10 percent earlier this year may be partially restored, but are "unlikely to be restored to the previous commitment level," the NIH notice says.

NCI's budget will be reduced to $4.78 billion, $293 million less than in fiscal 2012. The 5.8 percent cut will lower 2013 grant success rates, said NCI Director Harold Varmus in a May 7 email to grantees and contractors (The Cancer Letter, May 10).

"Although I recognize that there may be resistance in Congress to returning our budget to FY2012 levels or better, it is encouraging to note that the President has proposed a significant increase above FY2012 for the FY2014 budget," Varmus wrote.

The Obama administration seeks to restore the sequestration cuts and fund NIH at $471 million above fiscal 2012—a 1.5 percent increase that would bump the budget to $31.331 billion.

In a May 15 hearing held by the Senate Subcommittee of Labor and HHS, NIH Director Francis Collins testified in support of the president's budget request. Five institute directors, including Varmus, were present at the hearing.

"Within the administration's FY 2014 budget, we will continue to increase Research Project Grants,

NIH's funding mechanism for investigator-initiated research," Collins said.

"NIH expects to support 10,269 competing RPGs in FY 2014, an increase of 1,283 over FY 2012 levels. For FY 2014, NIH anticipates funding a total of 36,610 RPGs.

"The budget request allocates resources to areas of the most extraordinary promise for biomedical research, while maintaining the flexibility to pursue unplanned scientific opportunities and address unforeseen health needs.

"I want to emphasize that while all of these ambitious new scientific endeavors provide unprecedented promise for advancing human health, we cannot ignore the impact the sequester is having on groundbreaking medical research.

"If the Budget Control Act-imposed caps on discretionary programs continue, and NIH funding is reduced proportionally over the next 10 years, funding will decline by about $19 billion," Collins said.

"With this new reality, more and more investigators will be unable to pursue the bold ideas that NIH has traditionally supported."

ASCO: 4 of 5 Practices Affected by Sequestration

According to the results of a recent survey conducted by the American Society of Clinical Oncology, nearly 50 percent of oncology practices are unable to continue caring for Medicare patients unless patients have supplemental insurance.

"While practices are working hard to continue providing care for Medicare patients, many are being forced to send patients to hospitals for chemotherapy and a smaller number are no longer able to see Medicare patients at all," ASCO said in a statement. "Over time, these changes may radically alter the cancer delivery system in the U.S."

Drawn from the responses of over 500 ASCO members, the survey said that half of the respondents reported sending their Medicare patients elsewhere for chemotherapy—primarily to more expensive hospital outpatient infusion centers.

"Sequestration is not just a trivial matter of inconvenience to patients who may be referred to other treatment facilities to receive their chemotherapy," said ASCO President Sandra Swain in a statement. "Cancer patients are very sick, often elderly, and may struggle with great fatigue and discomfort.

"Having to travel just an additional 10 miles and be treated in a larger system can be a traumatic experience for these patients."

The ASCO survey comes after The Washington Post reported that payment reductions are prompting office-based oncology clinics to "turn away" thousands of Medicare patients.

In conjunction with lobbying by oncology organizations, the report persuaded Congress to produce a bill called the Cancer Patient Protection Act of 2013.

Introduced by Rep. Renee Ellmers (R-N.C.), the bill—HR 1416—seeks to repeal sequestration as it affects drugs and biologicals administered by office-based physicians to cancer patients, directing Medicare to pay back any reduced payments made since the cuts took effect April 1. At this writing, the bill has 68 co-sponsors.

The sequestration cuts may indeed have a considerable effect on office-based oncology practices, but sources say that patients are still receiving treatment, even if the decisions on referring out Medicare patients likely differ from practice to practice (The Cancer Letter, April 26).

Outcomes Research

PCORI Awards $88.6 Million To 51 Research Projects

The Patient-Centered Outcomes Research Institute approved 51 awards, totaling $88.6 million over three years, to fund patient-centered comparative clinical effectiveness research projects.

The projects, approved May 6 by the institute's board of governors, include studies in certain cancers, as well as in kidney disease, obesity, asthma, diabetes and various mental health conditions. Other projects explore patient decision-making, reducing specific health disparities, and improving healthcare delivery.

The awards are part of the institute's second cycle of primary research funding, which opened for submissions in September 2012, and were selected from among more than 400 applications. A full list of the awards can be found on the PCORI website.

Cancer-related studies include:

• **Treatment Preference and Patient Centered Prostate Cancer**, led by Ravishankar Jayadevappa and the University of Pennsylvania, to test the comparative effectiveness of a conjoint analysis intervention compared to usual care and identify preferred attributes of alternative prostate cancer treatments (including active surveillance) that will aid in designing ways to help patients weigh treatment attributes.

• **Patient Outcomes of a Self-Care Management**

Approach to Cancer Symptoms: A Clinical Trial, led by Susan McMillan and the University of South Florida, to test the efficacy of the COPE intervention with patients with symptoms of moderate to high intensity, distress, frequency, or interference with their lives as a result of their cancer, including 300 patients from a large comprehensive cancer center with large numbers of outpatients with breast, colorectal, lung, and prostate cancers.

• **Patient-Defined Treatment Success and Preferences in Stage IV Lung Cancer Patients**, led by KM Islam and the University of Nebraska Medical Center, to compare treatment preferences among different patient groups when available drugs offer the same survival but different side effects and then communicating patients' preferences to physicians to assess changes in clinical practice.

• **Ovarian Cancer Patient-Centered Decision Aid**, led by Lari Wenzel and the University of California, Irvine, to develop and test a new decision aid, the Patient Centered Outcome Aid, which would allow patients to identify trade-offs about the impact of intraperitoneal/intravenous therapy compared to IV-only therapy on their quality of life and survival, based on their own preferences and personal clinical characteristics.

• **Navigator Guided e-Psychoeducational Intervention for Prostate Cancer Patients and Their Caregivers**, led by Brian Rivers and the H. Lee Moffitt Cancer Center & Research Institute, to evaluate their Personalized Health Information Navigator, an Apple iPad application delivered by a patient navigator, and test whether it works better than NCI information booklets delivered by a patient navigator.

• **Impact of Radiation Therapy on Breast Conservation in Ductal Carcinoma in Situ**, led by Rinaa Punglia and the Dana-Farber Cancer Institute, to create a web-based decision aid for DCIS patients, presenting the trade-offs and expected treatment outcomes following breast-conserving surgery with and without radiation therapy, through studying patient-specific risk factors for having a new breast cancer after DCIS and the likelihood of breast-conserving surgery versus mastectomy if a woman has a second cancer diagnosis after DCIS and has not received radiation upfront, using four large data sets.

• **Generating Critical Patient-Centered Information for Decision Making in Localized Prostate Cancer**, led by David Penson and Vanderbilt University, to evaluate which prostate cancer treatments are most effective in which patients, by using an existing population-based study of 3,691 men diagnosed with prostate cancer in 2011, collecting patient-reported outcomes three years after their diagnosis, and comparing the effectiveness of contemporary surgical and radiation techniques—in terms of quality of life, side effects, cancer control and treatment complications.

• **Evaluating the Impact of Patient-Centered Oncology Care**, led by Sarah Scholle and the National Committee for Quality Assurance, and working with the National Coalition for Cancer Survivorship, the American Society of Clinical Oncology, Oncology Management Services, Independence Blue Cross, and RAND—the study's objective is to define the patient-centered oncology care model and evaluate whether it improves patient experience and quality of care, as well as tracking the model's adoption across a variety of practices.

• **Evaluating Cancer Survivorship Care Models**, led by Holly Mead and The George Washington University, to evaluate the impact different models of follow-up care have on patient-centered outcomes for cancer survivors, and to create tools to better understand what patients want and need and what care is currently being provided across the country.

• **Collaborative Care to Reduce Depression and Increase Cancer Screening Among Low-Income Urban Women**, led by Jonathan Tobin and the Clinical Directors Network Inc., to test whether an intervention that addresses depression and cancer screening needs at the same time among women aged 50-64 in the Bronx is more effective at improving cancer screening and patient-reported outcomes for women with depression than an existing, previously tested cancer screening intervention alone.

• **Utilizing Advance Care Planning Videos to Empower Perioperative Cancer Patients and Families**, led by Rebecca Aslakson and the Johns Hopkins University, to develop and evaluate a video-based decision aid for pancreatic cancer patients and families pursing aggressive surgical cancer treatment, based on previously existing decision aids and what cancer surgery patients and families report about those aids and their own perioperative experiences.

• **Relapsed Childhood Neuroblastoma as a Model for Parental End-of-Life Decision-Making**,

led by Jennifer Mack and the Dana-Farber Cancer Institute, to evaluate parental end-of-life decision making and address gaps in the literature in three respects: evaluating parental decision making over a time period, rather than focusing on decisions made in one point in time; assessing the extent to which parental decision making is informed and consonant with preferences, regardless of whether decisions lead to aggressive or palliative care; and focusing on a single disease, relapsed neuroblastoma, as a model for end-of-life decision making, as opposed to focusing on groups of childhood cancers.

• **Improving Communication for Chemotherapy: Addressing Concerns of Older Cancer Patients and Caregivers**, led by Supriya Mohile and the University of Rochester, to determine whether providing a web-generated geriatric assessment summary to older advanced cancer patients, their caregivers, and their physicians, can improve communication about age-related concerns that could affect chemotherapy outcomes. Other objectives are to determine if the intervention improves quality of life and patient and caregiver satisfaction with the decision-making process for chemotherapy.

• **Nueva Vida Intervention: Improving QOL in Latina Breast Cancer Survivors and Their Caregivers**, led by Kristi Graves and Georgetown University, to conduct a randomized controlled trial with 200 people, 100 survivor-caregiver pairs, to improve quality of life for survivors and caregivers. Survivor-caregiver pairs will be assigned randomly to the intervention or usual care. Those assigned to the intervention will attend eight group sessions, held twice a month. Each session will cover a different topic such as communication, stress management, treatment side effects, or impact of cancer on family. Topics will be chosen based on expressed survivor and caregiver needs and provider input, including medical oncologists.

In Brief

Sparano Named Vice Chair of ECOG-ACRIN Research Group

(Continued from page 1)

Sparano serves as associate director for clinical research at the Einstein Cancer Center, and leads the Einstein Breast Cancer Working Group, a multidisciplinary group of physicians and scientists focused on translational breast cancer research.

He also serves as vice-chair of the NCI Breast Cancer Correlative Science Committee, and vice chair of the AIDS Malignancy Consortium.

He is a medical oncologist whose research has focused on developmental therapeutic approaches for breast cancer, lymphoma, and HIV-associated cancers, and clinical application of genomic profiling in cancer management.

He joined ECOG in 1991 as a member of the Biological Response Modifier Committee and Breast Committee.

Since that time, he has chaired or co-chaired 16 ECOG trials, including the TAILORx trial, and co-authored approximately 180 publications.

This work included establishing a role for weekly paclitaxel as adjuvant therapy for breast cancer, defining tumor and host determinants of breast cancer recurrence, and defining a role for infusional therapy in lymphoma and biologic therapy for HPV-associated cancer.

FRANK MCCORMICK signed a consulting agreement with **SAIC-Frederick Inc.** to work with the **Frederick National Laboratory for Cancer Research** on behalf of the NCI, to develop a proposal for intensive study of cancer cells driven by mutations of the RAS gene.

McCormick is director of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, and associate dean of the UCSF School of Medicine.

McCormick, who recently completed his term as president of the American Association for Cancer Research, will help SAIC-Frederick develop a proposal to be submitted to NCI and its advisory boards and committees for their review and approval.

In an April 8 address to a plenary session of AACR's annual meeting in Washington, D.C., NCI Director Harold Varmus said his vision is to "finally, after 30 years, learn how to target the cancer cells that

exist in somewhere around a quarter of all human tumors that are driven by mutations in RAS."

ROY BEVERIDGE was appointed senior vice president and chief medical officer of **Humana Inc**., effective June 17.

Beveridge is chief medical officer for McKesson Specialty Health, a subsidiary of McKesson Corp. Prior to McKesson's acquisition of US Oncology in 2010, he served as the executive vice president and medical director at US Oncology. Beveridge was also the co-director of the Bone Marrow Transplant Program at INOVA Fairfax Hospital.

GIULIO DRAETTA was named interim vice president for operations of strategic research programs at **MD Anderson Cancer Center**. He will serve as administrator for the Moon Shots Program.

He is a professor of genomic medicine and director of the center's Institute for Applied Cancer Science. Searches for a permanent vice president are underway, according to MD Anderson President Ronald DePinho.

Prior to joining MD Anderson in 2011, Draetta was Dana-Farber Presidential Scholar, chief research business development officer and deputy director of the Belfer Institute for Applied Cancer Science at Dana-Farber Cancer Institute.

Obituary

Barbara Brenner, 61 BCA Executive Director

Barbara Brenner, a former executive director of Breast Cancer Action, died May 10 in her home in San Francisco. She was 61.

Brenner was first diagnosed with breast cancer when she was 41. A lawyer and activist, she joined the board of BCA, a grassroots advocacy organization in San Francisco started by women with breast cancer.

A year later, she became the organization's first full-time executive director.

"Barbara Brenner was powerful, at times obstreperous," said medical sociologist Gayle Sulik, author of Pink Ribbon Blues.

"She never seemed to be afraid to call things as she saw them, and it didn't seem to matter who got upset about it.

"Barbara reminded us that sometimes it takes ruffling a few feathers to dislodge complacency."

Brenner died from complications of amyotrophic lateral sclerosis, a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord.

By the time Brenner stepped down in 2010, an earlier retirement than planned because of her ALS diagnosis, the organization had grown from a mailing list of 3,500 to 50,000 members.

"Barbara made things happen in the world of breast cancer," said Cindy Pearson, executive director of the National Women's Health Network.

"She was responsible for changing the way women thought about breast cancer, and moved people from awareness to activism.

"Under her leadership Breast Cancer Action developed powerful campaigns that changed corporate behavior, clinical practice and research agendas."

Brenner's activism started early. Raised in Baltimore in a family of seven children, she remembers hearing Martin Luther King, Jr. speak when her mother took her to a civil rights march at age 10.

At Smith College, Brenner was active in the anti-war movement, which shut down the campus in 1970 as a protest against the war.

At graduate school in Princeton, she came out as a lesbian in the early 70s, and the experience transformed her into an activist. It was in Princeton that she met Suzanne Lampert, her partner of 38 years.

Together they moved to Los Angeles, Lampert's hometown. Brenner started working with the women's rights project of the ACLU of Southern California, where she realized that the law could be used to effect positive change.

It led her to attend UC Berkeley Boalt Hall School of Law, now Berkeley Law School, and intern at the ACLU of Northern California in San Francisco.

After law school, she clerked for U.S. District Court Judge Thelton Henderson, a distinguished jurist who had been the first African-American to work for the Civil Rights Division of the U.S. Justice Department.

She later became a partner at Remcho, Johansen & Purcell, a California law firm specializing in public policy and constitutional issues. Brenner also formed her own firm with Donna Hitchens, working primarily on civil rights and employment discrimination.

In addition to Lampert, Brenner is survived by her siblings Joseph Brenner, Mark Brenner, Nanci Grail (Donald Grail), Richard Brenner (Barbara), and Lawrence Brenner (Roderic Hooks), and eleven nieces and nephews, all of whom live in the greater Baltimore area.