THE CANCER LETTER

Vol. 35 No. 28
July 17, 2009

© Copyright 2009 The Cancer Letter Inc.
All rights reserved. Price $385 Per Year.
To subscribe, call 800-513-7042
or visit www.cancerletter.com.

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

ODAC Says Clear Clinical Benefit Required When Sponsors Claim Progression Delay

By Paul Goldberg

The FDA Oncologic Drugs Advisory Committee sent a resounding message July 15 to everyone involved in development of cancer drugs:

Delaying disease progression is not enough. It takes a demonstration of clinical benefit to get FDA approval.

The message was not subtle. It came through loud and clear in opening remarks by Richard Pazdur, director of the FDA Office of Oncology Drug Products:

"The approval process is not merely a screening process for drug activity. The goal of a registration trial is not merely to obtain a statistically significant result. The primary goal is to obtain a statistically reliable evaluation of the drug that represents a clinically meaningful result that yields in a favorable benefit/risk evaluation."

Pazdur said this twice in one day, first, in ODAC's morning session which resulted in a 13-1 vote against approval of Yondelis (trabectedin) in combination with Doxil (pegylated liposomal doxorubicin) for relapsed ovarian cancer.

Then, Pazdur recycled the conclusion, along with much of that

(Continued to page 2)

Capitol Hill:

House Subcommittee Rejects Doubling Budget For Cancer Research, Provides Increase To NIH

A House subcommittee that drafts the NIH spending bills last week disagreed with the administration's plan to double the institutes' spending on cancer research, and instead spread the increase across all institutes and centers.

In a statement July 10, Rep. David Obey (D-Wisc.), chairman of the Labor, HHS & Education Subcommittee, said the subcommittee was "rejecting the Administration's targeted funding approach and ensuring that all institutes and centers receive funding to offset biomedical research inflation."

The subcommittee gave NIH an additional $500 million, stipulating that these funds would have to be spent across the institutes and centers. The administration asked for $30.467 billion for NIH and the House subcommittee provided $30.967 billion. The current NIH budget is $30.025 billion.

Obey is also the chairman of the full House Appropriations Committee. The bill is tentatively scheduled to come to the floor on July 22. The Senate is yet to consider its version of the bill.

J&J Switched From Survival To Progression Delay In Trials

(Continued from page 1)

morning's remarks, during the afternoon session, which reviewed Doxil in combination with docetaxel for locally advanced or metastatic breast cancer patients who have received prior anthracycline therapy. In that case, ODAC voted 14-0 against approval.

The sponsor, Johnson & Johnson, sought regular approval for both drugs.

FDA's decision to throw an application to ODAC is never trivial. Sometimes the agency wants advice. Sometimes it wants to use the committee for political cover. And then there are times when the committee gets to amplify a message, to shout from the rooftop. On July 15, ODAC did just that, twice.

The similarities between the applications were striking. In both cases, Johnson & Johnson originally planned to conduct registration trials powered for survival. However, the regulatory environment began to change as FDA started to accept delay in disease progression. The company amended the protocols to measure time to tumor progression.

Both drugs went through FDA's special protocol assessment process before changes were made. Although the agency signed off on the changes, it inserted the caveats that J&J would have to do more than hit statistical targets. It would have to produce proof of meaningful clinical benefit.

In both cases, the drugs were claimed to produce modest improvements in delay of disease progression:

—The addition of Yondelis to Doxil in ovarian cancer improved progression-free survival by six weeks, compared to Doxil alone. The result was based on a phase III trial that enrolled 672 patients.

—The addition of Doxil to Taxotere improved time to progression by 2.8 months, compared with Taxotere alone. The company's trial randomized 751 patients.

Neither drug has been shown to improve overall survival, though follow-up in the trials continues.

"The magnitude of the effect size on the PFS endpoint is of great importance in evaluating a risk-benefit analysis," Pazdur said in opening remarks on Yondelis. "The magnitude of the effect size has a direct bearing on reliability and clinical relevance of the PFS.

"An improvement in overall survival has repeatedly been viewed as a direct clinical benefit and is very reliably assessed. In contrast, PFS is primarily considered either a surrogate, or a surrogate reasonably likely to predict for clinical benefit. If PFS is a surrogate for overall survival, the magnitude of the PFS effect should be greater than any subsequent anticipated effect on overall survival."

Pazdur's remarks on Doxil were similar. The transcripts of both talks appear on page 4.

"Buyer Beware"

At the meeting, the Yondelis application triggered a discussion of risks sponsors take by choosing a delay in progression endpoint.

The agency's sign-off on the protocol amendment didn't mean that J&J would just have to hit a statistical target to get approval, Pazdur said.

Before agreeing to changes, FDA warned the sponsor about the magnitude of improvement that would be required. "Basically, this was a buyer-beware," Pazdur said, describing interactions with J&J. "Please be aware, we are going to look at this very closely. It's not just go ahead and do it. It's at your own risk."

The results that came in were anything but robust. The Yondelis study was originally designed to have 90 percent power to detect a 4.7 month difference in overall survival, but ended up showing a six-week impact on PFS.

"We are not only dealing with the change in the endpoint, but also a magnitude change here," said Pazdur said at the meeting. "Obviously, a six-week impact on PFS is not going to result in a [4.7] month extension in overall survival."

ODAC chairman Gail Eckhard said this issue is

THE CANCER LETTER

® The Cancer Letter is a registered trademark.

Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg

Editorial: 202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
Letters to the Editor may be sent to the above address.

Subscriptions/Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724
General Information: www.cancerletter.com

Subscription $385 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Other than "fair use" as specified by U.S. copyright law, none of the content of this publication may be reproduced, stored in a retrieval system, or transmitted in any form (electronic, photocopying, or facsimile) without prior written permission of the publisher. Violators risk criminal penalties and damages. Founded Dec. 21, 1973, by Jerry D. Boyd.

likely to resurface at the committee's future meetings.

"It's a very contextual endpoint that really needs to be [considered] with regards to line of therapy, safety profile, and, certainly, the risk-benefit analysis," said Eckhard, head of the Division of Medical Oncology at the University of Colorado Colorado Cancer Center. "I think, in fact, as a panel, we will probably be having these same discussions many times, because many of us do agree that in certain circumstances PFS is an acceptable endpoint. However, each time you have to look within the context."

Michael Link, chief of the Division of Hematology/Oncology at Stanford University School of Medicine, asked the agency for a clarification of the process: "When you actually have these discussions, do you stipulate what you think a clinically meaningful prolongation of PFS will be? You say buyer beware, but when you look at the protocol, do you say six weeks wouldn't be good?"

PAZDUR: "I think it really depends at what we will eventually obtain. We don't know the toxicities, we don't know the results of the trial before they are done. The regulatory decision is a results-driven decision that will occur after we get the results."

Uncertain Benefits vs. Clear Toxicities

Toxicity of the two drugs may have contributed to FDA's apparent decision to use the J&J applications as teaching tools:

The addition of Yondelis to Doxil tripled grade 3 and 4 neutropenia, quadrupled febrile neutropenia, and increased grade 3 and 4 thrombocytopenia by the factor of six. Cardiac adverse events were increased threefold, and six patients suffered congestive heart failure.

Despite premedication, grade 3 and 4 transaminases elevations were 50 times more frequent on the Yondelis and Doxil arm, compared to Doxil alone. Six cases met the criteria of Hy's Law, a prognostic indicator of drug-induced injury to the liver. FDA has used this predictive tool to justify taking drugs off the market, though not in oncology, where the tolerance for risk is greater than in most other areas.

"In this setting, with the current trial design, it was very difficult to ascertain any magnitude of clinical benefit that would justify the toxicity," said ODAC Chairman Eckhardt. "I do think that the toxicities are manageable, it didn't meet the criteria for a risk-benefit analysis in this population."

The only vote for approval was cast by a patient representative, Martha Holland, of Southport, N.C.

The addition of Doxil to Taxotere in breast cancer produced a sixty-fold worsening of hand-foot syndrome, a three-fold worsening of stomatitis and a four-fold worsening of pneumonia. The toxicities apparently were so bad that 34 percent of patients dropped out of the trial.

Both cases also raised questions about target populations.

—In the case of Doxil, post hoc subset analyses suggested that the drug would be beneficial to patients who are sensitive but intolerant to anthracyclines. Retrospective analyses are notoriously unreliable and not accepted by FDA. In the case of Yondelis, to be eligible for randomization, patients were required to have measurable relapsed disease following one prior platinum-containing regimen and not expected to benefit from, be ineligible for, or unwilling to receive retreatment with platinum-based therapy.

The size of this cohort among ovarian cancer patients is uncertain, and was estimated to be between 5 and 20 percent by ovarian cancer experts at the meeting.

Stacy Nerenstone, an oncologist at the Helen and Harry Gray Cancer Center in Hartford, Conn., who served as a temporary voting member of the committee, said that about half of patients were not truly second-line patients, and therefore stood to benefit from carboplatin and Taxol, as opposed to single-agent Doxil, the control arm in the trial.

"The group that was looked at is not the group that they are asking for approval in," Nerenstone said at the meeting. "The implication is that the group they are asking approval in is first-line recurrent disease. We have a regimen that is shown to have a survival advantage. Overall, European data show says that carbo-Taxol in the first-line metastatic has a survival advantage.

"My concern is that we could be approving a drug that may have a survival disadvantage when compared to a standard treatment. These are patients some of whom may live a long time. It's sort of loosey-goosey as to who got on this trial, and it fact close to 50 percent of the patients did get subsequent platinum in second- or third-line."

Nerenstone said she uses Doxil regularly in her practice.

"In general, it's a very safe, easy to administer, well tolerated medication. This study didn't at all convince me that adding Yondelis is going in any way is going to make their lives better or help them live longer. If the company wants to go ahead—I think there may be some signals of activity—they need to do it in a very specific patient group, perhaps looking at the six to 12

month platinum interval patients, second-line treatment of recurrent disease, which is where Doxil is used, and very specific and very well defined patients and endpoints. I will, however, change my mind if overall survival is shown to be better, because survival does trump everything else."

According to the company, a futility analysis demonstrated that the chances of a positive survival outcome were estimated at less than 45 percent, and the result is between 18 months and two years away.

—The relevance of the Doxil breast cancer trial to the U.S. population is unclear because all but 4 percent of patients came from outside the U.S. The vast majority of patients were accrued in Russia and Eastern Europe, where estrogen receptor and HER-2/neu status is not routinely tested.

Usually, FDA accepts foreign data. However, in this case, patient selection criteria were a factor in the committee discussion, as the lack of information on receptors which might affect the biology of the disease did not represent the standard of care in the U.S.

"I voted against it, because the combination didn't offer any substantial improvement over monotherapy," said Aman Buzdar, professor in the Department of Medical Oncology at M.D. Anderson Cancer Center and a temporary voting member of ODAC.

After breast cancer becomes metastatic, oncologists generally use a succession of monotherapies.

"I didn't see a role for the combination," said Carmen Allegra, chief of the Division of Hematology/Oncology at the University of Florida Shands Cancer Center and a temporary member of the committee. "It's of limited clinical benefit, and in the U.S. population usually sequential singles are the rule, and there are certainly other available doublets that may be as toxic as this one, but at least have the survival advantage."

Pazdur Argues For Clinical Benefit In Progression Studies

In opening comments to ODAC discussion of both applications, Richard Pazdur, director of the FDA Office of Oncology Drug Products, spelled out the agency's requirement of rigorous demonstration of clinical benefit in trials that measure time to progression:

Yondelis Opening Comments

This morning's session deals with the application for Yondelis (trabectedin) for the proposed indication for the treatment of patients with relapsed ovarian cancer.

The clinical trial supporting this application is a multicenter, multinational, open-label, randomized, controlled trial in patients with ovarian cancer previously treated with only one platinum-based chemotherapy regimen.

Patients had either disease recurrence or progression after initial platinum-based chemotherapy. Patients were randomized to receive trabectedin plus Doxil or Doxil alone.

The primary efficacy endpoint was initially overall survival and the sample size was calculated based on OS with the ability to detect a median difference of 4.7 months with 90% power. After 68% patients were randomized, the sponsor sought to amend the primary endpoint from OS to progression-free survival.

The sample size remained the same in order to detect the OS difference as originally planned. With this sample size, the expected median PFS difference to be detected was 6 weeks with 90% power.

The issue that we will be asking ODAC's advice on with this application is the balance of benefit vs. risks.

Trabectedin in combination with Doxil showed a median six week difference in PFS, compared to Doxil monotherapy, as assessed by the independent radiologic review. The median PFS was 7.3 months for the combination versus 5.8 months for Doxil and the hazard ratio was 0.79 (0.65, 0.96).

The addition of trabectedin to Doxil was associated with a greater number of adverse events compared to Doxil monotherapy. Grade 3-4 neutropenia was three times more frequent, febrile neutropenia was four times more frequent and grade 3-4 thrombocytopenia six times more frequent.

Despite steroid premedication, grade 3-4 transaminases elevations were 50 times more frequent with combination arm compared to Doxil monotherapy and six cases in the trabectedin group met Hy's Law criteria for hepatic toxicity compared to none observed with Doxil monotherapy. Cardiac adverse events were increased three times more in the trabectedin arm, including six patients who had congestive heart failure. Other adverse events increased in the trabectedin-containing arm include pulmonary embolism and catheter-related events.

There are several issues that I would like to ODAC members to consider in their deliberations.

In our initial discussion with ODAC and workshops conducted over the past several years to review approval endpoints, FDA has continued to emphasize that the acceptance of either progression-free survival or time-to-progression should not be viewed as a lower standard for approval.

We would expect not only a statistically persuasive finding, but one that would be clinically relevant in the proposed indication and a positive benefit-risk analysis. We have underscored the necessity of having effects that are of sufficient magnitude both to be clinically relevant and be reliably assessed aware of the problems of discordant rates of evaluating radiological examinations.

When the sponsor requested a change in the trial's endpoint, we cautioned their approach stating [that] "whether PFS will be acceptable as the primary endpoint for approval will depend on the magnitude of benefit and the risk-benefit."

FDA protected the integrity of this trial for subsequent analysis of overall survival by emphasizing that irrespective of which endpoint was to be the primary endpoint –OS or PFS—that the trial continued to be powered for overall survival.

Hence, if a positive risk-benefit analysis is not viewed for this current application with a PFS endpoint, a subsequent submission could be made when the survival is mature and a risk-benefit analysis can be made with the efficacy endpoint being overall survival.

A risk-benefit analysis should be viewed in the clinical context of the application. We have accepted considerable serious and life-threatening toxicities that would not be considered in other therapeutic areas due to the life-threatening nature of the diseases treated in oncology.

In evaluating the risks and benefits associated with a therapy, one should also consider other therapies that can be offered to patients. In a situation, where all therapeutic options have been exhausted, there may be a greater acceptance of risks. With the application at hand, other treatments are available, including re-treatment with platinum.

The acceptance of this application should also be viewed also in a regulatory context. This application is a new NDA—not a supplement—and is supported on only one randomized trial.

A different regulatory situation existed for the approval of gemcitabine in ovarian cancer using a PFS endpoint. The agency noted that the totality of past information, both safety and efficacy, directed our ultimate approval decision.

Unlike the trabectidin application, Gemcitabine had been marked for over a decade in the United States with three prior approvals, extensive worldwide post-marketing and clinical trial experience. With supplements of marketed drugs where extensive off-label use is anticipated, the Agency also considers the benefit to the medical community and patients of having FDA-reviewed data in the product label to guide treatment use.

In the mid-1980's, on the advice of the ODAC, overall survival was recommended as the primary endpoint for registration in part due to the substantial toxicity of oncologic drugs. Our acceptance of time-to-progression or progression-free endpoints was, in part, to allow drugs whose efficacy analysis may be confounded by cross-over or subsequent therapies to be better evaluated.

In addition, overall survival may not be a practical endpoint in diseases with long natural histories, such as indolent lymphomas. As more novel targeted drugs are developed with fewer toxicities, a re-evaluation of endpoints in a risk-benefit analysis should occur. With drugs demonstrating less toxicity compared to conventional chemotherapy drugs, PFS and TTP may have greater acceptance.

The magnitude of the effect size on the PFS endpoint is of great importance in evaluating a risk-benefit analysis. The magnitude of the effect size has a direct bearing on reliability and clinical relevance of the PFS.

An improvement in overall survival has repeatedly been viewed as a direct clinical benefit and is very reliably assessed. In contrast, PFS is primarily considered either a surrogate or a surrogate reasonably likely to predict for clinical benefit.

If PFS is a surrogate for overall survival, the magnitude of the PFS effect should be greater than any subsequent anticipated effect on overall survival.

The estimation of PFS can be confounded by missing scans, introduction of unplanned therapies, and divergent readings of radiographs between expert radiologists and clinicians. A large effect on PFS may compensate for these shortcomings.

In summary, the approval process is not merely a screening process for drug activity. The goal of a registration trial is not merely to obtain a statistically significant result. The primary goal is to obtain a statistically reliable evaluation of the drug that represents a clinically meaningful result yielding a favorable benefit/risk evaluation.

Doxil Opening Comments

A single randomized trial was submitted in support of this supplemental NDA for the following proposed indication:

"Doxil in combination with docetaxel for the treatment of patients with locally advanced or metastatic

breast cancer who have received prior anthracycline treatment."

This supplemental NDA relies upon a single clinical trial to support demonstration of efficacy and a favorable benefit-risk ratio. The trial randomized patients to either doxil plus docetaxel or single-agent docetaxel. An improvement in the primary endpoint of time to tumor progression was reported. The median TTP was 9.8 months for the combination versus 7.0 months for docetaxel montherapy. The hazard ratio was 0.65 (0.55 to 0.77).

The trial was originally designed and powered to show a 3.6 month improvement in overall survival. However, no improvement in OS was demonstrated at the time of the final analysis. The difference in objective response rates between the two arms was less than 10%---35% for the combination arm and 26% for the docetaxel monotherapy arm. All responses were partial responses; no complete responses were observed.

The single randomized trial submitted in support of this supplemental NDA accrued poorly in the United States (4%) and was conducted predominantly in Russia and Eastern Europe.

Please note that important disease characteristics that are currently used in the United States for selecting breast cancer therapies were unknown. Thirty percent of patients had an unknown ER/PR status and 50% of patients enrolled in the trial had unknown HER-2/neu status. This lack of these important baseline characteristics questions the applicability of this trial to a contempory U.S. population of patients to be treated in this disease setting.

Also calling into question the relevance of the study to the U.S. is the selection of the control arm. While the FDA acknowledged that single-agent docetaxel is used to treat metastatic breast cancer in the U.S., FDA advised the sponsor to use a docetaxel plus capecitabine combination as the control since this combination was associated with a three-month survival advantage over docetaxel monotherapy.

This combination was thought to be a more appropriate comparator for a population of women with metastatic breast cancer in whom combination therapy was warranted. The sponsor disregarded this advice.

The Doxil plus docetaxel combination was poorly tolerated with a markedly increased incidence of stomatitis and hand-foot syndrome that, along with other toxicities, resulted in frequent cycle delays and dose reductions, as well as permanent discontinuation of Doxil in a third of patients. There was also an increase in pneumonias in the Doxil arm--75% of which were serious adverse events and one of which was fatal during cycle 1 of treatment.

Similar to my comments to the committee regarding the Trabectetin application, the issue that we will be asking ODAC's advice on this application is the balance of benefit versus risk.

Also, similar to the application that was discussed in the morning session, the sponsor changed the primary endpoint. In June, 2006 when 70% of patients had been enrolled and 138 events had been observed, the protocol was amended to change the primary endpoint from overall survival to TTP.

Similar to the previous advice given the sponsor for the morning application, the FDA explicitly cautioned the sponsor that "for a regular approval, a clinically relevant and statistically significant magnitude of the TTP with an acceptable risk/benefit ratio may be considered. Overall survival results with at least a strong trend towards improvement at the interim OS analysis will also need to be demonstrated."

Unlike the Traebectetin application where overall survival data has yet to mature, the overall survival data for this application are mature and do not show a statistically significant advantage to the addition of doxil to docetaxel. The median survival was 20.5 months for the combination arm of doxil plus docetaxel compared to 20.6 months for single agent docetaxel. The hazard ratio was 1.02 with a hazard ratio greater than 1 favoring the control arm.

I would like to reinterate some of the points made in the my morning comments. In our initial discussions with ODAC and in workshops conducted over the past years to evaluate endpoints used in regulatory trials, the FDA has continued to emphasize that the acceptance of progression-free survival or time-to-progression should not be viewed as a lower standard of approval.

We would expect not only a statistically persuasive finding, but one that would be clinically relevant in the proposed indication and a favorable benefit-risk analysis. We have underscored the necessity of having effects that are of sufficient magnitude to be both clinically relevant and be reliably assessed and measured aware of the problems of discordant rates of evaluating radiological examinations.

In the current application, differences in the absolute median TTP in the two arms as well as the difference between the arms, between the independent radiologist review and the investigator call into question the true magnitude of TTP improvement. While the difference in median TTP by the independent radiologist was 2.8 months, the difference in median TTP by

investigator assessment was approximately half that, only 1.5 months.

In the mid-1980's, on the advice of the ODAC, overall survival was recommended as the primary endpoint for registration in part due to the substantial toxicity of oncologic drugs. Our acceptance of time-to-progression or progression-free endpoints as regulatory endpoints was to allow drugs whose efficacy analysis may be confounded by cross-over or subsequent therapies to be better evaluated.

In addition, overall survival may not be a practical endpoint in diseases with long natural history, such as indolent lymphomas or chronic lymphocytic leukemia. As novel targeted therapies are developed with less toxicity, a re-evaluation of endpoints in a risk-benefit analysis should occur. With drugs demonstrating less toxicity compared to conventional chemotherapy drugs, PFS and TTP may have greater acceptance.

The magnitude of the effect size on the PFS endpoint is of great importance in evaluating a risk-benefit analysis. The magnitude of the effect size has a direct bearing on reliability and clinical relevance of the PFS.

Please note that the change to the altering the primary endpoint, not only changed the primary endpoint to TTP but was also associated with a markedly smaller effect on PFS than OS. The original difference in overall survival was 3.6 months with at least 80% power; the protocol amendment changed the endpoint to TTP with an estimated difference of 1.8 months with 80% power.

An improvement in overall survival has repeatedly been viewed as a direct clinical benefit and is very reliability assessed in clinical trials. In contrast, PFS is primarily considered either a surrogate or a surrogate reasonably likely to predict for clinical benefit.

If PFS is a surrogate for overall survival, the magnitude of the PFS effect should be greater than any subsequent anticipated effect on overall survival.

The estimation of PFS can be confounded by missing scans, introduction of unplanned therapies, and divergent readings of radiographs between expert radiologists and clinicians. A large effect on PFS may compensate for these shortcomings.

A risk-benefit analysis should be viewed in the clinical context of the application. We have accepted considerable serious and life-threatening toxicities that would not be considered in other therapeutic areas due to the life-threatening nature of the diseases treated in oncology.

In evaluating the risks and benefits associated with a therapy, one should also consider other therapies that can be offered to patients. In a situation, where all therapeutic options have been exhausted, there may be a greater acceptance of risks. With the application at hand, other treatments are available that have demonstrated an improvement in overall survival.

In summary, the approval process is not merely a screening process for drug activity. The goal of a registration trial is not merely to obtain a statistically significant result. The primary goal is to obtain a statistically reliable evaluation of the drug that represents a clinically meaningful result that yields in a favorable benefit/risk evaluation.

HHS News:

Regina Benjamin Nominated For U.S. Surgeon General

President Barack Obama nominated Regina Benjamin, an Alabama family physician, as surgeon general.

Benjamin repeatedly rebuilt her clinic in Bayou La Batre, Ala., a town of 2,500, after two hurricanes and a fire destroyed it. She used the first installment of a $500,000 MacArthur Foundation "genius grant" to help fund the operations of the clinic.

"Health care reform is about every family's health and the health of our economy," Obama said in a statement announcing the appointment. "And if there's anyone who understands the urgency of meeting this challenge in a personal and powerful way, it's the woman who will become our nation's next Surgeon General, Dr. Regina Benjamin. I look forward working with her in the months and years ahead."

Benjamin, if confirmed by the Senate, would be the nation's 18th surgeon general. The post has been vacant since 2006, when the term of Richard Carmona, the last surgeon general under the Bush administration, expired.

As surgeon general, Benjamin would oversee 6,200 uniformed health professionals in the Commissioned Corps of the U.S. Public Health Service. The position also can be used to advance specific public health issues.

Benjamin the immediate past-chairman of the Federation of State Medical Boards of the United States, and previously served as associate dean for Rural Health at the University of South Alabama College of Medicine.

In 2002, she became president of the Medical Association of the State of Alabama, making her the

first African American woman to serve as president of a state medical society in the U.S.

Benjamin holds a BS in Chemistry from Xavier University. She was in the second class at Morehouse School of Medicine and earned her medical degree at the University of Alabama at Birmingham, and a master's in business administration from Tulane University. She completed her residency in family medicine at the Medical Center of Central Georgia.

Benjamin received the Nelson Mandela Award for Health and Human Rights in 1998, and was elected to the American Medical Association Board of Trustees in 1995, making her the first physician under age 40 and the first African-American woman to be elected. She received the 2000 National Caring Award which was inspired by Mother Teresa, as well as the papal honor Pro Ecclesia et Pontifice from Pope Benedict XVI.

NIH News:

NIH Conference On DCIS Planned For Sept. 22-24

NCI and the NIH Office of Medical Applications of Research plan to convene a State-of-the-Science Conference on Diagnosis and Management of Ductal Carcinoma In Situ, Sept. 22-24, in Bethesda, Md.

The conference is open to the public and has been approved for AMA PRA Category 1 Credit. Registration and additional information is listed at http://consensus.nih.gov. Individuals unable to attend are encouraged to register to view the webcast or receive the conference statement at http://consensus.nih.gov/dciswebcast.htm.

Although the natural course of DCIS is not well understood, this intraductal carcinoma can become invasive cancer and spread to other tissues. It also is a marker of increased risk for developing cancer elsewhere in the same or opposite breast. However, not all DCIS will progress to invasive disease, and it is thought that DCIS can be present in some individuals without causing problems over a long period. Unfortunately, it is currently not clear which lesion types are more likely to become invasive, leading to difficult treatment decisions for patients and providers. Because of this uncertainty, DCIS patients typically are treated promptly following diagnosis and generally have a good prognosis. However, there is still uncertainly regarding the most effective treatment modality and how this may vary by specific tumor and patient characteristics.

After weighing the evidence from a systematic literature review, expert presentations, and audience input, an impartial, independent panel will present a statement of its collective assessment of the evidence to address six key questions: (1) What are the incidence and prevalence of DCIS and its specific pathologic subtypes, and how are incidence and prevalence influenced by mode of detection, population characteristics, and other risk factors? (2) How does the use of MRI or sentinel lymph node biopsy impact important outcomes in patients diagnosed with DCIS? (3) How do local control and systemic outcomes vary in DCIS based on tumor and patient characteristics? (4) In patients with DCIS, what is the impact of surgery, radiation, and systemic treatment on outcomes? (5) What are the most critical research questions for the diagnosis and management of DCIS?

NCI News:

ANDREW FREEDMAN was appointed chief of the Clinical and Translational Epidemiology Branch in the NCI Epidemiology and Genetics Research Program. The branch supports, directs, and stimulates research on clinical, environmental, and genomic factors that influence cancer progression, recurrence, new primary cancers, and mortality.

Freedman joined the NCI Division of Cancer Control and Population Sciences in 1997 as a molecular epidemiologist in the Applied Research Program's Risk Factor Monitoring and Methods Branch. He developed and supported a program of research in cancer risk prediction, genetic susceptibility testing, pharmacoepidemiology, and pharmacogenomics, and managed research contracts, interagency and cooperative agreements, and a grant portfolio pertaining to these research areas.

Freedman is chairman of the Trans-NCI Pharmacoepidemiology and Pharmacogenomics Working Group, and represents NCI on the Trans-NIH Pharmacogenomics Working Group and the Institute of Medicine Roundtable on Translating Genomic-Based Research for Health.

Save Time And Money:
Switch From Print to Online

Print subscribers, switch to the online version of The Cancer Letter and get the news the moment it's posted online, as well as online access to all back issues. **Switch by Aug. 1 and get a one-month extension on your subscription.** Call Kirsten Goldberg at 202-362-1809 or email news@cancerletter.com.

Distribution Policy for The Cancer Letter

Thank you for your purchase of this issue of The Cancer Letter! Because issue and subscription sales are our major source of revenue, we wouldn't be able to provide you with the information contained in this newsletter without your support. If you have any questions or comments about the articles, please contact the editors (see page 2 of your issue for contact information).

We welcome your use of the newsletter and encourage you to send articles once in a while to colleagues. But please don't engage in routine distribution of The Cancer Letter to the same people week after week, unless your organization has purchased a site license or group subscription. If you aren't sure, ask the person who is paying for this subscription. If you are sending the newsletter to an unauthorized list, please stop; your actions are against Federal law. If you received this newsletter under an unauthorized arrangement, know that you are in receipt of stolen goods. Please do the right thing and purchase your own subscription.

If you would like to report illegal distribution within your company or institution, please collect specific evidence from emails or photocopies and contact us. Your identity will be protected. Our goal would be to seek a fair arrangement with your organization to prevent future illegal distribution.

Please review the following guidelines on distribution of the material in The Cancer Letter to remain in compliance with the U.S. Copyright Act:

What you can do:

- Route a print subscription of the newsletter (original only) or one printout of the PDF version around the office.
- Copy, on an occasional basis, a single article and send it to a colleague.
- Consider purchasing multiple subscriptions. We offer group rates on email subscriptions for two to 20 people.
- For institution-wide distribution or for groups larger than 20, consider purchasing a site license. Contact your librarian or information specialist who can work with us to establish a site license agreement.

What you can't do without prior permission from us:

- Routinely copy and distribute the entire newsletter or even a few pages.
- Republish or repackage the contents of the newsletter in any form.

If you have any questions regarding distribution, please contact us. We welcome the opportunity to speak with you regarding your information needs.

The Cancer Letter
PO Box 9905
Washington DC 20016
Tel: 202-362-1809
www.cancerletter.com