THE CANCER LETTER

Vol. 32 No. 15
April 21, 2006

A Message From NCI: "We Deeply Regret The Need To Eliminate This Program"

By Kirsten Boyd Goldberg

A dozen cancer researchers competing to take part in one of NCI's new high-priority programs recently received an email from James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis:

"It is with great regret that we inform you that the Academic Public Private Partnership Program (AP4) from the Developmental Therapeutics Program is one of the new initiatives that will not be funded this fiscal year," Doroshow wrote.

"The Division is aware of the huge expenditure of time and effort that you, your staff and your potential partners have put into this program over the past several years, and we deeply regret the need to eliminate this program.

"We hope that this will not decrease your interest in other NCI initiatives."

The abrupt demise of AP4 stunned academic investigators and their

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NSABP's STAR Trial Finds Raloxifene Equivalent To Tamoxifen In Reducing Risk Of Breast Cancer

By Paul Goldberg

The Eli Lilly drug Evista (raloxifene) was found to be equivalent to tamoxifen in reducing the risk of invasive breast cancer in women at high risk of developing the disease, a trial by the National Surgical Adjuvant Breast and Bowel Project has found.

The conclusion of the Study of Tamoxifen and Raloxifene, STAR, was announced earlier this week, and the data will be presented at a plenary session of the annual meeting of the American Society of Clinical Oncology in Atlanta.

Lilly said it would seek additional indications for raloxifene based in part on the latest results. Raloxifene is approved for prevention and treatment of osteoporosis in postmenopausal women.

The findings are significant because raloxifene, widely accepted as an osteoporosis drug, doesn't have the marketplace stigma that was associated with tamoxifen, which many experts say was being underutilized.

"Tamoxifen is out there, but it has a relatively small use for breast cancer prevention," said D. Lawrence Wickerham, NSABP associate chairman and STAR protocol officer. "Now we have a drug—raloxifene—that is being widely utilized in 500,000 postmenopausal women in the US today for

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AP4 Applicants Spent Millions Before NCI Pulled The Plug

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private-sector partners who had devoted years to prepare grant applications for the novel program.

"This was probably the most time-consuming NCI initiative I've ever been through," said S. Gail Eckhardt, director of the Developmental Therapeutics and GI Malignancies Programs at University of Colorado Cancer Center and one of the AP4 applicants. "Not only were we not getting funding, but the whole mechanism was cut."

If Eckhardt's 500-page application is an indication, the waste of time and money for the applicants was substantial. Eckhardt estimates that her institution spent $100,000 and its commercial partners spent at least as much to prepare the application, receiving only $50,000 in a planning grant from NCI. If all the 14 institutions that received AP4 planning grants spent the same amounts, at least $2.8 million in federal, private, and state cancer research funds have been wasted on the applications.

Additional money would have been spent by NCI to design the program, issue a book of instructions for applicants, and conduct peer review.

The demise of AP4 shows how drastic NCI's cost-cutting decisions have become. The program that had been touted as a giant step toward reaching NCI Director Andrew von Eschenbach's goal to "eliminate suffering and death due to cancer by 2015" was expected to begin on April 1. But instead of funding six grants of up to $650,000 in first-year funding, NCI dispatched what Eckhardt described as a "Dear John letter" dated March 20.

The rushed cost-cutting decisions being made by NCI officials as they struggle to contain the financial crisis have the potential to shape cancer research for decades to come and raise questions about management of NCI's $4.793 billion budget, observers say.

Grant funding commitments made in previous years have caught up with flat or falling appropriations—NCI took a $32 million cut in real terms in fiscal 2006—at the same time the institute has continued to implement large new programs. Earlier this year, the White House proposed to cut NCI's budget again in fiscal 2007, this time by $40 million.

In remarks at the annual meeting of the American Association for Cancer Research, NCI Chief Operating Officer John Niederhuber told cancer researchers that "we must simply become leaner and better at what we do" (The Cancer Letter, April 7).

However, some programs appear to be more untouchable than others. Niederhuber recently told the House appropriators that he planned to preserve or increase funding for the Specialized Programs of Research Excellence (The Cancer Letter, April 14). That's despite having proposed a funding plan that would cut the NCI-designated cancer centers and SPOREs budget by 0.5 percent next year. It probably helped that advocacy groups have worked behind the scenes in recent months to lobby Congress and NCI to maintain funding for the SPOREs.

Unlike the SPOREs, newer programs like AP4 lack strong constituencies.

"When you have great big huge programs like nanotechnology and the cancer genome that have $100 million budgeted out for five years, it puts a huge stress on everything else," said Paul Bunn, director of the University of Colorado Cancer Center and principal investigator on an AP4 planning grant. "It's putting a huge stress on R01s and P01s and everything else. Over the last five years, NCI has not stopped any major, huge initiatives and has added a whole bunch of new initiatives.

"NCI is in tough money times, but why that wasn't figured out and some adjustments made sooner, I wouldn't be able to answer that," Bunn said. "One would have thought that this wouldn't have come as a surprise at the last minute."

NCI's external advisory boards weren't involved in discussions that led to the elimination of AP4. "I can't

THE CANCER LETTER

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General Information/FAQ: www.cancerletter.com

Subscription $355 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.
Founded Dec. 21, 1973, by Jerry D. Boyd.

really comment on how the decision to not fund the AP4 program was made," said Robert Young, chairman of the NCI Board of Scientific Advisors and president of Fox Chase Cancer Center. "The concept of the AP4 program was approved by the BSA three years ago at a time when the funding was not nearly so bleak.

"One of the serious problems the NCI faces is to try to deal with the fact that a huge portion of their funds are already committed to continuing grants," Young said. "Thus, those grants not currently funded will undoubtedly get the closest scrutiny going forward."

The decision was misguided, said Brian Druker, professor of medicine at Oregon Health & Science University, whose collaboration with drug companies resulted in development of the drug Gleevec.

"It seems to me that programs that improve cooperation and collaboration with industry are a good thing," said Druker, who wasn't an AP4 applicant. "You have to think of ways to improve academic-industry collaborations in order to get therapies to our patients."

Von Eschenbach Called AP4 "A New Paradigm"

AP4 was one of the first new programs to emerge from von Eschenbach's NCI, and the controversial director often cited it as a model for the future of cancer research and drug development.

The program was designed to encourage universities to partner with pharmaceutical and biotech companies, as well as state research initiatives. The companies and state programs were to match the NCI grant money and gradually take over full funding of the research.

The AP4 centers were expected to tackle preclinical research projects aimed at validating targets or therapies for orphan tumors—diseases that affect fewer than 200,000 Americans annually.

Von Eschenbach's weekly "Director's Update" regularly praised the program:

—"Through the Academic Public-Private Partnership Program, NCI will establish a new paradigm in drug discovery, development, and delivery," von Eschenbach wrote on Oct. 7, 2003.

—"This model will enable discovery of new cancer drugs and ensure their rapid translation to human clinical trials," he elaborated on Dec. 9, 2003.

—"Through AP4, we believe we can significantly enhance the marginal success rate of current academic/industry partnerships, open exciting new doors for partnership and collaboration, and quickly generate new interventions that will benefit many patients," he added on Jan. 25, 2005.

In 2004, NCI funded 14 one-year planning grants of about $50,000 each to help academic institutions set up the AP4 centers. The centers would have been funded as U56 cooperative agreements, a mechanism that allows for industry and government involvement.

The principal investigators found industry partners and enlisted university and company lawyers to iron out extensive agreements involving intellectual property issues and the governance of the partnerships. If the PIs secured commitments of at least $450,000 a year from the private-sector partners, NCI would have chipped in $650,000 the first year. For less than $450,000 of private money, NCI would provide only $450,000.

Over three to five years, the NCI share of funding would have decreased as therapies were either abandoned or moved into commercial development.

Last year, 12 groups applied for the full-fledged AP4 grants and went through peer review at NCI. Colorado was told it received the highest priority score, of 150, Eckhardt said. That would seem to be within the current funding range, compared to P01s, sources said.

The institute had planned to fund six of the grants, for a total of about $4.7 million, in fiscal 2005 (The Cancer Letter, March 14, 2003).

Last fall, as Congress delayed approval of the NIH budget, the top-scoring PIs were urged to keep their groups together. Funding would come through in FY 2006, they were told.

On March 20, the PIs received an email from Jill Johnson, of the NCI Developmental Therapeutics Program:

"The final decision on funding for the AP4 initiative has been made. As you can see from the attached letter, budgets cuts for fiscal 2006 created difficult choices. The AP4 grants will not be funded. With the budget for fiscal 2007 expected to be very limiting for NCI as well, we do not expect this initiative to be reconsidered. A hard copy of this letter will be sent to you today."

Attached to the email was a letter from Doroshow:

"In the face of declining budgets, the National Cancer Institute has completed its very difficult budget deliberations for fiscal year 2006. As a result of those deliberations, a number of initiatives, new and old, that the Division of Cancer Treatment and Diagnosis was planning to fund in FY2006, will receive reduced funding or will not be funded at all. It is with great regret that we inform you that the Academic Public Private Partnership Program (AP4) from the Developmental Therapeutics Program is one of the new initiatives that

will not be funded this fiscal year.

"The Division is aware of the huge expenditure of time and effort that you, your staff and your potential partners have put into this program over the past several years, and we deeply regret the need to eliminate this program. We hope that this will not decrease your interest in other NCI initiatives."

NCI "Prioritized" Funding

The decision to kill the program was made by the NCI Executive Committee, Doroshow said in an interview.

"The Executive Committee had a series of meetings at the end of February and beginning of March, where a process of discussion and review led to the prioritization of a large number of requests for funds in 2006," Doroshow said. "Through that process, which involved the entire Executive Committee, the AP4 program was discontinued. I shouldn't say discontinued. The funds were not made available."

The committee "prioritized" many NCI programs, Doroshow said.

"The priority for that program was viewed against many other meritorious programs and viewed not to have the sufficient priority to be funded," he said. "The best way I can characterize the process it that it was quite open, and we put all of the requests… on the table, and each was discussed in turn by the entire Executive Committee and were weighed one against the other."

Asked whether the priority scores for the AP4 grants had any influence on the funding decision, Doroshow said he couldn't comment on "the peer review process."

Meetings of the Executive Committee are not open to the public.

Doroshow declined to discuss the list of the committee's priorities, either for NCI or his division. "Since the budget process involved the institute as a whole—it wasn't a division-by-division process, it was an institute-wide process—I would have to refer you to the press office," he said. "At my level, it wouldn't be appropriate for me to provide an overview for the institute. Clearly, in the current budget environment, everyone is working as hard as possible to make our funds stretch as far as they can."

The NCI press office provided this response:

"As a general rule, we do not provide information on unfunded programs and on applications on which funding has not yet been determined. We will be happy to provide you with information on funded projects, once they are awarded. At this time, we do not have the full details available. It would be inappropriate to provide specifics on projects that are in the process of negotiation for award.

"Please refer to the following documents, which provide more information on the NCI budget allocation process:

"April 4, 2006, Cancer Bulletin, http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_040406/page3.

"Dr. Niederhuber's remarks at AACR: http://www.cancer.gov/aacr2006/directoraddress."

"We Heard Nothing, Heard Nothing"

"When we got the planning grant, it took a full year, a tremendous amount of effort, to convince the university and the companies that we signed up to consider this new intellectual property model that was mandated by the AP4 structure," said Stephen Howell, head of the Cancer Pharmacology Program at the Moores Cancer Center at University of California, San Diego.

"We did more than 45 presentations to companies all around the country and we managed to sign up four leading companies: Biogen Idec, Genprobe, Althea, and Torrey Pines Institute for Molecular Studies," Howell said. "Our mission was to develop drugs and develop the diagnostic tools that would guide their individualization. We submitted the grant, then we waited nine months and tried to keep everyone warm. The challenge was to keep lines of communication open with the companies, keep everyone interested.

"Then we heard nothing, heard nothing, heard nothing, and then we got a letter that said the whole program was cancelled."

Howell said $250,000 would be "a crude estimate" of the amount of money his institution and its partners spent to put together the grant application.

"We're disappointed with this, and I guess we're somewhat angry," Howell said. "I suspect the folks who had to make the final decisions were stuck with the budget crunch. I guess they are stuck with the fact that we're spending $150 million a day in Iraq and there wasn't enough money to fund these programs.

"But it also reflects a huge waste of effort on our part," Howell said. "It certainly makes you very leery of bothering to apply for new NCI initiatives."

NCI's Developmental Therapeutics Program produced a nine-chapter book outlining the requirements for the AP4 grants.

"You had to have signed membership agreements from the pharma partners, bylaws, a strategic plan,

a steering committee," Eckhardt said. "We also had an external advisory board. We had meetings with companies. AstraZeneca flew everyone in from Europe. We had legal counsel working about 20 percent FTE getting legal bylaws together, working on the intellectual property agreements."

Colorado spent about $100,000 and estimated that its partner companies—AstraZeneca, Eli Lilly, OSI Pharmaceuticals, Array BioPharma, GlobeImmune, and Tapestry Pharmaceuticals—likely spent the same amount or more, Eckhardt said.

"The amount of time and money spent not only at NCI, but also at the individual institutions, was incredible," she said. The pharma partners agreed to provide a total of $525,000 a year, she said.

Colorado's AP4 center also had the involvement of the Lung Cancer Alliance advocacy group and the Fitzsimons Redevelopment Authority, which is involved in new initiatives on the Aurora campus. The FRA's involvement ensured that the center would be able to build more space if needed.

At the University of Iowa, M. Sue O'Dorisio, Distinguished Professor in the Division of Pediatric Hematology/Oncology, put together an AP4 grant application that focused on neuroendocrine tumors, with the involvement of the industry and the state. "It's clear that in the U.S. today, orphan tumors don't capture the fancy of industry, precisely because they are not able to make money doing it," O'Dorisio said.

"By putting together five small biotech companies—one that makes peptides, one that radiolabels peptides, one that can use peptides in a specific diagnostic way the operating room, one that makes radiolabeled compounds, and one that makes gene therapy products—we had a terrific group of companies that came together, agreed that none of them could afford to do an orphan tumor alone, but that together as a group we would have all the specialties we needed to be able to do this," O'Dorisio said. "At the institution, we had the patients and the physicians. We were really excited about it."

The extensive application was like nothing O'Dorisio had seen in 30 years of being an NCI-funded investigator.

"It was like a Small Business Investigational Research grant, a P01, and an entrepreneurial business grant all rolled into one," O'Dorisio said.

Funding Decline "Handwriting Was On The Wall"

NCI staff in the Developmental Therapeutics Program were working on the AP4 concept before von Eschenbach took office. Yet, the program seemed to have been designed with his themes in mind.

Von Eschenbach has often talked about the need to improve the "collaboration and cooperation" between the public and private sectors. He has spoken extensively about "leveraging" NCI funding with funds from the private sector, philanthropy, and other government agencies.

"So why this doesn't pass that test is leaving many of us somewhat mystified, specifically since this would do exactly what they said they were going to be doing," said Edward Sausville, the former director of DTP who developed the AP4 concept before leaving NCI in 2004.

AP4 was based on the National Science Foundation's Industrial/University Cooperative Research Centers, created 25 years ago to stimulate industrial-academic partnerships for materials science. In fiscal 2000, NSF funds of about $5 million for the centers supported a total of $68 million in research.

"A large number of people both inside and outside NCI worked real hard to scope out a fundamentally different way of funding research by mixing private moneys with federal dollars, and it's just really too bad that the current situation doesn't allow that opportunity to be seized as a new way of approaching things," said Sausville, now associate director for clinical research at the University of Maryland Greenebaum Cancer Center.

"Even in 2002, the handwriting was on the wall that funding levels were going to go down," Sausville said.

Earlier this year, NCI said it would fund only the top 11 percent of R01 grants.

"My own view is that they are going to hit somewhere around the 8th percentile in 2008," Sausville said. "So, this was a way of leveraging federal funding with private funds. AP4 was a way of beginning to have corporate responsibility for at least some portion of the research. We built into AP4 that each AP4 center, while it could come in for renewal once, was in some sense self-destructing. It had to go away by year 10. Even before year 10, it had to be essentially independent of federal dollars. Each program would be phased out over three to five years."

While the planning grant process was underway, Sausville was making plans to leave NCI.

Since Maryland had become an applicant for the AP4 planning grant, he recused himself from writing the RFA for the full-fledged grants. Acting Greenebaum Center Director Steven Schimpf was the PI on the planning grant. Current Greenebaum Cancer Center

Director Kevin Cullen became PI of Maryland's subsequent AP4 center application, while Sausville was to be the scientific coordinator, a role not representing Maryland back to NCI, with approval from the NCI ethics officer, Maureen Wilson.

"We primarily visualized this as funding discovery-related research that would be related to orphan or underserved disease, that would be well-poised to go into later-stage development," Sausville said. "The AP4 product would be something that would be ready to take into advanced development, such as formulation and toxicology, potentially under the sponsorship of one of the companies. It was to present clinical trials opportunities.

"Alternatively, it could conceivably provide support not for classical phase I or phase II drug trials, but biomarker oriented trials, e.g. to see whether cells from patients with cancer would respond to a drug or immunologic challenge. That would be 'proof of principle' that the idea of the therapeutic strategy that would give it greater attractiveness to potential development."

AP4 filled a gap in drug development, Sausville said.

"Right now, there's no problem getting financial backers for something that's already in phase I," he said. "Venture firms are very hungry for something that makes it into the clinic and doesn't overtly kill anybody. What they for the most part are not interested in funding is the preclinical research that qualifies the candidate drug for phase I."

NCI and FDA recently established a process called "phase 0" for giving micro-doses of new drugs to patients prior to filing a full IND, but that initiative doesn't alleviate the need for a mechanism like AP4, Sausville said.

"AP4 would create, ideally, a range of candidates that are dressed up and ready to go into phase I," he said. "While the current phase 0 initiative might also address the need, it really doesn't address the need to facilitate discovery of novel chemotypes."

Gregory Curt, senior medical director AstraZeneca and former NCI clinical director, worked with Colorado as one of its AP4 partners.

"We thought it was a great opportunity to collaborate with academic colleagues," Curt said. "Anything that we can do to make working relationships more seamless between academia and pharma will only benefit patients in the long run."

The most time-consuming aspect of collaboration is "developing a very comfortable relationship with groups you don't deal with very often," Curt said. "Having done it once, there is a real advantage to making that initial investment. The next time it's that much easier."

AP4 was attractive to pharma because of the peer review process, Curt said. "The good thing about peer review is that the pharmaceutical companies could be assured that the centers they were dealing with were of high caliber."

"It's Dead, Gone"

The AP4 investigators were particularly irritated at the lack of communication from NCI following peer review.

"There was no discussion about whether the program was being considered to be cut," said Paul Bunn, director of the University of Colorado Cancer Center and the PI on its AP4 planning grant. "One day this email showed up with a copy of a letter attached, indicating that people who hadn't been involved in the development of the program had decided that they were not going to fund the program.

"It's dead, gone," Bunn said. "It's not like, 'well, Sausville had a really good idea, we'll rejuvenate this later.'"

That type of decision is "unusual" for NCI, Bunn said.

"Many NCI grants might have different words, but they are meant to be partnerships," he said. "Cooperative groups are supposed to be a cooperation between the NCI and the group. It's not a standard grant or contract, it's a cooperative agreement. This partnership was supposed to be similar.

"Generally, one would think that a partnership or a cooperative agreement would require communication and discussion at all stages," Bunn said. "Certainly, if one was going to cut the cooperative groups, one would think that you might talk to them about it beforehand. That didn't happen here."

Sausville, too, said he was surprised by the circumstances of the program's demise. "This is brand-new, the fact that something would be scuttled in its entirety," he said. "Considering the amount of work that went into this—the last year and a half of my NCI life was spent putting together this thing—it leaves a very problematic taste in one's mouth about how creative these people are being about responding to what is going to be a difficult time in terms of funding.

"The idea that they aren't even trying this to see how it works is disappointing," Sausville said. "This is a relatively small amount of money to get a bona fide new

mechanism. Even if NCI funded all 12 of them, it would be a relatively small amount of money for something fundamentally different."

P01s Cost More Than AP4

NCI will accept P01 grant applications from the AP4 applicants, Doroshow said.

"We've certainly encouraged those investigators that applied to consider other mechanisms of support for those activities," Doroshow said. "I believe that some are intending to submit program project applications to carry out this work. It's my understanding that there is interest in doing so, which we would encourage."

The funds for P01s come from the Research Project Grant budget line, while the AP4 program would have been funded through the 15 percent of the RPG budget that NCI sets aside for directed research.

Some of the AP4 investigators plan to take Doroshow's invitation to submit P01 grant applications.

However, those grants are likely to cost NCI several times more than the AP4 grants, because industry funds can't be used, said Eckhardt. "In the face of the current funding crisis at the NCI, it's ironic that they would turn down several million dollars of support from pharma to hasten cancer drug development," she said.

The current budget environment could cause NIH study sections to become more conservative in their deliberations, Sausville said. "How to reasonably leverage more 'risky,' but well-founded drug discovery strategies emanating from the academic sector remains undefined," he said. "The nature of drug discovery, unfortunately, remains fairly stochastic. One has to take projects that are at an early phase and provide some basis for backing things that may not be obvious.

"While I hope that there is continued success by our corporate colleagues in targets that have been well-validated and with approaches that are currently 'active' in the clinic, we've got to ask where is the next generation of new target ideas allied to particular structures are going to come from?

"Historically, the pharmaceutical industry has regarded NIH-funded research as a fertile source of ideas and targets," Sausville said. "Given the conservatism of study sections that we see now becoming unfortunately a fiscal reality, what's going to be the basis for breaking through that conservative tendency and bringing forward the targets of tomorrow? One approach is to say industry is going to do it by itself. There is no lack of companies that are allied to particular targets, and that's good. But I also think that academia also remains a very important source of those ideas, and this program could have been a way of continuing to support that effort.

"The facts are, for any idea that makes a licensed drug, it's a single-digit to less than single digit percentage of the molecules that started in a drug, or for that matter antibody or protein screen," Sausville said. "If you don't want that type of risk to be solely funded by federal dollars, you've got to try to mix with potential users, and that's what this was AP4 was trying to do.

"It's sad that apparently that fiscal circumstances preclude this, because I think it would have been a terrific opportunity to think out of the box and to actually address many of NCI's stated goals."

Bunn said he hopes that NCI would revive the AP4 concept.

"I hear they are considering doing partnership agreements with other types of grants in the future to try to leverage money with pharma," he said. "It seems like the goals are still reasonable—leveraging money, breaking down barriers, getting cooperation.

"I'm an optimist, so I would hope someday something similar would be rejuvenated," Bunn said. "I would hope that many of the ideas and the principles be adopted into a similar mechanism."

Raloxifene Equal To Tamoxifen For Risk Reduction, Trial Finds

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osteoporosis treatment and prevention, and if it receives approval for breast cancer prevention, it's likely that it will continue to be used widely."

Following announcement of the STAR data, Lilly said it plans to seek new indications for the drug.

Raloxifene is also being tested in the Raloxifene Use for the Heart, RUTH, study with primary endpoints of invasive breast cancer risk and cardiovascular risk reduction. Final results from that study are expected to be presented later this year, the company said.

RUTH and STAR, combined with data from Multiple Outcomes of Raloxifene Evaluation (MORE), and Continuing Outcomes Relevant to Evista (CORE), would be included in a potential supplemental new drug application filing package, the company said.

Lilly said its patents covering Evista's use in osteoporosis would assure U.S. market exclusivity until 2014. Tamoxifen, formerly exclusively available from AstraZeneca, is sold by generic manufacturers.

STAR enrolled 19,747 postmenopausal women who were at increased risk of the disease. Participants were randomly assigned to receive either 60 mg of raloxifene or 20 mg of tamoxifen daily for five years.

The data and safety monitoring board for the NSABP met last week for a regularly scheduled meeting and after reviewing the full analysis of the trial agreed that the results should be announced. "This is the second large breast cancer prevention trial," Wickerham said, referring to the cooperative group's Breast Cancer Prevention Trial, which established the proof of principle that the risk of breast cancer can be reduced. "If raloxifene gets approved, it's more than just proof of principle. It's truly an attractive alternative for breast cancer prevention."

The statistical data needed to make the noninferiority claim will be released at the ASCO presentation.

In STAR, raloxifene appeared to be generally better tolerated than tamoxifen, but the trial wasn't powered to produce statistically significant comparisons of toxicity.

"Raloxifene doesn't appear to be as effective in preventing non-invasive breast cancer as tamoxifen," Wickerham said. "This is a finding that has been seen in prior raloxifene trials. It's biologically intriguing—we are trying to sort through the possibilities of why it would occur."

Participants in STAR are receiving information about which drug they were taking. Women assigned to raloxifene will continue to be provided with the drug until they have completed five years of treatment. Women assigned to tamoxifen will be able to continue taking tamoxifen or to switch to raloxifene to complete five years of treatment.

Study details include:

• The numbers of invasive breast cancers in both groups were statistically equivalent. Among the 9,745 women in the raloxifene group, 167 developed invasive breast cancer, compared to 163 of 9,726 women in the tamoxifen group.

• More than half of the women who joined STAR had had a hysterectomy. For those women with a uterus, 36 of 4,732 who were assigned to take tamoxifen developed uterine cancers (mainly endometrial cancer) compared to 23 of 4,712 women who were assigned to take raloxifene.

• In STAR, women in the raloxifene group had 29 percent fewer deep vein thromboses and pulmonary embolisms than women in the tamoxifen group.

• The number of strokes occurring in both groups of women was statistically equivalent: 53 of 9,726 women in the tamoxifen group and 51 of 9,745 women in the raloxifene group had a stroke during the trial. There was no difference in deaths from strokes.

• While tamoxifen has been shown to reduce, by half, the incidence of lobular carcinoma in situ and ductal carcinoma in situ, raloxifene did not have an effect on these diagnoses.

Further details: www.nsabp.pitt.edu/STAR/Index.asp.

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