Summary Minutes of the
Oncologic Drugs Advisory Committee
July 24, 2007
Location: Center for Drug Evaluation and Research Advisory Committee
5630 Fishers Lane, Rockville, MD. Room: 1066

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the July 24, 2007 of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on ____10/8/2007_____.

I certify that I attended the July 24, 2007 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Nicole Vesely, Pharm.D., R.Ph.
Designated Federal Official, ODAC

_____/s/_____
Maha H. Hussain, M.D.
Committee Chair-AM session

_____/s/_____
S. Gail Eckhardt, M.D.
Acting Chair- PM Session

Meeting of the Oncologic Drugs Advisory Committee
July 24, 2007

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 24, 2007 in the Advisors and Consultants Conference Room, Room 1066, 5630 Fishers Lane, Rockville, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Maha Hussain, M.D. (Committee Chair); the conflict of interest statement was read into the record by Johanna Clifford, M.Sc. (Designated Federal Official). There were approximately 300 persons in attendance. There were three speakers for the Open Public Hearing session.

Issue: The committee discussed new drug application 022-042, Evista (raloxifene hydrochloride) Tablets, Eli Lilly & Company, proposed indications for the reduction in risk of invasive breast cancer in post menopausal women with osteoporosis, and for the reduction in risk of invasive breast cancer in postmenopausal women at high risks of breast cancer.

Attendance:
Oncologic Drug Advisory Committee Members Present (Voting):
S. Gail Eckhardt, M.D., David Harrington, Ph.D., Maha Hussain, M.D. (chair), Michael Link, M.D., Gary Lyman, M.D., Joanne Mortimer, M.D., Michael Perry, M.D., Ronald Richardson, M.D.

Special Government Employee Consultants (Voting):
Aman Buzdar, M.D., Otis Brawley, M.D., James Couch, M.D., Curt Furberg, M.D., Pamela Haylock, RN (consumer representative), Wyndham Wilson, M.D, Helen Schiff (patient representative)

Non-voting Participants:
Antonio Grillo-Lopez, M.D. (Industry Representative)

Oncologic Drugs Advisory Committee Members Not Present:
Ronald Bukowski, M.D.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Robert Justice, M.D., Patricia Cortazar, M.D., Rajeshwari Sridhara, Ph.D., Bhupinder Mann, MBBS, Kun He, Ph.D., John Johnson, M.D. (via telephone)

Designated Federal Official:
Johanna Clifford, M.Sc, R.N., BSN

Open Public Hearing Speaker:
Connie Rufenburger – The Catherine Peachey Fund, Inc.
Jane Zones – Breast Cancer Action
Carolina Hinestrosa – National Breast Cancer Coalition

The agenda was as follows:

Call to Order and Introductions	**Maha Hussain, M.D.** Committee Chair Oncologic Drugs Advisory Committee
Conflict of Interest Statement	**Johanna Clifford, MSc, RN, BSN** Designated Federal Official Oncologic Drugs Advisory Committee
Introduction and Background	**Richard Pazdur, M.D.** Director, Office of Oncology Drug Products FDA Center for Drug Evaluation and Research

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Designing & Analyzing Trials With Active Control Arms	**David Harrington, Ph.D.** Dana Farber Cancer Institute

Sponsor Presentation – Eli Lilly & Company:

Introduction	Gwen Krivi, Ph.D.
Benefits & Risks of Evista MORE/CORE/RUTH	Steven R. Cummings, M.D. Director, San Francisco Coordinating Center Professor of Medicine and Epidemiology (emeritus) CPMC Research Institute and UC, San Francisco
Benefits and Risks of Evista - STAR	Larry Wickerman, M.D. National Surgical Adjuvant Breast and Bowel Project
Benefits & Risks of Evista - Conclusions	George Sledge, M.D. Indiana University School of Medicine
FDA Presentation:	**NDA 22,042** Patricia Cortazar, M.D. Clinical Reviewer, DODP, OODP, CDER & Bhupinder Mann, MBBS Clinical Reviewer, DODP, OODP, CDER
	Open Public Hearing
	Break
	Questions to the Committee
	Adjournment

Questions to the Committee:

SUMMARY

Evista is marketed for the treatment (1999) and prevention (1997) of osteoporosis in postmenopausal women. Results of four double-blind randomized trials are submitted in support of the two above new indications. Patients do not have cancer. Thus an especially careful consideration of the risk/benefit ratio is required.

The RUTH, MORE and CORE trials are placebo controlled. The STAR trial has an active control (tamoxifen). The most important data supporting the proposed new indications comes from the RUTH and STAR trials. Data from the MORE and CORE trials are less important for the following reasons. The MORE trial was not a breast cancer prevention trial. The primary endpoints were clinical vertebral fracture and bone mineral density of the lumbar spine and femoral neck. Breast cancer incidence was assessed only as a safety endpoint. The CORE trial was a continuation of the MORE trial. Breast cancer was added as the primary endpoint. However, patients were not re-randomized and prior randomization was lost because only approximately 52% of the MORE patients participated in the CORE trial. Only about 42% of MORE patients received study drug (Evista or placebo) in the CORE trial.

Results of the RUTH, CORE and MORE placebo-controlled studies indicate that Evista reduces the risk of invasive breast cancer. However, only ER positive breast cancers are reduced. There appears to be no reduction in ER negative breast cancers. Almost all of the invasive breast cancers are Stage I or II and thus have a high cure rate. This is achieved at a cost of an increase in serious adverse events such as deep vein thrombosis, pulmonary embolism, and possibly stroke death.

In the RUTH trial comparing Evista with Placebo, 5044 women were treated with Evista every day for a median of five years to prevent 30 invasive breast cancers, almost all Stage I or II. Described another way, 862 women must be treated for one year to prevent an invasive breast cancer in one woman.

The studies provide less support for the proposed new indication to reduce the risk of invasive breast cancer in postmenopausal women at high risk. The STAR trial compared Evista to an active control (tamoxifen) in postmenopausal women with a high risk of developing invasive breast cancer as indicated by a Modified Gail score of $\geq$ 1.66 or lobular carcinoma in situ (LCIS) treated by excision only. Evista was not better than tamoxifen. Non-inferiority analysis results are consistent with Evista potentially losing up to 35% of the tamoxifen effect on the incidence of invasive breast cancer seen in the NSABP-P1 trial. In addition there were fewer non-invasive breast cancers in the tamoxifen group (60) than in the Evista group (83). For all breast cancers the non-inferiority analysis results are consistent with Evista potentially losing up to 47% of the tamoxifen effect in the NSABP P-1 trial. ODAC advice is requested on whether these results are acceptable in view of the Evista adverse effects.

The efficacy results in the RUTH, MORE, CORE and STAR trials must be weighed against the increased risk of deep vein thrombosis, pulmonary embolism and possibly stroke death. A careful consideration of the risk/benefit ratio is especially important for these two proposed new indications in post menopausal women who do not have cancer. ODAC advice is requested.

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 Thus it is unlikely the incidence of Evista serious adverse events will be less in general use than in the clinical trials. We can not expect to improve the clinical trial results in general use by precautions and warnings in the Evista labeling.

QUESTIONS FOR THE ODAC

Indication: "Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis"

The RUTH, MORE and CORE Evista trials were placebo controlled. The demonstrated Evista benefit of invasive breast cancer reduction in these trials must be weighed against the Evista adverse effects.

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

Vote : ***Yes = 8*** ***No = 6*** ***Abstain = 1***

Indication: "Reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer"

In the STAR trial comparing Evista with tamoxifen in post-menopausal women at high risk of invasive breast cancer, Evista was not superior to tamoxifen in reduction of risk. Non-inferiority analysis results are consistent with Evista potentially losing up to 35% of the tamoxifen effect on the incidence of invasive breast cancer seen in the NSABP-P1 trial. 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% of the tamoxifen effect in the NSABP P-1 trial.

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? VOTE.

Vote : ***Yes = 10*** ***No = 4*** ***Abstain = 1***

In the interest of time, the aforementioned questions were presented to the committee together. Each committee member was asked to address each question and provide comments. A vote was taken on each question after comments were lodged. The committee comments are summarized as follows:

- The committee overall agreed that the RUTH, MORE and CORE were well designed placebo controlled trials and felt overall that raloxifene did demonstrate a risk reduction vs. placebo but that the side effects remain unclear with long term use.
- Some consultants felt that, compared to tamoxifen, raloxifene seems to show a better therapeutic ratio but whether the risk/benefit ratio favors it's use as a preventive measure is unclear with the data presented.
- The committee felt that the labeling should clearly include exclusion criteria and restrictions should be placed on duration of administration.
- There was concern from some committee members regarding the toxicities presented and the persistence of the toxicities with the administration of the drug over time, especially given the stroke risk in older women and women at high risk for cardiac complications.
- There were general concerns with a prevention trial in which the applicant chooses not to show survival.
- The committee agreed that there needed to be narrower, clearer focus regarding the patient population in which whom the product will be of benefit.
- There were concerns with respect to the number of the patients that needed to be treated in order to receive benefit.
- The committee felt overall that there was a lack of long term data with respect to toxicities and efficacy and the absence of a survival benefit.
- The committee felt that with the absence of data presented in the population of low risk women, it is unclear as to population of patients or candidates eligible to receive the product and whether the data can be extrapolated to a larger population of high risk women.
- The committee felt that a long-term surveillance should be instituted in order better understand safety profile of the drug.
- The committee recommended that a drug management guide should be instituted if the drug is approved.

==========*Lunch Break*==========

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 24 2007 in the Advisors and Consultants Conference Room, Room 1066, 5630 Fishers Lane, Rockville, Maryland. Prior to the meeting, members and invited consultants were provided the background material from the FDA and the sponsor. The meeting was called to order by S. Gail Eckhardt, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Johanna Clifford, M.Sc. (Designated Federal Official). There were approximately 300 persons in attendance. There were seven speakers for the Open Public Hearing session.

Issue: The committee discussed new drug application 021-801, Orplatna (satraplatin capsules) , GPC Biotech, Inc., proposed indication for the treatment of patients with androgen independent (hormone refractory) prostate cancer (HRPC) that has failed prior chemotherapy.

Attendance:
Oncologic Drug Advisory Committee Members Present (Voting):
S. Gail Eckhardt, M.D. (chair), David Harrington, Ph.D., Michael Link, M.D., Joanne Mortimer, M.D., Michael Perry, M.D., Ronald Richardson, M.D.

Special Government Employee Consultants (Voting):
James Anderson (patient representative), Otis Brawley, M.D., William Dahut, M.D., John Farrar, M.D., Steven Krasnow, M.D., Pamela Haylock, RN (consumer representative), Wyndham Wilson, M.D.

Non-voting Participants:
Antonio Grillo-Lopez, M.D. (Industry Representative)

Oncologic Drugs Advisory Committee Members Not Present:
Ronald Bukowski, M.D., Maha Hussain, M.D., Gary Lyman, M.D.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Robert Justice, M.D., Martin Cohen, M.D., Rajeshwari Sridhara, Ph.D., Ethan Basch, M.D., M.Sc., John Johnson, M.D. (via telephone)

Designated Federal Official:
Johanna Clifford, M.Sc, R.N., BSN

Open Public Hearing Speaker:
Joel Nowak – Director for Advanced Prostate Cancer.
Jim Waldenfels
Thomas Kirk – President & CEO, US TOO International
Katherine Meade
Merel Nissenberg, J.D. - President, NASPCC

The agenda proceeded as follows:

Call to Order and Introductions	**S. Gail Eckhardt, M.D.** Acting Committee Chair Oncologic Drugs Advisory Committee
Conflict of Interest Statement	**Johanna Clifford, MSc, RN, BSN** Designated Federal Official Oncologic Drugs Advisory Committee
Introduction and Background	**Richard Pazdur, M.D.** Director, Office of Oncology Drug Products FDA Center for Drug Evaluation and Research

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Sponsor Presentation – GPC Biotech, Inc.:

Introduction to NDA 21-801: Satraplatin Capsules	Martine George, M.D. Senior Vice President, Clinical Development
Second Line Chemotherapy for HRPC	Nicholas Vogelzang, M.D. Director, Nevada Cancer Institute

Efficacy & Safety of Satraplatin: SPARC Trial Summary and Conclusions	Marcel Rozencweig, M.D. Chief Medical Officer
FDA Presentation:	**NDA 21, 801**
Clinical Review	Martin Cohen, M.D. Clinical Reviewer, DODP, OODP, CDER
	&
Methods Used to Assess & Report Pain-Related Endpoints	Ethan Basch, M.D., M.Sc. Office of New Drugs, CDER, FDA
	Open Public Hearing
	Break
	Questions to the Committee
	Adjournment

SUMMARY

The pivotal study for this NDA is the SPARC study in 950 patients sponsored by the Applicant. A small EORTC study in 50 patients is submitted as a supportive study.

The SPARC study is a multicenter, multinational, double-blind, placebo-controlled trial with 950 patients with androgen-independent prostate cancer that has failed one (and only one) prior chemotherapy regimen. Patients were randomized 2:1 to Orplatna plus prednisone or placebo plus prednisone. **Placebo patients were not crossed over to Orplatna after progression.** The co-primary efficacy endpoints are progression-free survival (PFS) and overall survival (OS). Progression events were adjudicated by a blinded independent committee of radiologists and oncologists.

The first issue is the definition of one of the two co-primary endpoints, PFS. PFS is defined as a composite endpoint, consisting of radiographic progression, symptomatic progression (pain, analgesics, ECOG performance status, weight loss and other clinical events related to prostate cancer) and skeletal-related events. The FDA has no prior experience with this endpoint. This was clearly communicated to the Applicant during the development phase. FDA will seek ODAC advice on the acceptability of this composite PFS endpoint.

Orplatna was better than placebo on the composite PFS endpoint with a median PFS of 11.1 weeks versus 9.7 weeks (a difference of 10 days) and HR of 0.67 (0.57, 0.77). Orplatna was also better than placebo on PFS defined as only radiologic progression or death with a median PFS of 36.3 weeks versus 20.0 weeks and HR of 0.64 (0.51, 0.81). Whether this will translate into an OS benefit is unknown at this time.

The second issue is that the 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 raises the question whether radiologic PFS could be reliably assessed in this clinical trial.

The third issue regards the assessment of pain progression. Note that pain progression is both part of the composite PFS co-primary endpoint and also the basis for the secondary endpoint of time to pain progression. Because of Orplatna toxicities, it is unlikely that blinding was maintained. In addition, based on a review of background materials provided by the Applicant describing the methods for assessing pain intensity in the SPARC Study, the FDA has determined that the single item Present Pain Intensity Scale (PPI), derived from the McGill Pain Questionnaire (MPQ), has not been adequately validated for use in this study. The MPQ PPI instrument 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. Also in the mitoxantrone study the primary endpoint was reduction in pain intensity, while in the Orplatna study the main pain endpoint is time to pain progression. Finally, the FDA Center for Drug Evaluation and Research standards for pain assessment has changed in the interval. In addition, the SPARC protocol did not specify any plan for pain management and pain progression based on increased analgesic use varied widely between countries. Non-narcotic pain medication usage was not considered in determining pain progression.

The fourth issue is that only 51% of patients had prior docetaxel. Docetaxel is the only drug shown to improve survival in patients with HRPC. All patients should have had prior docetaxel. However, the SPARC trial was started before FDA approval of docetaxel for this use. Subgroup analyses in patients with and without prior docetaxel show that the Orplatna

PFS advantage is maintained in both subgroups. Whether there will be a survival advantage in the subgroup with prior docetaxel remains to be seen.

The fifth issue is whether the FDA should wait for the final survival analysis before taking action on the Orplatna application. An interim analysis of overall survival after 463 deaths does not show that Orplatna is better than placebo. The final analysis of overall survival will occur when there are 700 deaths which is estimated to be near the end of 2007.

The main Orplatna toxicity is hematologic with grade 3-4 neutropenia in 21.1% of patients and grade 4 neutropenia in 4.1% of patients. Infectious episodes occurred in 23.7% of Orplatna patients compared to 11.5% of placebo patients. Grade 3-4 thrombocytopenia occurred in 21.8% of Orplatna patients. Only 2 (0.3%) Orplatna patients had grade 4 thrombocytopenia. Gastrointestinal disorders including nausea, vomiting and diarrhea occurred in 58.5% and 29.1% of Orplatna and placebo patients, respectively. Only 1.9% of Orplatna patients had grade 3-4 diarrhea and 1.6% had grade 3-4 vomiting.

Of note, 14 (2.2%) patients with renal failure were reported in the Orplatna group versus 2 (0.6%) in the placebo group. Serum creatinine elevations were seen in 20.9% (62/313) of the patients in the placebo group and 17.0% (102/629) of the patients in the Orplatna group. A potential interaction between severe hepatic impairment and development of acute renal failure was suggested by a pharmacokinetic study in which 2 of 5 patients with severe hepatic impairment (Child-Pugh Class C) experienced acute renal failure following 1 or more cycles of Orplatna 80 mg/m^2 dx5 q35d. The safety and efficacy of Orplatna in patients with moderate to severe renal impairment, determined by (calculated) creatinine clearance <50 mL/min, have not been established. Biochemical markers for renal function (creatinine and BUN) and hepatic function should be monitored prior to initiating each cycle of treatment and as appropriate.

QUESTIONS FOR THE ODAC

1. PFS in the SPARC trial is a composite endpoint consisting of several components: radiologic progression, skeletal events progression and symptomatic progression, including pain, ECOG performance status, weight loss and other events. The FDA has no experience with this endpoint.

   In the absence of an overall survival advantage, is PFS as defined above an acceptable primary efficacy endpoint in this disease setting? DISCUSS and VOTE.

   Due to time constraints, Question 1 was not addressed by the committee.

Questions 2 and 3 were addressed by the committee together. Each committee member was asked to address each question and provide comments. There was no vote taken for either question. The committee comments regarding radiologic and pain progression are summarized as follows under each question.

2. The two blinded independent radiologists had differing assessments of progression in 336 of 950 (35.4%) patients in the SPARC trial.

   Was radiologic progression reliably assessed in this trial? VOTE.

   - The committee overall felt that the radiologic progress was not reliably assessed, commenting that the number of radiology assessments confounded the actual results of the study.
   - The committee had further reservations in that radiologic progression should be a surrogate for clinical benefit and the sponsor did not demonstrate any survival benefit in this population.
   - The committee felt that given the regulations that accelerated approval must be based on a "robust" endpoint (if it varies from overall survival), the committee felt the trial exhibited methodological flaws (for both pain and radiologic progression) that could lead to a lack of reliability in the data.
   - The committee acknowledged that it is difficult assess progression based on bone scans.

3. Was pain progression reliably assessed in this trial? VOTE.

- The committee agreed that pain model used in the trial did not meet the standard for adequately assessing pain.
- The committee felt that the use of opioids and non-sterioidals confounded the results of the trial.
- The committee suggested that a pain response was easier to assess than a time to pain worsening. h

4. The interim survival analysis in the SPARC trial had a data cut-off date of June 15, 2006. Orplatna was not better than placebo. With a total of 463 deaths Orplatna median survival was 61 weeks and placebo was 57 weeks, HR= 0.9, p=0.296. The 700 deaths required for the final survival analysis are estimated to occur by late 2007. Docetaxel showed a 2.4 month median survival improvement in androgen independent prostate cancer patients without prior chemotherapy (19% had prior estramustine).

   Should the FDA wait for the final survival analysis of the SPARC trial before deciding whether this application is approvable? VOTE.

Each committee member was asked to address each question and provide comments. A vote was taken on each question after comments were lodged. Given the comments above and the absence of the overall survival data the committee was asked simply to take a vote on this question. The results are as follows and the comments are summarized below.

Vote: ***Yes = 12*** ***No = 0*** ***Abstain = 0***

The committee felt overwhelming that without a survival endpoint, Orplatna (satraplatin) reliance on pain progression as measured was not possible in this study to established benefit.

The meeting adjourned at approximately 5:00 p.m.