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ODAC Recommends Approval Of Evista For Breast Cancer Risk Reduction

By Kirsten Boyd Goldberg

The FDA Oncologic Drugs Advisory Committee July 24 voted to recommend approval of Eli Lilly's drug Evista (raloxifene) to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for breast cancer.

The committee voted 8-6 in favor of Evista for use in postmenopausal women with osteoporosis, and 10-4 in favor of use of the agent in postmenopausal women at high risk for breast cancer.

The recommendation for use of Evista in women at high risk of breast cancer was based on the results of the NCI-funded Study of Tamoxifen and Raloxifene (STAR). In the study, Evista was not better than tamoxifen in

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FDA Advisors Unanimously Turn Down GPC Biotech's Orplatna For Prostate Cancer

By Paul Goldberg

FDA's clinical advisors earlier this week unanimously recommended against accelerated approval of the prostate cancer drug Orplatna (satraplatin) for patients with hormone-refractory prostate cancer patients who have failed chemotherapy.

In a 12-0 vote, the Oncologic Drugs Advisory Committee rejected a novel composite endpoint of progression-free survival developed by GPC Biotech, the drug 's sponsor, and urged the agency to wait for the survival data from the company's ongoing pivotal trial.

At the meeting July 24, FDA officials said that the company was made aware of the problems posed by its PFS metric, which consisted of radiographic progression, pain, analgesic consumption, ECOG performance status, weight loss, skeletal events, and clinical events related to prostate cancer.

During the "special protocol assessment" process in 2003, GPC was told that the composite metric was untested, and that the study should rely on survival data instead, Richard Pazdur, director of the FDA Office of Oncology Drug Products said at the ODAC meeting.

"Although a special protocol assessment was submitted to the agency, the agency did not agree with the definition of PFS and stated that the acceptability of the sponsor-defined PFS endpoint would be a review issue," Pazdur said at the ODAC meeting.

This apparent agreement to disagree on a co-primary endpoint wasn't

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Despite Limitations Of STAR, ODAC Sees Benefit For Evista

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reducing the incidence of breast cancer, but the women taking Evista experienced fewer side effects. The trial, which enrolled nearly 20,000 women, excluded women who were at risk for deep vein thrombosis, pulmonary embolism, or stroke, because Evista can worsen those conditions.

Several ODAC members noted that STAR had many limitations and didn't provide as solid evidence as they would have liked to support a recommendation for healthy women to begin taking a drug to prevent or delay breast cancer. Some committee members who voted in favor of the therapy suggested that the sponsor include clear warnings on the package insert about the risk of thromboembolic events.

Nevertheless, the ODAC vote clearly endorsed the STAR results as showing an overall favorable risk-benefit profile for the use of Evista in women at high risk of developing breast cancer, said Norman Wolmark, chairman of the National Surgical Adjuvant Breast & Bowel Project, which conducted the trial.

"The ODAC recommendation to approve raloxifene for the reduction of 'risk of invasive breast cancer' in postmenopausal women is a strong affirmation of the value of well-conducted clinical trials in the breast cancer prevention setting," Wolmark said to The Cancer Letter. "In particular, the 10-4 vote in favor of supporting the efficacy of raloxifene in reducing the risk of invasive breast cancer in postmenopausal women at 'high risk for breast cancer' is an unequivocal endorsement of the contribution of NSABP protocol P-2 and the NCI sponsorship of this study. The decision clearly underscores the fact that trials such as P-2 can have far-reaching public health implications and have the potential to benefit countless postmenopausal women.

"If the FDA accepts the advice of ODAC, raloxifene will become a new standard of care in the field of breast cancer chemoprevention," Wolmark said.

The recommendation is a step forward for cancer prevention, said Peter Greenwald, director of the NCI Division of Cancer Prevention, which funded the STAR trial. "This is wonderful news," Greenwald said. "With FDA approval, post-menopausal women at high risk for breast cancer and those with osteoporosis, with their physicians, can consider the option of taking raloxifene to reduce breast cancer risk. I'm delighted that the STAR trial was able to lead to a drug that soon should be available for breast cancer prevention. This is a very positive step for women's health and for cancer prevention."

Evista, a selective estrogen receptor modulator, is approved for the prevention and treatment of osteoporosis in postmenopausal women. Last November, Lilly submitted a new drug application to FDA requesting approval for breast cancer risk reduction, based on the results of four randomized clinical trials.

"Today is an especially good day for postmenopausal women," said Gwen Krivi, vice president of Lilly Research Laboratories. "If approved, Evista would be the first and only therapy available to address two leading health issues for postmenopausal women—osteoporosis and breast cancer. Following today's vote, our intention is to continue working with the FDA to make this important option a reality for patients."

Uncertain Future For Large Prevention Trials

The ODAC endorsement comes on the heels of NCI Director John Niederhuber's decision not to fund NSABP's proposed P-4 study, which the cooperative group describes as the next logical step for breast cancer chemoprevention (The Cancer Letter, June 22).

P-4 would randomize 12,800 healthy women to Evista or letrozole, an aromatase inhibitor that may work better than Evista in reducing the risk of breast cancer. The study was approved by NCI peer review committees, as well as the Executive Committee. Niederhuber declined to fund the study due to "numerous scientific concerns," according to a letter dated June 19 from NCI to NSABP officials.

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Announcing its decision to kill P-4, NCI described the risk-benefit profile of chemoprevention as unfavorable:

"While the P-4 study may provide another possible option for women at risk of breast cancer, the dangers of introducing these drugs, with their many known side effects, outweighs their potential until we are better able to determine who will benefit from these interventions and what the longer term effect may be," the letter stated.

After NCI announced the director's decision not to fund the study, Niederhuber outlined "a new paradigm for cancer prevention" for the institute. "We are beginning to view our approach to prevention research differently, and it's an approach NCI hopes will lead to more dramatic advances," he wrote in the NCI Cancer Bulletin, an in-house publication, June 26. "This approach is defined by the use of advanced tools and technologies—such as those employed in genomics, proteomics, and metabolomics—to pursue the molecular events associated with the mechanisms and early signs of cancer development."

In an editorial published June 30, The Lancet called for an investigation of Niederhuber's decision. "The science of cancer chemoprevention is advancing rapidly and it is reasonable to ask whether new approaches are needed," the editorial stated. "But it is troubling that the NCI director stepped in after the reviews were complete to halt a trial that had been given high marks by seven NCI committees, including the NCI's Executive Committee. The action clearly undermines the NCI's review process, and an independent investigation into how the decision was made and whether it was made fairly is warranted."

NSABP's Wolmark said the ODAC recommendation validates the rationale for conducting P-4. "The decision of the panel, which carefully weighed the benefits and risks of raloxifene, also reaffirms the propriety and timeliness of NSABP protocol P-4 which, had it been allowed to go forward, would have compared raloxifene to letrozole and may have resulted in a 70 percent reduction in risk," Wolmark said to The Cancer Letter. "Whereas the ODAC decision is a significant step forward for breast cancer prevention, the failure on the part of the NCI director to translate these recommendations into further gains is an unfortunate lost opportunity."

George Sledge, professor of medicine and pathology at Indiana University, who spoke at the ODAC meeting on behalf of Lilly in favor of Evista, said the committee members weren't enthusiastic about the results of the STAR trial.

"I think what the ODAC emphasizes is that we need to have a new way of looking at prevention," Sledge said to The Cancer Letter. "If, with a huge, 20,000-patient study, we don't have the statistical power to please everyone, then it's going to be impossible to do chemoprevention going forward. The current way is probably not acceptable.

"My understanding of the NCI decision on P-4 was that it was primarily a money issue," Sledge said. "It's reasonable for NCI to ask how best to spend $50 million to $100 million. There are several problems that I see. First, is the fact that these studies are huge and require long follow-up. Second, with the current U.S. patent system the way it is, it's hard to imagine a drug company getting a return on its investment from a prevention study. We need a new solution to approaching this problem."

Solutions could include surrogate biomarkers for benefit, or some other way of judging who will benefit the most from an intervention, Sledge said. "Even with Gail model, we have a somewhat higher-risk population, but not a truly high-risk population, so the numbers needed to treat [with Evista] remain huge," he said. In STAR, 300 women needed to take Evista for one woman to benefit from the therapy, according to data presented by Lilly.

At the ODAC meeting, Sledge said he thought the decision on Evista was "fairly straightforward," because raloxifene "is a safer drug" than tamoxifen. "Postmenopausal women at high risk for breast cancer now should have a choice," he said.

The sponsor conducted a non-inferiority analysis of STAR, comparing the trial's results with those of NSABP P-1, which tested tamoxifen against placebo. The results of the analysis indicated that, compared to placebo, Evista may be less effective in preventing breast cancers than tamoxifen, FDA officials said.

"Non-inferiority results are consistent with Evista potentially losing up to 35 percent of the tamoxifen effect on the incidence of invasive breast cancer seen in the NSABP P1 trial comparing tamoxifen with placebo," said Richard Pazdur, director of the FDA Office of Oncology Drug Products. "In addition, there were fewer non-invasive breast cancers in the tamoxifen group (60) than the Evista group (83). For all breast cancers, the non-inferiority analysis results are consistent with Evista potentially losing up to 47 percent of the tamoxifen effect in the NSABP P-1 trial."

Besides the STAR trial, the committee reviewed three studies of Evista:

—Postmenopausal women with known or at increased risk for coronary disease in the Raloxifene Use for The Heart (RUTH) trial.

—Postmenopausal women with osteoporosis in the Multiple Outcomes of Raloxifene Evaluation (MORE) and Continuing Outcomes Relevant to Evista (CORE) trials.

Side effects of Evista aren't likely to be better in clinical practice than they were in the clinical trials, Pazdur said. "In general, the protocols for the STAR, RUTH, MORE and CORE trials excluded women who were at risk for deep vein thrombosis, pulmonary embolism or stroke with exception of the RUTH trial where patients were at increased risk of coronary adverse events and presumably at increased stroke risk," Pazdur said. "Thus, it is unlikely the incidence of Evista serious adverse events will be less in general use than in the clinical trials. We cannot expect to improve the clinical trial results in general use by precautions and warnings in the Evista labeling."

FDA didn't take a position on the application, but sought ODAC's advice.

ODAC Discussion and Vote

FDA asked ODAC members to address two questions:

1. Is the risk-benefit ratio favorable for use of Evista to reduce the risk of invasive beast cancer in postmenopausal women with osteoporosis?

2. Is the risk-benefit ratio favorable for use of Evista to reduce the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer?

The final round of discussion prior to the vote follows:

Otis Brawley, professor of hematology/oncology and medicine, Emory University: "For question one, I think we have three very well-controlled trials, so I think, yes. In terms of the reduction in the STAR trial, despite the fact that STAR compares tamoxifen and raloxifene, I think one has to be cautious in comparing the two. I asked for the sponsor to show the slide where the Gail model is put up against tamoxifen and raloxifene. That, to me, is overwhelming evidence that raloxifene reduced [breast cancer] versus placebo. I am moved by the fact that I did hear that a 60,000-person trial would have been required for a non-inferiority trial, so I do believe raloxifene is effective in reducing the risk of breast cancer. I believe it reduces the period prevalence, by the way, and that is the time in which this drug is used. I do not believe we should be rigorous in comparing raloxifene and tamoxifen."

Michael Link, chief, Division of Hematology/Oncology, Stanford University: "I am worried about the number needed to treat, but overall, I think that since tamoxifen has been approved for this indication, I am swayed by the need to have a better therapeutic ratio, if you will, admitting the possibility that this will have less prevention effect, but more likely to be tolerated by women. I don't understand what is to be gained by the first indication."

Michael Perry, director, Division of Hematology/Medical Oncology, University of Missouri: "I am going to vote yes on both of these. I think raloxifene clearly has benefit, and I think the side effects have been somewhat exaggerated. The confidence intervals on some of these side effects cross the one boundary, so I don't think they are statistically significant. I think they bear watching. I think that a lot of people get deep vein thrombosis, and I think if you pick your patients carefully, you can reduce the risk of these particular side effects. I think the reason a lot of women are not on tamoxifen who might be is that tamoxifen is off patent and there is no manufacturer pushing the drug. There is no more Nolvadex, there is only tamoxifen. Astra Zeneca has given it up and there is no competitive advantage in that market."

Ronald Richardson, consultant in medical oncology, Mayo Clinic: "I am troubled by all of this. Tamoxifen and Evista, in reality, both have minimal activity for either of these indications. They have toxicities that are significant. The long-term side effects aren't really known, but seem to persist over time. I am particularly troubled by some of Dr. Couch's remarks with respect to stroke risk in older women. I find the number of patients needed to treat for some benefit is astounding."

Maha Hussain, professor of medicine and urology, University of Michigan: "I would begin fundamentally by making a disclaimer which is, in general, I have a problem with prevention trials that don't look at how many lives we are saving. So this is a different philosophical issue. I think that the trials—considering that it's going to be impossible to do the most perfect trial in terms of numbers—have accomplished what they were started to prove. In both accounts, I think the risk-benefit ratio is a yes. I do think that some restrictions ought to be put on duration. Leaving it up to the primary care physician is not a good thing. I also think that clear exclusion criteria have to be included and potentially, consideration for contraindications altogether."

S. Gail Eckhardt, director of developmental therapeutics and GI malignancies programs, University of Colorado Cancer Center, : "On the first issue, I think

about it as a little bit of value added for a patient being treated for osteoporosis. Normally, you would discuss the risk-benefit in relation to other drugs being used for osteoporosis, and we didn't talk about that. I think the second question is tougher for me. What we are seeing is that these trials are often flawed for many reasons, and the drugs have flaws, but they can have true benefit in a focused patient population. My concerns lie in the further narrowing of the patient population that can truly benefit in this setting, and clearly, duration of therapy. Those are two hurdles, because as we are comparing this to tamoxifen, this is considered by many people to be a flawed drug."

Wydham Wilson, chief of the NCI Lymphoma Therapeutics Section: "I, too, am struck by the large number of patients that need to be treated in order to received benefit from tamoxifen as well as this agent, as well as the lack of long term safety data, long term efficacy data, and the absence of a survival benefit for tamoxifen. From a biological point, I continue to be concerned that we are delaying or modifying the natural history of breast cancer but we may not ultimately be stopping it overall. I do think the STAR trial does show, in my view, that raloxifene does have some prevention benefit. Whether or not it is equivalent to tamoxifen or slightly less, I think is still an open question. It does appear to be somewhat less toxic. If one felt that the short term benefit of tamoxifen was worth approving, that based on that alone, there would be some merit in approving raloxifene. I have a larger problem with the first indication because if one looks at the absolute benefit, it would appear that it is mostly going to be in high risk patients, those with Gail scores over 1.67. That is the group that would fall into the second indication, therefore they could be getting that drug as part of the second indication. That leaves the patients at low risk of disease, where the benefit is going to be very small. Because this drug is mostly going to be given by general medical doctors or OB/GYNs, I don't think the relative risk of the Gail model is going to be well explained, and I would hate to see the benefit of this question of breast cancer obscuring other balances of risk-benefit when patients are trying to decide whether they should be getting anything for osteoporosis or whether another osteoporotic drug might have a better profile."

Joanne Mortimer, professor of clinical medicine and medical director, Moores UCSD Cancer Center: "In answer to the first question, I think the three very well-designed placebo-controlled trials did show that raloxifene does decrease the incidence of breast cancer, and whether the risk-benefit profile actually favors its use as a preventive agent is really a hard one to answer with the data we have at hand. The recent data from the Women's Health Initiative would suggest that early hormone replacement therapy in younger women has a protective effect, and an opposite effect in older women makes me worry that as we use these SERMs in older women, that they really may have a risk-benefit ratio that is adverse. Nonetheless, I think the sponsor did demonstrate a decreased incidence in breast cancer. I have more difficulty in sending this to the population at large of high-risk women on the basis that whether the data is conflicted or not. I am worried that if the bone is an end organ and the breast is an end organ for hormonal effect, that probably the natural history of this disease is not the same in osteoporotic women as other women, and in the absence of data that says that they are, I am concerned about extrapolating the data to the high-risk women without osteoporosis. Secondly, I am consistently troubled by the lack of the decrease in ductal carcinoma in situ. DCIS is a precursor for invasive cancer. Why in the MORE study and the RUTH study and STAR was there not a benefit for decrease in DCIS? For those reasons, I have a hard time sending this to the larger population."

Gary Leyman, associate center director for health services and outcomes research, Wilmot Cancer Center, University of Rochester Medical Center: "I think that the sponsor has worked with NSABP, NCI, and the FDA to design the studies and monitor the studies of Evista as a chemopreventive, and they do need to be commended for that. I do think, however, that we all as clinical trialists need to listen to what all of us are saying to one another, and even the advocacy community is saying, in that we need to think about longer term follow up in our controlled clinical trials, and nowhere is that more a need than in the prevention setting, where the event rates are low and potential toxicity benefit profile could possibly be unfavorable. We might want to discuss the possibility of mandating or updating the post-approval monitoring that needs to be done in the populations, the osteoporotic and the high-risk population, because I think both sustained efficacy and toxicity issues have been eloquently discussed and we want more data and we want longer term follow up. Having said all that, as a breast cancer oncologist, I do think the use of raloxifene to reduce the risk of breast cancer in women, many of whom are already taking the drug for osteoporosis prevention and treatment, seems reasonable. The data from the randomized, placebo-controlled trials seem to offer a reasonably favorable risk-benefit profile as far as the data goes. I am also somewhat reassured by

the survival data, though limited and not powered for survival outcomes, and not necessarily significant, but, if anything, trending to a favorable survival outcome, and that's reassuring after considering all these other issues. For the high-risk population, compared to tamoxifen, as I read the data, raloxifene seems to be similar in efficacy and similar or somewhat better in terms of the safety profile. I am not at all comfortable with the non-inferiority analysis that we have been forced to consider, given the lack of a placebo group in the STAR trial, and I think that data figures little in my decision to vote Yes in these two indications."

David Harrington, chairman, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute: "I am going to vote No on the first question, because I think that the population there is too broad. Even though those were the populations in the trial, they include postmenopausal women at low risk of breast cancer, and I didn't see clear evidence for continued use of raloxifene in postmenopausal women with osteoporosis who progress on their osteoporosis and for whom you would them remove raloxifene as an osteoporosis drug, and whether the risks are worth continuing to prevent breast cancers in the future. Question two is a tough one because of the non-inferiority analysis here in a trial that is not placebo-controlled. I am going to vote Yes on that one, because we have got another drug out there, tamoxifen, with its advantages and its possible flaws, and I think that's a setting where, in women at high risk of breast cancer, it would be very nice to have a second option, because there the risk-benefit ratio comes into much sharper focus, because the potential comparisons are the side effects of raloxifene versus the side effects of tamoxifen."

Pamela Haylock, oncology consultant: "I think on question one, the value of the drug has been shown, but I am very concerned about the issue of the candidates for taking the drug, especially people who are unknown risk for stroke. The incidence of stroke seems to go up, while the age of stroke survivors goes down, and I think there was a real lack of defining properties of that population in the study. It's a big concern when this drug is available in clinical practice, again for the issue of thromboembolic events, particularly stroke, in these populations because so many people are not being monitored for stroke or have unknown risk for stroke. In the second question, I think that the risk of invasive breast cancer in these women is high, so I think that I would be more in favor of a Yes vote."

Helen Schiff, patient representative: "I agree with what Dr. Richardson said, and I am going to vote No on both of these, because I really think we don't know the long range effects in terms of survival, and I think that's an important question when you can't decide individually who's at high risk of breast cancer but you are looking at such big populations. In addition to that, I think we know about the healthy women effect. The women in these trials are going to be healthier than women who get this drug outside of the trial. I would add that with the FDA not having the power that it needs to pull a drug off the market or to regulate direct-to-consumer advertising, that although this is not the typical consideration for ODAC, it is a consideration for an advocate. I spent a year getting the tamoxifen ad pulled from Prevention. They had put in the relative risk reduction from breast cancer and the absolute risk of side effects. So, in that whole context, I am voting No on both of these. I think our money can be spent on finding out really who is at high risk before we start giving people dangerous drugs."

James Couch, associate chairman, Neuroscience Service, University of Oklahoma Health Sciences Center: "I am not an oncologist and will not vote. I would advocate that a long term surveillance program must be put in place. There may be subgroups here that may influence the stroke risk to a greater or lesser extent, so it may be possible to identify a subgroup that would have a greater or lesser risk, and perhaps identify a subgroup that you really minimize and use the drug in that situation. There is not going to be one drug that is going to fit one situation here. I think we might be able to identify a subgroup at lower risk for stroke, or a higher risk for stroke where we certainly wouldn't want to use this medication. It would be important to look at 10- and 20-year follow up."

Aman Buzdar, professor of medicine, M.D. Anderson Cancer Center: "The question is, is the risk-benefit ratio favorable? I think the data from MORE, CORE, and RUTH clearly demonstrate that, yes, we can make use of this. The question is, there is no data presented whether this risk-benefit ratio, because we also saw substantially increased risk of stroke and other thromoboembolic complications associated with estrogenic properties. I would say the benefit is there, but the question of whether the risk-benefit profile is favorable, it's not really clear from the data which was presented. The same for question number two, is the risk benefit profile favorable, Evista is somewhat less effective in reducing noninvasive breast cancer and even invasive breast cancer, and the risk benefit profile is not really defined."

Curt Furburg, professor, Department of Public Health Sciences, Wake forest University: "I am basically supportive, but only with some safeguards. I think there should be strong safeguards to limit potential harm. That should be done both at the time of initiation of therapy to lay out the contraindications, and also during follow up. People change their status and the risk of complications may change. The other safeguard is to somehow restrict overuse. I worry about direct-to-consumer advertising. Every other women in the U.S. can be on the drug unless you try to restrict use to the women where the drug has been shown to be effective. So there are three solutions I propose. One is the labeling, possibly a black box, to bring to people's attention that there are risks involved. Focus on the thromoboembolic events and other complications. The other one is for the sponsor to commit to a medication guide, a document that would be given to every women getting the drug, laying out the rationale for treatment, what should they pay attention to, and when they should contact their doctors. I agree with a couple of other people who suggested post-market surveillance. I think that's critical. It really should go beyond five years and set up a patient registry with a pre-specified hypothesis. I wish we in the U.S. had the European model where re-review of the drug would occur automatically after a certain number of years. I would like to see a re-review, say by five years, to see what the experience has been and whether the drug should stay on the market."

Antonio Grillo-Lopez, non-voting industry representative: "I think the data are clear and I would be willing, based on the data as presented to make a recommendation. We have to accept that tamoxifen is approved and on the market, and raloxifene shows at least similar efficacy and perhaps a better safety profile. Given the comments of some of my colleagues on the committee, I would like to provide a word of caution. Although some of the concerns are very real and valid, the data are what they are, and we cannot ask these trials to show what they were not designed to show. The questions were not asked. It would be nice to have had twice as many patients in these studies, but they are large enough as it is, and these studies are very costly, it takes a long time to enroll patients, and you have to stop somewhere. Also, the observation time is what it is. You cannot expect to have 20- or 30-year observation time, when the studies haven't been enrolling for that long. So we have to put aside some of those concerns, valid though they are, and the committee has to vote based on the information that is available."

The committee's votes were:

Question 1: Yes—Brawley, Link, Perry, Hussain, Mortimer, Lyman, Eckhardt, and Furburg. No—Buzdar, Schiff, Haylock, Harrington, Wilson, and Richardson. Abstain—Couch.

Question 2: Yes—Brawley, Link, Perry, Richardson, Hussain, Wilson, Lyman, and Harrington, Haylock, and Furburg. No—Buzdar, Schiff, Mortimer, and Eckhardt. Abstain—Couch.

FDA Didn't Approve Of GPC's Endpoint In Protocol Review

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acknowledged in the Sept. 2, 2003, GPC press release, which announced "the culmination of the company's satisfactory completion" of the SPA for development of the oral platinum compound.

"GPC Biotech AG… today announced that it has received written confirmation from the FDA that the company may initiate a phase III registrational trial with satraplatin plus prednisone in patients with hormone-refractory prostate cancer who have failed prior treatment with chemotherapy," the document states.

"Primary endpoint for accelerated approval will be time to disease progression," states the document posted at www.gpc-biotech.com/en/news_media/press_releases/2003/2003-09-02.html.

Wall Street views special protocol assessments as positive factors in valuation of stocks, because SPA letters—which are viewed as contracts between the agency and the sponsors—can reduce the level of uncertainty in drug development.

After the ODAC meeting, a Morgan Stanley analyst wrote that he was surprised to learn that FDA and the company weren't in agreement about a key element of the satraplatin development strategy, a disclosure that he saw as contradictory to "the understanding on the Street." This understanding "played a big role in the conviction of the bulls and restrained criticism from the bears," the analyst wrote.

GPC Biotech is based in Munich, and has a subsidiary in Princeton, N.J. The company licensed satraplatin from Spectrum Pharmaceuticals Inc., of Irvine, Calif., which now seeks to terminate the licensing agreement, claiming multiple breaches of contract. The European rights to satraplatin are held by Pharmion GmbH, and Yakult Honsha Co. Ltd. holds the Japanese rights.

After ODAC's recommendation, GPC's stock price dropped by about $7.20 and closed at $13.16 on July 25, and dropped by another $2 a day later. On

July 26, a New York law firm filed a shareholder suit against the company. An announcement of the suit was is posted at http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/07-26-2007/0004633688&EDATE.

A disclosure of "risk factors" in a recent SEC filing by the company acknowledges that the agency may not accept the PFS data, but doesn't mention the agreement to disagree on the co-primary endpoint:

"FDA will review the progression-free survival, or PFS, data from our phase III registrational trial, called SPARC, in considering whether to grant such an approval. Even though, the statistical threshold for significance was met for the primary (PFS) and secondary (time to pain progression) endpoints at the time of the NDA submission, the FDA may not grant an accelerated approval, for example, if it concludes that the data do not demonstrate that satraplatin provides a meaningful therapeutic benefit to patients over existing treatments or that the data are otherwise inadequate to support the granting of an accelerated approval due to weaknesses, inconsistencies or differences in the data with respect to data subsets or subpopulations in the treatment group."

"No Experience" With GPC's Metric

At the ODAC meeting FDA's Pazdur said that the agency urged GPC to employ a more standard metric.

"The FDA has no prior experience with this endpoint," he said of the company's definition of PFS. "This concern was communicated to the commercial sponsor during the development phase. The FDA has strongly recommended the primary endpoint of the trial be overall survival in several meetings and correspondence with the company."

Impact on the level of the prostate-specific antigen was not included in the composite metric, company filings show. PSA hasn't been accepted by the agency as a measurement of efficacy in prostate cancer.

"The acceptability of this [PFS] endpoint would be subject to the evaluation of the magnitude of effect on the endpoint's components, the reliability and objectivity in the measurement of the endpoint, and clinical significance of the claimed effect on the endpoint's components," Pazdur said, describing the agreement with the company.

"FDA will seek ODAC advice on the acceptability and reliability of this composite PFS endpoint as the basis of marketing approval," he said to the advisory committee. "Because of the uncertainty of the acceptability and execution of this endpoint, a co-primary endpoint of overall survival was incorporated in the trial."

The agency's guidance document on SPAs states that "having agreed to the design, execution, and analyses proposed in protocols reviewed under this process [i.e., carcinogenicity protocols, stability protocols, and phase III protocols for clinical trials that will form the primary basis of an efficacy claim], the agency will not later alter its perspective on the issues of design, execution, or analyses, unless public health concerns unrecognized at the time of protocol assessment under this process are evident."

However, sponsors aren't required to take FDA's advice, and the agency has no authority to stop clinical experiments because of disagreements over design. If a dispute occurs in negotiation of SPA documents, these disputes should be "clearly documented in writing," either in the SPA letter or in the minutes of meetings with the sponsors, the agency guidance states. Only studies that pose safety concerns can be halted.

The fact that FDA asked the committee to address the acceptability of PFS appears to confirm Pazdur's statement that the question was not resolved during the SPA process, FDA-watchers say.

In a teleconference following the ODAC meeting, GPC CEO Bernd Seizinger said that during the SPA process, the company received multiple comments from FDA, and altered its protocol accordingly.

"We requested, and the FDA conducted and completed, a special protocol assessment," Seizinger said. "In addition, we had an end-of-phase II meeting with the agency, to be sure we discussed the whole array of issues around the trial. As a result of comments received from the FDA during these processes, we revised our protocol to implement their commands, and resubmitted this to the FDA. They provided us additional guidance, which we also incorporated. We then received a letter from the agency indicating that they had no further comments to our protocol."

Thomas McKearn, GPC's vice president, medical affairs, said it was FDA that suggested the pain measurement metric used in the protocol.

"The issue of the proper metric of pain was addressed during the SPA process," McKearn said at the teleconference. "The original protocol in May of 2003 did not include PPI [Present Pain Intensity Scale, the metric used in the study]. It included another pain score. At their suggestion, we put the PPI in, along with the threshold that we would propose using, as we did this measure of progression of pain. It was all part of the PFS endpoint.

"Our basis for putting the particulars of this PPI into the protocol were derived from the EORTC [European Organization for Research and Treatment of Cancer] study [submitted as a confirmatory study for satraplatin]. That study served as the model of designing this protocol. This was why and how we chose the particular thresholds that we did."

McKearn said the company first learned about FDA's objections to the PFS metric shortly before the ODAC meeting. "That came to us as it came to you, folks, in the briefing documents," McKearn said. "So we have not heard any feedback along those lines through our interaction with the review staff."

GPC officials said some questions were left to be settled as "review issues" at the time of approval. "FDA by statute says that they have the right to wait until the review process to finalize their acceptance of all of these components, all of the constructs that were proposed and at least provisionally accepted at the time we started the trial," McKearn said.

The webcast of the teleconference is posted at www.gpc-biotech.com/en/investor_relations/webcasts/index.html.

Committee Opts To Wait For Survival Data

GPC's current predicament suggests that words of caution about PFS may have been justifiable.

With no dissention, the committee rejected PFS as a surrogate for survival, nixing the chance of an accelerated approval, and urging the agency to wait for survival data. Based on a protocol-prespecified survival analysis last month, satraplatin wasn't better than placebo.

The 700 deaths required for survival analysis were expected to occur by late 2007, though the company said that the death rates have slowed down in recent months.

According to the interim analysis using the composite endpoint, progression-free survival was extended by 10 days, and was 11.1 weeks for satraplatin, and 9.7 weeks for placebo, with the HR of 0.67 (0.57, 0.77). Using another metric, with PFS defined as radiologic progression or death, median PFS was 36.3 weeks for satraplatin vs. 20 weeks for placebo, with the HR of 0.64 (0.51, 0.81).

"I guess I don't share the optimism that the survival results will emerge as positive; they may, but they very well may not," said David Harrington, a biostatistician at Dana-Farber Cancer Institute and a member of ODAC. "But an accelerated approval must be based on a robust endpoint that can stand for overall survival. I don't see robustness. I don't know whether radiologic assessment was valuable, I don't know whether pain assessment was assessed properly. I don't see robustness."

While patients who spoke at the public hearing urged approval of the drug, the patient representative on the panel voted against accelerated approval. The claimed 10-day increase in PFS wasn't worth the cost of toxicity associated with the compound, said Jim Anderson, the patient representative on the committee.

"As a patient rep, I am concerned about us suggesting that this group of men, who have seen extreme toxic side effects, be subjected to more without better proof that there is a benefit here for them," Anderson said.

In addition to raising questions about PFS, FDA asked the committee to address the following problems:

—The company's two independent radiology readers disagreed on the progression status in 336 of the 950 patients (35.4%), requiring adjudication by a third independent radiology reader. "This discrepancy raises the question whether radiologic PFS could be reliably and objectively assessed in this clinical trial," Pazdur said. "The majority of radiologic progressions were based solely on bone scan evidence."

—The agency questioned the company's assessment of pain progression. "Because of satraplatin toxicities, it is unlikely that blinding was maintained," Pazdur said. "In addition, based on a review of background materials provided by the Applicant describing the methods for assessing pain intensity the FDA has determined that the single item Present Pain Intensity Scale (PPI), derived from the McGill Pain Questionnaire, has not been adequately validated for use in this study."

The PPI metric was used "a decade ago in the approval of mitoxantrone for treatment of HRPC, but different criteria for pain response and pain progression were used," Pazdur said. "Also in the mitoxantrone study the primary endpoint was reduction in pain intensity, while in the satraplatin study the main pain endpoint is time-to-pain progression.

"The protocol did not specify any plan for pain management and pain progression based on increased analgesic use varied widely between countries," Pazdur said. "Non-narcotic pain medicine usage was not considered in determining pain progression."

Patients in the trial could easily deduce what therapy they were receiving, committee members said.

"I am very concerned that this was not truly a blinded trial," said Steven Krasnow, section chief,

oncology section at the Washington, DC, VA Medical Center. "Not only might [patients] suspect their assignment by symptoms, but they also probably had access to their CBC [complete blood count] results. By knowing that their white blood count is two, they probably knew what they were getting."

Unblinded studies measuring pain control are notoriously unreliable since placebo effect can be activated in patients who believe they are receiving the drug, committee members said.

These analgesic effects, even if they are real, don't justify approval of satraplatin based on PFS, said James Farrar, clinical associate professor at the University of Pennsylvania Department of Neurology. "Given the toxicity of the treatment, if this were a drug that was vying for approval for pain, I would argue that the benefits don't outweigh the risks."

In the Cancer Centers:

M.D. Anderson Begins Effort To Develop Women Faculty

M. D. ANDERSON Cancer Center has begun a new effort to recruit, retain, and develop women faculty, said **Elizabeth Travis**, the center's first associate vice president for women faculty programs.

"Academic medicine has a cultural issue," Travis said. "It's not intentional, or malicious. It's just a fact. We are partnering with our division heads and department chairs to help them in this initiative."

Travis, on the faculty since 1982, is a professor in M. D. Anderson's Departments of Radiation Oncology and of Pulmonary Medicine and served as associate vice president for academic affairs before her new appointment.

The initiative is important, said Provost and Executive Vice President Raymond DuBois, who joined M. D. Anderson in June after leading Vanderbilt-Ingram Cancer Center. "I came from an institution where half of the basic science chairs were women and much of the leadership team had a very balanced gender mix," DuBois said. "It will be important for the success of M. D. Anderson to make sure we advance the careers of women faculty."

According to the American Association of Medical Colleges 2006 study of gender and rank in medical schools, 32 percent of medical school faculty are women, which breaks down into 7 percent of instructors, 15 percent of assistant professors, 6 percent of associate professors and 4 percent of full professors. In leadership ranks, women are 10 percent of deans, department and division chairs. Very few women are found at the top ranks of an institution. The gender demographics of M. D. Anderson faculty do not differ greatly from these numbers, Travis said.

An advisory committee to Travis will help direct the initiative. Additional projects are development of recognition for leaders who support the advancement and contributions of women faculty and helping women build competencies for leadership positions and skills in navigating institutional politics.

Travis is collaborating with M. D. Anderson's institutional diversity office and faculty development staff to develop a mentoring program for all faculty that will include specific sessions for women.

Another important aspect is to build an academic framework that encompasses gender issues and organizational change. Past efforts to help women have focused on remedies aimed at skill-building for women in academics. However, rather than "fixing the women, we need to focus on fixing the academic environment instead," Travis said.

Funding Opportunities:

RFA-AI-07-031: U.S.-India Bilateral Collaborative Research Partnerships (CRP) on the Prevention of HIV/AID. R21. Letters of Intent Receipt Date: Sept. 18; Application Submission/Receipt Date: Oct. 18. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-AI-07-031.html. Inquiries: Kishor Bhatia, 301-480-4137; bhatiak@mail.nih.gov.

RFA-AT-07-004: Mechanisms of Immune Modulation. R01. Application Submission/Receipt Date: Nov. 14. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-AT-07-004.html. Inquiries: Young Kim, 301-496-0126; yk47s@nih.gov.

RFA-AT-07-005: Mechanisms of Immune Modulation. R21. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-AT-07-005.html.

PA-07-403: Nutrition and Alcohol-Related Health Outcomes. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-403.html. Inquiries: Sharon Ross, 301-594-7547; rosssha@mail.nih.gov.

PA-07-404: Nutrition and Alcohol-Related Health Outcomes. R03. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-404.html.

PA-07-405: Nutrition and Alcohol-Related Health Outcomes. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-405.html.

RFP PHS-2008-1: Solicitationn of the NIH and the CDC for Small Business Innovation Research Contract Proposals. Response Due Date: Nov 5. Full text: http://www.fbodaily.com/archive/2007/07-July/15-Jul-2007/FBO-01341729.htm. Inquiries: Office of Extramural Programs, Office of Extramural Research, NIH, 301-435-2688; sbir@od.nih.gov.

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