THE CANCER LETTER

Vol. 38 No. 13
March 30, 2012

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FDA News

ODAC Votes for Marqibo Accelerated Approval; Two Sarcoma Drugs Pose Classic Question: How Much PFS Does it Take to Get a Nod?

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee recommended accelerated approval for Marqibo (vincristine sulfate liposomal injection) for recurrent or relapsed acute lymphoblastic leukemia.

The recommendation—reached in a 7-4 vote with two abstentions—is evidence of the committee's continuing willingness to recommend accelerated approval based on intriguing signals from single-arm phase II studies in difficult-to-treat populations.

ODAC accepted the story of Marqibo's potential to get responses that could allow patients to move on to transplantation.

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Appropriations

Additional Level of Grant Review Proposed As NIH Prepares For Cost Cutting in 2013

By Conor Hale

During the next fiscal year, NIH plans instill an additional level of review to new grant proposals from any principal investigator who already receives $1.5 million or more of NIH money in total annual costs, NIH Director Francis Collins told a Congressional subcommittee.

Approximately 6 percent of NIH-funded investigators fit into this category, Collins said. The additional review will be conducted by each institute's advisory council.

Collins made this announcement as he and NCI Director Harold Varmus made their annual trip to Capitol Hill March 28, to present their case for biomedical research funding in the 2013 federal budget.

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In Brief

Komen Brand Takes a Hit After PR Disaster

LaSALLE LEFFALL stepped down from his position as chairman of the board at **Susan G. Komen for the Cure**. The Howard University surgeon will remain on the foundation's board.

Last week, **Dara Richardson-Heron**, the head of Komen's Greater New York City affiliate and **Katrina McGhee**, the executive vice president and chief marketing officer of Komen's national organization announced their exits from Komen.

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Marqibo May Propel ALL Patients To Curative Transplant Setting

(Continued from page 1)

"I felt that this drug was able to convert the patients who were in a palliative setting to a potentially curative setting," said ODAC member Mikkael Sekeres, associate professor of medicine at the Cleveland Clinic Taussig Cancer Institute Department of Hematologic Oncology and Blood Disorders, at the meeting March 21. "That's a meaningful change in goals of therapy for patients."

These responses were seen in a 65-patient study. Five of the patients who responded moved on to transplantation, and, for two of them, the transplants were beneficial.

In another rare disease, sarcoma, the committee considered two applications, recommending full approval for one and nixing the other. These votes were noteworthy, because the committee tackled what has become a classic ODAC question: how much of an advantage in progression-free survival is enough to support approval?

Here is how the committee answered these questions on March 20:

• Thumbs up: The committee voted 11-2 for approval of Votrient (pazopanib hydrochloride) tablets for patients with advanced soft tissue sarcoma who have received prior chemotherapy. The median PFS was 4.6 months in the pazopanib arm and 1.6 months in the placebo arm. The hazard ratio was 0.35 [95% CI: 0.26, 0.48; $p < 0.001$].

• Thumbs down: The committee voted 13-1 against approval of Taltorvic (ridaforolimus) tablets for metastatic soft tissue sarcoma or bone sarcoma whose disease has not progressed after at least four cycles of chemotherapy. In this novel approach—maintenance—the drug produced a median PFS of 17.7 weeks, compared to 14.6 weeks in the placebo arm. The hazard ratio was 0.72 (95% CI: 0.61, 0.85) with $p = 0.0001$.

The agency's recalculation shrunk this miniscule advantage to 16.1 weeks in the ridaforolimus arm and 14.0 weeks in the placebo arm with a HR of 0.74 (95% CI: 0.63, 0.88), $p = 0.0006$. The final analysis of overall survival, showed a median OS of 20.8 months in the ridaforolimus arm and 19.6 months in the placebo arm with a HR of 0.93, ($p = 0.46$).

Marqibo is sponsored by Talon Therapeutics Inc. Votrient is sponsored by GlaxoSmithKline and is approved for advanced renal cell carcinoma. Taltorvic is sponsored by Merck Sharp & Dohme Corp.

Marqibo vs. the Goal Posts?

Marqibo is a liposomal formulation of vincristine. The formulation is intended to prolong circulation of the drug in the blood and accumulation at the tumor site.

Marquibo enabled dose-intensification which produces a larger milligram dose per unit of body surface area (2.25 mg/m^2 versus 1.4 mg/m^2) and elimination of the need for the dose capping that is routinely applied to standard vincristine, the company said.

The committee recommended approval for Marqibo for adults with Philadelphia Chromosome-negative acute lymphoblastic leukemia in second or greater relapse or those whose disease has progressed following two or more treatment lines of anti-leukemia therapy

The efficacy signal ODAC was asked to interpret was faint. Based on FDA review, the rate of complete responses and CRs with incomplete hematological recovery, or CRi, was 15.4 percent (10 out of the 65 patients enrolled in a single-arm phase II study) with three CRs and seven CRis.

"I voted yes. Barry Kramer is going to kill me," said ODAC temporary member Mark Levis, associate professor of oncology and medicine at the Kimmel Comprehensive Cancer Center at Johns Hopkins School of Medicine.

Levis' wisecrack merits an explanation. Kramer, director of the NCI Division of Cancer Prevention and Control, is an acknowledged dean of skeptics in oncology, who frequently says that reliance on soft

THE CANCER LETTER

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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.

endpoints amounts to moving the goalposts further apart at a football game. (He has no position on Marqibo.)

"I think that this is a real response rate," Levis continued. "It does offer something as a practicing leukemia doctor, that even as a skeptic I think I am going to believe. And I will be fully expecting FDA to yank this drug if they don't show a real improvement in overall survival in a reasonable amount of time."

Committee member Deborah Armstrong, an associate professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Hopkins and an associate professor in gynecology and obstetrics at the Hopkins School of Medicine, also voted for approval.

"This is a very difficult population," Armstrong said. "Half of the patients have had prior transplants. They have really extensive disease. It's very hard for us to know how to compare what we saw to other treatments available. But I thought that there was enough there to say that this was something that looks like it's benefits those patients."

Biostatistician Brent Logan was unable to discern the signal Levis found compelling.

"Although this is an accelerated approval setting and we don't need definitive evidence of benefit, but we still need reasonable likelihood of benefit for patients," said Logan, an ODAC member and a professor at the Division of Biostatistics at the Medical College of Wisconsin. "The response rate was very modest. And it was unclear to me that this was driven by the therapy. I think the modest response rate is going to make it very difficult for the subsequent phase III trials to be successful. I also have concerns about the feasibility of accrual. I would like to see accrual ongoing so that we could assess whether it's feasible before accelerated approval is considered."

ODAC member Frank Balis, a pediatric oncologist and pharmacologist at the Children's Hospital of Philadelphia, said he saw no evidence that would demonstrate that a liposomal formulation of vincristine was better than just plain vincristine.

"I didn't see the potential advantage of placing this already known activation into this liposome delivery package in terms of the pharmacologic perspective," said Balis, the Louis and Amelia Canuso Family Endowed Chair for Clinical Research in Oncology at the University of Pennsylvania. "I didn't see evidence that it's better than what's out there, although it's a difficult thing to judge. I am not convinced that it's less toxic at this point."

Balis said that he is concerned that the agent is given in doses that are only a little lower than the dose that had been found to have unacceptable toxicity.

ODAC Chair Wyndham Wilson described Marqibo as one of the most difficult cases he encountered while on the committee.

"I struggled down to the wire on this," said Wilson, head of the NCI Metabolism Branch Lymphoma Therapeutics Section. "I am very cognizant of the need for single-arm trials to be robust. I was more voting against the lack of other things, perhaps than I was voting for the efficacy of this agent. But it did, in fact, induce complete remissions morphologically. That's a tall order in a group like this. I am not at all convinced that it's going to be that much more active—or more active at all—than vincristine.

"But it is a drug that is active, and we know a lot about its toxicity, and so I felt that it was better to give the benefit of the doubt to this drug, given this very rare and unfortunate setting," Wilson said. "I too, have great concerns about their phase III trials, both the feasibility of getting it finished, and also whether it's going to show a positive result. And I think that FDA should hold all sponsors to finishing these confirmatory trials in a reasonable time frame."

Marqibo's sponsor, Talon, is conducting a confirmatory trial is an earlier setting, newly-diagnosed ALL. The trial is listed in the clinicaltrials.gov database: http://www.clinicaltrials.gov/ct2/show/NCT01439347?term=ttx404&rank=1.

Separately, Talon is conducting a phase II trial in metastatic malignant uveal melanoma: http://www.clinicaltrials.gov/ct/show/NCT00506142?order=4

This was Marquibo's second appearance before ODAC. In December 2004, the committee voted unanimously against an accelerated approval for the drug in relapsed aggressive non-Hodgkin's lymphoma (The Cancer Letter, Dec. 10, 2004).

The PDUFA date for the ALL indication is May 13.

Implications for Accelerated Approval

The Marqibo case allowed FDA to spell out its position on accelerated approvals.

FDA meeting materials included a discussion of the standards for accelerated approval, the role phase II trials play in such approvals, as well as the standards for confirmatory trials.

The text, based on discussion at the ODAC meeting Feb. 11, 2011, is important, because it shows precisely how the agency boiled down the committee's advice on accelerated approval:

"Overall, ODAC members agreed that randomized controlled trials should be the standard and that single

arm trials should be the exception. Committee members commented that single arm trials may be used in the following situations: 1) rare diseases and 2) high level of activity of the agent or pronounced treatment effect.

"It was also mentioned that the toxicity of the agent must be taken into account in a risk/benefit analysis in the situations in which single arm trials may be used.

"Committee members noted that it would be helpful to have a definition of rare diseases. Members also noted that the bar for accelerated approvals should not be lowered to move products on to the market faster through single arm trials, but rather single arm trials should only be used in certain situations and randomized controlled trials should be the standard.

"Overall, members agreed that at least two controlled trials should be needed for accelerated approval commitments. Most members agreed with this statement with the caveat that in rare diseases and pediatrics this may not be feasible.

"Overall, members felt that a well designed development plan is needed prior to the application being filed. Most also preferred that the sponsor have studies already ongoing at the time of application."

In the past, an accelerated approval was almost as valuable to a sponsor as a full approval. Drugs remained on the market as long as there was even a weak signal (or an illusion) that they may be helping some patients.

However, in recent years, the agency has demanded more rigorous deadlines for concluding confirmatory trials, and last year, it stripped an accelerated approval of the Genentech Avastin (bevacizumab) for metastatic breast cancer.

Now that FDA has initiated the process for withdrawal of accelerated approvals, it remains to be seen whether the agency has the stamina to use it against lower-profile drugs intended for smaller indications.

Standards for Maintenance Indications?

The sponsors of Taltorvic, too, had a novel story to tell.

The drug was to be given as maintenance to patients who had received treatment for sarcoma, thereby causing ODAC to discuss standards for maintenance therapies, which are given to patients to delay recurrence.

Yet, ODAC didn't buy that storyline, and a patient representative cast the sole vote for the approval of the drug.

"I believe it's very important for the patients to retain the final say on which treatment they pursue, and I don't feel comfortable taking that away from them," said Kareem Shaya, explaining his position.

Taltorvic is a kinase inhibitor of the mammalian target of rapamycin (mTOR).

"I think the maintenance setting to be a unique one, one that is not standard," said ODAC chair Wilson. "One would not normally treat a patient who doesn't have progressive disease. I personally would like to see a more robust benefit in order to justify what is almost certainly overtreatment of a large number of patients.

"I very much feel that crossover designs for the placebo arms to the treatment arm to me is the way to both get the data that the company presented today, but also to answer the question of whether early vs. delayed treatment will improve the outcome, or if there is an equivalent outcome, whether the toxicity will be less.

"We faced that in the lung cancer setting, where there was a survival advantage to maintenance, but the question of whether or not using the drug later on might have given you the same survival advantage but not exposed patients for as long to a drug was not answered.

"I feel that crossover designs should be used more doing these maintenance studies."

Sekeres said he likes the idea of conducting a maintenance trial in sarcoma, but was concerned about the drug's toxicity, which he said "outweighed even a sliver of benefit in PFS."

Lee Helman, scientific director of clinical research at the NCI Center for Cancer Research, said he found the drug intriguing, but the data didn't justify approval. "I want this drug," said Helman, a temporary member. "I want to try this drug in combinations, and I hope this isn't the end of our ability to test this in sarcomas.

"I think in the end of the day, I neither read anything before this meeting or heard anything at this meeting that made me have any comfort that it should be recommended at this point in time."

The safety profile of ridaforolimus is similar to that of other mTOR inhibitors. The number of patients who discontinued due to an adverse event (14 percent ridaforolimus, 2 percent placebo) is of particular concern in a drug intended for use as maintenance therapy, FDA reviewers said.

Patients were more likely to experienced grade 3-4 events (64 percent ridaforolimus, 25 percent placebo). Grade 1-4 adverse events occurring in more than 20 percent of patients included stomatitis, asthenia/fatigue, infection, rash, cough, diarrhea, nausea, decreased appetite, headache, edema, abdominal pain, dyspnea, and fever.

FDA said adverse events of particular concern included pneumonitis, infection, and renal

failure/impairment. Laboratory abnormalities included hematologic toxicity (11 percent gr 3-4 thrombocytopenia), hyperglycemia, hyperlipidemia, and increased ALT (3 percent gr 3-4).

Ephraim Casper, head of the Division of Network Medicine Services at Memorial Sloan-Kettering Cancer Center and a temporary member of ODAC, said he found it painful to vote against approval.

"There is clearly an unmet need," he said. "The toxicity of this compound, while non-trivial, is manageable, but the real question is efficacy."

As Marginal as What's Out There

For Votrient, a three-month margin of improvement in PFS turned out to be enough.

"I look at this within the context of what's being done out there," Wilson said. "I agree that the effect here is very marginal, but this is a group of folks that don't have really good options, that the effect appears to be biologically real. I am more taken by the fact that there appear to be some folks who benefit from this for long periods of time.

"I know that one does get a better understanding of a drug once it is approved and then goes into multiple clinical trials. I fee the effect is marginal, but it seems to be as marginal as what's out there, and it is a different class of agents."

Votrient is a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and-β, and c-kit tyrosine kinases.

The drug would be indicated for patients with advanced soft tissue sarcoma who have received prior chemotherapy. The company seeks limitations on use of the agent since its phase III STS trial population excluded patients with adipocytic STS or gastrointestinal stromal tumors.

Appropriations

NIH Needs a Raise, Senators Say As Collins, Varmus Present Budget

(Continued from page 1)

In a tense financial atmosphere, Collins and Varmus appeared eager to discuss their plans for making the best out of what they could get from Congressional appropriators—by making changes to the institutes' grant-making procedures, among other cost-cutting measures. The directors touted the significant returns that investments in NIH basic research have produced, while only requesting a meager increase in their funding for the next year.

"Our employees are ready to tighten their belts," said Collins to the Senate appropriations subcommittee responsible for NIH's budget. "And take whatever needs to be done in an honorable, fair-minded way, as far as helping out with the difficulties our government faces."

President Barack Obama's 2013 budget proposal includes a request for $30.86 billion for NIH, approximately the same as the $30.62 billion estimate for the 2012 fiscal year.

If passed, NIH expects to fund 9,415 new and competing research project grants in with that funding in the 2013 fiscal year—672 more than current 2012 estimates—at an average cost of $431,000 each. The institutes estimate the total number of 2013 project grants to be around 35,888.

The president's budget requests $5.07 billion for NCI, an increase of $2.7 million over comparable 2012 levels.

Collins and Varmus testified along with Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases; Richard Hodes, director of the National Institute on Aging; Thomas Insel, director of the National Institute of Mental Health and acting director of the National Center for Advancing Translational Sciences; and Griffin Rodgers, director of the National Institute of Diabetes and Digestive and Kidney Diseases.

In his testimony, Collins laid out the plan for NIH to "maximize funding for investigator-initiated grants, and to continue our support of first-time researchers."

"We propose to reduce budgets for non-competing RPGs by 1 percent from the FY 2012 level and to restrain growth in the average size of new awards. We will also no longer assume out-year inflationary increases for new and continuing grants.

"To nurture early-career scientists, we will continue our efforts to ensure that the success rates

for investigators submitting new R01 applications are the same whether the applicant is first-time or more experienced."

These plans and modest budget requests come at a time when the threat of sequestration hangs over the heads of Congressional appropriators.

Budget sequestration was agreed to in the Budget Control Act of 2011, which ended the fight over the federal debt ceiling. The act included the provision that, if Congress is unable to come to an agreement to significantly lower the deficit, automatic, across-the-board spending cuts would be enacted.

"[The Congressional Budget Office] has estimated that most non-defense discretionary programs such as NIH would be cut by about 7.8 percent next January if Congress does not enact a plan before that time," said subcommittee chairman Sen. Tom Harkin (D-Iowa). "If that cut were applied equally across the government, the number of new NIH grants for promising research projects would shrink by more than 1,600 in 2014—and by more than 16,000 over the next decade."

While NIH appeared meek with its funding request—almost seeking to be accommodating—this modesty left some committee members rankled. With all the benefits, why was NIH not leading the charge for increased funding? Sen. Richard Shelby (R-Ala.) admonished the institute directors and the Obama administration for not asking for more.

"A continued commitment to NIH is essential to addressing our nation's growing health concerns and spur medical innovation for the next generation of treatment and cures," he said.

"Unfortunately the NIH budget request for the year 2013 abandons that commitment.

"In 2011, NIH research funding supported 432,000 jobs nationwide. Research carried out by the NIH and its network of 325,000 researchers at 3,000 institutions across the country serves this nation with the goal of improving human health."

"Without sustained support for the NIH, the translational discoveries from bench to bedside will be dramatically slowed, and the U.S. will surrender its role as a world leader in scientific research.

"Further, the administration's request does not keep pace with biomedical research inflation," Shelby continued. "As a result, in inflationary-adjusted dollars, the NIH is 17 percent—that's right, 17 percent—below where they were 10 years ago."

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Sequestration: Automated Budget Cuts

"CBO has estimated a 7.8 percent cut," said Harkin. "Could you give us a thumbnail sketch of what that would mean for NIH?"

"Senator, I appreciate the question," responded Collins. "It is a very serious one."

"If the sequesters were to kick in on Jan. 2, 2013, NIH would expect to lose 7.8 percent of the budget, about $2.4 billion. That would of course happen with the fiscal year already three months along.

"The estimate that has been put forward would result in roughly 2,300 grants that we would not be able to award in fiscal year 2013 that we otherwise would have expected to. That represents almost a quarter of our new and competing grants.

"That would result in success rates for applicants who come in competing applications falling to historically low levels. It would be devastating for many investigators who are seeking to continue programs that they have funded in the past and are back for their competing renewal, or who are starting things that are entirely new.

"I think the burden would hit particularly heavily on first time investigators who are seeking to get their programs up and going. And upon learning of something of this sort, what is already a considerable sense of anxiety in that cohort—who are our future—would only go up. This would have across the board implications in terms of both basic and clinical science.

"We would of course attempt to prioritize those things that are most critical, but there's no question that an influenza vaccine would be slowed down, that efforts in cancer research would be slowed down, that in the common fund…we would not be able to start new programs. All of those things would be put at great risk by this kind of outcome."

Harkin then turned to Varmus, asking, "Even if we can avoid sequestration, the budget's likely to remain tight. You've been managing the NCI with smaller increases since your return. What strategies have you found or do you plan that will allow you to continue to make progress against cancer with these tight budgets?"

"Well we've done several things to try and cope with the tight budgets—I can't print money, but that would be the ideal solution," said Varmus.

"But we have been looking very carefully at grants that get lower priority scores to see if they are grants that meet higher priority topics to make sure those get funded. We've been reorganizing our clinical trials cooperative groups to make sure they operate effectively and are answering deep scientific questions.

"We have started a new program that emphasizes the bringing together of the scientific community to help define the great unanswered questions of cancer research, the so-called Provocative Questions, an initiative that's solicited over 750 applications to study these deeper questions and empower the scientific community to help us define what needs to be answered in the future.

"We have the ability to act on our new conception of what the genetic underpinnings of cancer are through the collaborative project we've undertaken with The Genome Institute through The Cancer Genome Atlas.

"All of these things are helping us, but these strategies do not solve the underlying problem of having adequate resources to support science—which costs real money."

Stability, and NIH Morale

"This is a somewhat scary time," said Collins.

"In terms of the likelihood of being funded, if you send your best ideas to NIH, has traditionally been, over the last 40 years, in the range of 25 to 35 percent. In the last year for which we have full numbers for, that number fell to 17 percent. That means that an awful lot of that effort comes away without support.

"And certainly, if I had to pick one thing that I would say would be most healthy for the American biomedical research future, it would be stability.

"This feast-or-famine just doesn't work in this circumstance—you want to give investigators the confidence that if they have good ideas, and if they work hard, and if they produce publications that change the direction of a particular fields—they make insights, they make breakthroughs, they take risks—that there's a career there.

"And it's difficult when things are bouncing around, as they currently are. They begin to wonder if this is a career that they want to invest themselves in. That's not something that's happening in other countries, but that's happening, certainly, in the U.S."

"Would research scientists in the United States conduct their research elsewhere?" asked Sen. Jerry Moran (R-Kan.). "Are we competing in a global economy for the best talent?"

"We are," replied Collins. "We have greatly benefited over the years of being able to recruit the best talent from other countries. We continue to. In many instances those individuals would come and be trained in our country and then would stay and become part of this remarkable innovative community.

"It is less likely now that those individuals will stay. It's easier in many ways to go back to their countries where there is more support now, and perhaps they see the environment here as not as friendly. The dynamics have certainly changed."

"I want to talk about federal employees," said Sen. Barbara Mikulski (D-Md.). "I'm deeply concerned… of this ongoing hazing, harassment, snarky comments, throwaway one-liners, and so on… Now that's how I feel. Could you tell me, Dr. Collins, how that impacts your recruitment and retention? Or do I just have a soft heart toward federal employees?"

"We thank you for your soft heart, it means a lot," said Collins. "But this is a serious issue in terms of morale.

"For individuals like the 17,000 that work at NIH to read about themselves in the comments from individuals who have never met anybody who works at NIH, and who talk about these being employees who are simply overpaid and contributing little, is deeply hurtful.

"I am so proud to stand at the helm of an organization with such incredibly dedicated people, some of whom you see here at this table with me. And all of those, in terms of senior scientific positions, who could easily be employed at much better financial rates in other parts of the public and private sectors, and who are doing this work because of their hopes of making a difference—because of their public spirit; because of their determination to make the world a better place.

"And to have that kind of dedication characterized in the way that seems to be done, in a sweeping way, by people talking about federal employees as if they are some sort of parasite upon the public, it is really deeply hurtful.

"And of course that has translated into decisions in terms of ways in which federal employees are being treated in terms of financial aspects. I think our employees are ready to tighten their belts and take whatever needs to be done in an honorable, fair-minded way, as far as helping out with the difficulties our government faces. But why gang up on them? Why try to single them out?"

"Here is my question," said Mikulski, "Since all of the activities going on around pensions, extended pay freezes and so on, do you see an upsurge in requests for retirement? And I'm not only talking about the PhD's, we're talking about the lab people, the one's that run that fire department. There's a lot of support staff that goes on to enable the scientist to be the scientist."

"Indeed, and we depend on those people critically or we couldn't do our work," said Collins. "I don't know whether there is an actual statistical indication of an

upsurge in retirements, but certainly as an indicator of general morale, I would not be surprised if that is the case.

"And when it comes to your other question about hiring people, the kinds of hires that I'm trying to be involved in generally are the high-level senior scientists and this question comes up. 'Is this a good time to come and work for the federal government? All the things we're reading about in the paper makes it sound as if we're not going to be considered as the leaders that we hope to be.' It is a serious issue.

"They're not necessarily being well received, as they should be, for their dedicated service."

Both Varmus and Collins' testimonies can be found at http://www.cancerletter.com/categories/documents.

Varmus' testimony submitted to the subcommittee follows:

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Cancer Institute (NCI) of the National Institutes of Health (NIH). The Fiscal Year (FY) 2013 NCI budget of $5,068,864,000 includes an increase of $2,717,000 over the comparable FY 2012 level of $5,066,147,000.

As many of you will read upon its release later today, the 2012 Annual Report to the Nation on the Status of Cancer offers a generally encouraging view of cancer trends. The Report documents that death rates from all cancers combined for men, women, and children in the United States continued to decline between 2004 and 2008, the latest year for which we have complete analysis. Age-adjusted mortality rates for 11 of the 18 most common cancers among men and for 14 of the 16 most common cancers in women have declined. The overall rate of new cancer diagnoses, also known as incidence, among both men and women also declined over similar periods, although for women the decline leveled off from 2006-2008.

These continued declines in death rates for most cancers, as well as the overall drop in incidence, are powerful evidence that our nation's investment in many fields of cancer research produces life-saving approaches to cancer control. The breadth of the nation's cancer portfolio and our ability to pursue many different approaches to cancer research must match the heterogeneity of cancer itself, which we now understand to be literally hundreds of genetically distinct diseases with many avenues to prevention, screening, diagnosis, and treatment.

Basic Science

A large part of the NCI basic research portfolio uses molecular biology and genetics to deepen our knowledge about the origins and behavior of cancers and to develop drugs and understand drug resistance. For example, decades of basic research culminated in development of the molecularly targeted drug Gleevec (imatinib). Since FDA approved the drug in 2001, it has been the treatment of choice – and a very effective one – for CML, or chronic myelogenous leukemia, as well as a few other cancers. Targeted drugs usually inhibit enzymes – in this case, kinases – that are essential to the survival of cancer cells, rather than broadly killing all rapidly dividing cells in the body. In CML, the target is the abnormal protein made by fused genes, BCR-ABL, in cancerous blood cells, where in its activated or "on" state the mutant enzyme pushes white blood cells into overdive, causing disease. Gleevec blocks the mutant enzyme, kills cancer cells, and returns the blood system and the patient to a normal state.

But despite Gleevec's generally powerful effects, some CML patients relapse when new mutations make the BCR-ABL protein resistant to Gleevec, allowing the abnormal enzyme to drive white blood cell growth again despite treatment. This phenomenon, drug resistance, is now being encountered with the several other targeted therapies more recently introduced for lung cancer, melanoma, and other cancers. So it is encouraging to report that NCI-supported research has identified a number of drugs targeting BCR-ABL proteins even after they acquire mutations that confer resistance to Gleevec. Two of these, approved a few years ago, did not overcome one relatively common resistance mutation. But a third generation of drugs is able to do that, in an interesting new way, by freezing the target protein in an inactive conformation, so that its enzyme cannot work. This example illustrates another important point. Many different research streams – from genetics to structural biology to pharmacology – were required for these advances in treatment. The need to bring together multidisciplinary teams to focus on key questions like drug resistance in cancers increasingly defines modern biomedical research.

To strengthen NCI's ability to drive similar discoveries, NCI this year consolidated a number of its genomics initiatives – including the flagship program TCGA (The Cancer Genome Atlas) – into a single Center for Cancer Genomics. TCGA's aim is to characterize comprehensively the genomic alterations in hundreds of samples of about 20 known tumor types. With the project nearing completion on schedule, the

vast influx of data promises to dramatically alter our knowledge of the genetic changes that drive cancer development. The new Center will work with other components of NCI to ensure that the findings are applied to developing new diagnostics and therapeutics and are integrated swiftly into medical practice.

Screening and Prevention

Early detection of cancer can enhance therapy. Last year I briefed this Subcommittee on the recently concluded National Lung Screening Trial, which had demonstrated that current and former smokers who were screened with low-dose helical computed tomography were 20 percent less likely to die of lung cancer compared to others who received standard chest x-rays.

Recent findings from another long-term study also point to screening as an effective way to cut deaths from another common cancer – colorectal adenocarcinoma, which kills about 49,000 Americans every year. Clinical studies, several funded by NCI, have consistently demonstrated that tests for fecal blood and direct observation of the colon with endoscopy can effectively reduce the mortality rates associated with colorectal cancer – by up to 50 percent, according to one recent estimate. NCI also is investing in studies to understand behavioral and economic barriers to screening to increase screening rates, especially among minority populations.

Diagnosis and Treatment

One of the most critical aspects of cancer is its remarkable heterogeneity – cancer is actually a collection of hundreds of genetically distinct diseases, each with its unique vulnerabilities. Lung adenocarcinomas, for instance, develop through a variety of genetic changes, and each pattern of changes requires a different therapeutic approach. Just a few years ago, it was recognized that up to 7 percent of lung adenocarcinomas contain a fused chromosome that activates the protein made by a gene called ALK to cause cancerous growth. FDA last fall approved crizotinib to treat patients with the abnormal ALK gene. Crizotinib blocks the activity of the enzyme, again a kinase, produced by the fused ALK gene, similar to the action of Gleevec in CML. This oral drug has been approved by the FDA and must be used with a companion molecular test to make sure it is used to treat only tumors with the abnormal ALK gene.

Another potential treatment recently emerged from academic research laboratories, this one for metastatic prostate cancer. MDV-3100 is a so-called anti-androgen therapy that prevents male hormones from stimulating the growth of prostate cancer cells through androgen receptors – preventing testosterone from binding to androgen receptors and preventing the androgen receptor from initiating the production of proteins that induce tumor growth. Current anti-androgen drugs suppress the growth of prostate cancer cells temporarily, but in most patients the cancer ultimately develops resistance to these drugs by increasing the amount of receptors. MDV-3100, by contrast, binds so tightly to the androgen receptors that it prevents them from functioning even when the receptor numbers are very high. The new drug performed so well that the clinical trials were halted early, and the drug now awaits approval at FDA.

Provocative Questions

During the past 14 months, NCI has brought together researchers to propose, craft, and debate what they consider to be the critical questions in cancer research that may fall outside our current sphere of focus, but that could lead to important discoveries about the causes and behaviors of cancers. NCI convened 17 workshops across the country that identified some 24 Provocative Questions, and NCI has set aside an initial $15 million from its FY 2012 budget to fund some of the more than 750 applications received under this program. While this initiative does not replace the NCI's longtime and essential emphasis on funding investigator-initiated research, it represents a useful new approach to making the greatest impact with our research dollars.

Congress' past investments in cancer research are the reason we are able to report promising scientific findings each year, and why the Report to the Nation continues to show steady progress against a wide range of cancers. We are now able to define genetic changes that cause cancer, use them to control cancer with more precise tools, and thereby reduce the Nation's cancer burden. The President's budget for 2013 for the National Cancer Institute will provide the support for discoveries in basic science, cancer control and prevention, for early detection and diagnosis, and for methods to prevent, treat, and in some instances cure, cancers.

Epidemiology

Cancer Rates Report Focuses On The Impact of Obesity

Death rates from all cancers combined for men, women, and children continued to decline in the United States between 2004 and 2008, according to the Annual Report to the Nation on the Status of Cancer, 1975-2008.

The incidence rate among men decreased by an average of 0.6 percent per year between 2004 and 2008. Overall cancer incidence rates among women declined 0.5 percent per year from 1998 through 2006, with rates leveling off from 2006 through 2008.

The report is co-authored by NCI, the Centers for Disease Control and Prevention, the North American Association of Central Cancer Registries, and the American Cancer Society.

It was published online in the journal Cancer, and will appear in print in the May issue.

The special feature section highlights the effects of excess weight and lack of physical activity on cancer risk. Esophageal adenocarcinoma, cancers of the colon and rectum, kidney cancer, pancreatic cancer, endometrial cancer and breast cancer among postmenopausal women are associated with being overweight or obese.

"This report demonstrates the value of cancer registry data in identifying the links among physical inactivity, obesity, and cancer," said CDC Director Thomas Frieden. "It also provides an update of how we are progressing in the fight against cancer by identifying populations with unhealthy behaviors and high cancer rates that can benefit from targeted, lifesaving strategies, and interventions to improve lifestyle behaviors and support healthy environments."

For more than 30 years, excess weight, insufficient physical activity and an unhealthy diet have been second only to tobacco as preventable causes of disease and death in the United States. However, since the 1960s, tobacco use has declined by a third while obesity rates have doubled, significantly impacting the relative contributions of these factors to the disease burden. Excess weight and lack of sufficient physical activity have been linked to increased risk of cardiovascular disease, hypertension, diabetes, and arthritis, as well as many cancers.

"In the United States, 2 in 3 adults are overweight or obese and fewer than half get enough physical activity," said John Seffrin, chief executive officer of the American Cancer Society. "Between children and youth, 1 in 3 is overweight or obese, and fewer than 1 in 4 high school students get recommended levels of physical activity. Obesity and physical inactivity are critical problems facing all states. For people who do not smoke, excess weight and lack of sufficient physical activity may be among the most important risk factors for cancer."

The Report to the Nation was first issued in 1998. In addition to drops in overall cancer mortality and incidence, this year's report also documents the second consecutive year of decreasing lung cancer mortality rates among women. Lung cancer death rates in men have been decreasing since the early 1990s.

Colorectal cancer incidence rates also decreased among men and women from 1999 through 2008. Breast cancer incidence rates among women declined from 1999 through 2004 and plateaued from 2004 through 2008. Incidence rates of some cancers, including pancreatic, kidney, thyroid, liver and melanoma, increased from 1999 through 2008.

"The continued declines in death rates for all cancers, as well as the overall drop in incidence, is powerful evidence that the nation's investment in cancer research produces life-saving approaches to cancer prevention, screening, diagnosis, and treatment," said NCI Director Harold Varmus. "But, it is also important to note that investments we make today are critical if we hope to see these declines in incidence and death from cancer reflected in future Reports to the Nation."

Among children age 19 or younger, cancer incidence rates increased 0.6 percent per year from 2004 through 2008, continuing trends from 1992, while death rates decreased 1.3 percent per year during the same period. These patterns mirror longer-term trends.

Among racial and ethnic groups, the highest cancer incidence rates between 2004 and 2008 were among black men and white women. Cancer death rates from 2004 through 2008 were highest among black men and black women, but these groups showed the largest declines f˙or the period between 1999 and 2008, compared with other racial groups. The differences in death rates by racial/ethnic group, sex, and cancer site may reflect differences in risk factors, as well as access to and use of screening and treatment.

"While the sustained decline in cancer mortality rates is good news, the persistence of disparities among racial and ethnic groups continues to concern us," said Betsy Kohler, executive director of NAACCR. "The collection of comprehensive cancer surveillance data on all patients may provide clues to understanding

these differences and addressing them."

The report notes that continued progress against cancer in the United States will require individual and community efforts to promote healthy weight and sufficient physical activity among youth and adults.

The report is posted at: http://wileyonlinelibrary.com/journal/cancer-report2012.

In Brief

Komen Brand's Decline Trumped Only by Fannie Mae's in 2009

(Continued from page 1)

McGhee oversees Komen's more than 200 corporate partnerships and 140 races that bring in more than $350 million in annual revenue, The New York Times reported (http://www.nytimes.com/2012/03/22/us/calls-grow-for-leader-of-susan-g-komen-for-the-cure-to-resign.html?_r=1&ref=health).

Komen was harmed by its decision earlier this year to bar its affiliates from funding Planned Parenthood (The Cancer Letter, Feb. 3, Feb. 10). The foundation ultimately backtracked, but this apparently wasn't enough for its former supporters.

The PR fiasco has eroded the value of Komen's brand, Harris Interactive reported earlier this week. Based on findings reported in the 2012 Harris Poll EquiTrend study, Komen's current brand equity score of 55.1 represents a 21 percent drop in brand equity over the prior year—a historic drop in the study's 23-year history, surpassed only by Fannie Mae in 2009.

The Harris report is posted at http://www.harrisinteractive.com/NewsRoom/PressReleases/tabid/446/ctl/ReadCustom%20Default/mid/1506/ArticleId/994/Default.aspx.

JOHN MENDELSOHN will receive the **American Association for Cancer Research Margaret Foti Award** for Leadership and Extraordinary Achievements in Cancer Research at the association's annual meeting April 1.

Mendelsohn is co-director of the MD Anderson Cancer Center's Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalised Cancer Therapy. He is also chair of the National Cancer Policy Forum of the Institute of Medicine.

He served as the president of MD Anderson from 1996 to 2011, stepping down to return to clinical and translational research. Mendelsohn established the Center for Global Oncology, an organization that coordinates MD Anderson's formal affiliations with more than 24 foreign academic, healthcare and government entities.

Mendelsohn was the founding editor-in-chief of Clinical Cancer Research, one of the seven journals of the AACR.

STEPHEN FESIK will receive the **AACR Award for Outstanding Achievement in Chemistry in Cancer Research**.

Fesik, the Orrin H. Ingram II chair in cancer research at Vanderbilt University, will also be honored at the AACR's annual meeting, where he will deliver the lecture, "Drugging the undruggable using fragment-based methods."

Fesik is being recognized for the use of nuclear magnetic resonance to discover small molecules capable for use as cancer therapeutics. He was one of the first researchers to utilize NMR spectroscopy for cancer drug discovery. He developed many NMR methods and determined the three-dimensional structures of several proteins, especially proteins involved in cell death.

GEORGE KOVACH became president of the **Association of Community Cancer Centers**.

Kovach is medical director of the Genesis Cancer Center and one of the founding members of the Iowa Oncology Society.

He served as ACCC treasurer. He has also been a member of the American Society of Clinical Oncology clinical practice committee. In addition, he is on the Medicare Carrier Advisory Committee, representing the subspecialty of hematology.

JEFF HUMPHREY was named senior vice president for drug development of

Kyowa Kirin Pharmaceuticals. He is the former vice president of oncology medical strategy at Bristol-Myers Squibb.