CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ONCOLOGIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 09/18-19/97

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AGENDA

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products

Oncologic Drugs Advisory Committee
54th Meeting
September 18-19, 1997
Holiday Inn Hotel - Bethesda
Versailles I & II

AGENDA

Thursday, September 18, 1997 **Open Session**

1:00 pm- Call to Order and Opening Remarks
Janice J. Dutcher, MD, Chairman
General Comments
Robert DeLap, Director
Division of Oncology Drug Products
Conflict of Interest Statement
LT Jannette O'Neill-Gonzalez, MHS,
Health Scientist Administrator / Executive Secretary

1:10 pm- Open Public Hearing - One half hour is allocated. The next agenda item will begin immediately if less than half of an hour is needed.

1:45 pm- Applicant's Presentation
NDA Supplement 20-451/S-022 Photofrin® (porfimer sodium) indicated for: a) reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer (NSCLC), and b) treatment of endobronchial carcinoma in situ or microinvasive NSCLC in patients for whom surgery and radiotherapy are not indicated.

QLT Photo Therapeutics Inc.

Introduction	Alexandra Mancini, MSc, Vice President, Regulatory Affairs
Clinical Data for Palliation of Obstructing Lung Cancer	Mohammad Azab, MD, MSc, Vice President, Clinical Research and Medical Afairs

	Clinical Data for Treatment of Superficial Lung Cancer	Eric Edell, MD, Associate Professor of Medicine , Mayo Medical School
	Conclusions	Mohammad Azab, MD, MSc
2:45 pm-	Committee Questions to Applicant	
3:15 pm-	BREAK	
3:25 pm-	FDA Presentation	Grant Williams, MD, FDA Reviewer
	ODAC Discussants	Richard Schilsky, MD, Committee Member
		David Johnson, MD, Committee Member
4:10 pm-	Committee Questions to FDA	
4:40 pm-	Committee Discussion	
5:25 pm-	Adjourn	

8:30 am- Call to Order and Opening remarks
Janice J. Dutcher, MD, Chairman
Conflict of Interest Statement
LT Jannette O'Neill-Gonzalez, MHS,
Health Scientist Administrator / Executive Secretary

8:35 am- Open Public Hearing. One half hour is allocated. The next agenda item will begin immediately if less than half of an hour is needed.

9:05 am- Applicant's Presentation
NDA 20-826 Paxene® (paclitaxel), "indicated after failure of first line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related Kaposi's Sarcoma."

Baker-Norton Pharmaceuticals, Inc.

Introduction	Dr. John Howes, Senior Director, Regulatory Affairs
Kaposi's Sarcoma	Dr. Jerome Groopman, Beth Israel/ Deaconess Medical Center-Boston
Study Protocol: IX-110-081	Dr. Parkash Gill, University of Southern California- San Diego
Comparative Results	Dr. Gregory Harriman, Medical Director
Patient Perspectives	Jim Molina Eric Fletcher Steven Carol Garvin Gray Michael Betts Miki Ilaw

10:05 am- Committee Questions to Applicant

10:35 am- BREAK

10:45 am-	FDA Presentation	Ken Kobayashi, MD, FDA Reviewer
	ODAC Discussants	Donald W. Northfelt, MD, FACP, Guest Expert
		David M. Aboulafia, MD Guest Expert
11:30 am-	Committee Questions to FDA	
12:00 am-	Committee Discussion	
12:45 pm-	Adjourn	

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ONCOLOGIC DRUGS ADVISORY COMMITTEE

CHAIRMAN

Dutcher, Janice, M.D. 6/30/99
Professor of Medicine
Montefiore Medical Center
Albert Einstein Cancer Center
111 East 210th Street
Bronx, New York 10467-2490

EXECUTIVE SECRETARY

Jannette O'Neill-Gonzalez, M.H.S.
Advisors & Consultants Staff, HFD-21
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 443-5455 FAX (301) 443-0699

MEMBERS

Swain, Sandra, M.D. 6/30/98
Medical Director
Comprehensive Breast Center
of Greater Washington
5335 Wisconsin Avenue NW
Suite 440, Washington, D.C. 20015-2034

Krook, James, M.D. 6/30/99
Medical Oncologist
The Duluth Clinic Limited
Internal Medicine Department
400 East Third Street
Duluth, Minnesota 55805

Ozols, Robert, M.D., Ph.D. 6/30/99
Senior Vice President, Med Science
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, Pennsylvania 19111

Johnson, David H., M.D 6/30/00
Director, Division of Medical Oncology
Department of Medicine
Vanderbilt University Medical School
1956 The Vanderbilt Clinic
Nashville, Tennessee 37232

Margolin, Kim A., M.D. 6/30/00
Staff Physician
Department of Medical Oncology
and Therapeutics Research
City of Hope National Medical Center
1500 East Duarte Road
Duarte, California 91010

Raghavan, Derek, M.D., Ph.D. 6/30/00
Associate Director,
University of Southern California
Norris Comprehensive Cancer Center
Head of Medical Oncology
1441 Eastlake Avenue, Rm. 3450
Los Angeles, CA 90033

Schilsky, Richard L., M.D. 6/30/00
Director, University of Chicago
Cancer Research Center
The University of Chicago Medical Center
5841 South Maryland Avenue, MC1140
Chicago, Illinois 60637

Santana, Victor M., M.D. 6/30/01
Associate Professor
Department of Hematology/Oncology
The University of Tennessee
332 North Lauderdale
Memphis, Tennessee 38101

Simon, Richard M., D.Sc. 6/30/01
Chief, Biometric Research Branch
National Cancer Institute
Executive Plaza North, Rm. 739
Bethesda, Maryland 20892

Consumer Representative
E. Carolyn Beaman, M.H.S. 6/30/99
President, Sisters Breast Cancer Network
123 Poinciana Street
Lake Jackson, Texas 77566

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THE FOOD AND DRUG ADMINISTRATION
ONCOLOGIC DRUGS ADVISORY COMMITTEE
September 18 & 19, 1997

GUEST EXPERTS

Donald W. Northfelt, MD, FACP,
Medical Oncologist, Hematologist, and AIDS Primary Care Physician
Assistant Clinical Professor of Medicine
University of California, San Diego
Palm Spring, CA

David M. Aboulafia, MD,
Medical Director, Bailey-Boushay House,
Attending Physician, Section of Hematology/Oncology, Virginia Mason Clinic
Clinical Associate Professor of Medicine, Division of Hematology, University of Washington
Seattle, WA

PATIENT REPRESENTATIVES

Kenneth Giddes - Photofrin®
Lung Cancer Advocate
Durnwoody, Georgia

Michael Marco, BA - Paxene®
AIDS Advocate
Organization: Treatment Action Group: Opportunistic Diseases
New York, NY

CONSUMER REPRESENTATIVE

Desmar Walkes, MD (Substitute)
Director, Private Clinic
Pharmaceutical Science Drugs Advisory Committee

THE FOOD AND DRUG ADMINISTRATION
ONCOLOGIC DRUGS ADVISORY COMMITTEE
September 18 & 19, 1997

Speakers: Open Public Hearing:

September 18, 1997 - Time: 1:10 pm - 1:45 pm

No one registered

September 19, 1997 - Time: 8:35 am - 9:05 am

William Li, MD - 10 minutes
The Angiogenesis Foundation
Cambridge, MA

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SLIDES (DR. LI's PRESENTATION)

Angiogenesis Foundation

Charting New Pathways to Health for the 21st Century

September 19, 1997

Paxene and Antiangiogenesis

I'm Dr. William Li, medical director of the Angiogenesis Foundation, a 501(c)(3) non-profit organization, whose mission is to coordinate global efforts in developing angiogenesis-based therapies. Today I have come to the FDA Oncologic Drugs Advisory Committee Meeting on Paxene (paclitaxel), to direct the Committee's attention to the angiogenesis inhibitory activity of paclitaxel, a property which we believe is under-recognized. The Committee should consider that Paxene's antiangiogenic effect may contribute to its cytotoxic effect on tumor cells.

Paclitaxel is an effective cancer chemotherapeutic agent that has been used to treat refractory ovarian cancer, metastatic breast cancer, advanced head & neck cancer, non-small cell lung cancer, and malignant melanoma. Several clinical trials suggest its effectiveness in regressing AIDS-associated Kaposi's sarcoma.

Paclitaxel has unique mechanisms of action. The mechanism commonly cited is its binding to the β2 subunit of tubulin. This prevents depolymerization and promotes stabilization of microtubules. Because of this, paclitaxel inhibits mitotic spindle formation, the G2 and M phase of the cell cycle, cell proliferation, cell motility and chemotaxis. This mechanism is thought to be directly responsible for paclitaxel's anticancer effect.

However, there is another mechanism by which paclitaxel inhibits tumor growth. Paclitaxel also inhibits angiogenesis, the process of new blood vessel formation.

Solid tumor growth is dependent upon angiogenesis. Without a new blood supply, tumors are restricted to a small size (< 2 mm in diameter). Once angiogenesis is initiated by tumor cells, the new vessels bring oxygen, nutrients and survival factors that allow for exponential tumor growth, invasion and metastases. "Antiangiogenesis" — designed to inhibit this process — is a new therapeutic modality being developed by pharmaceutical companies worldwide, and by the National Cancer Institute. We believe that paclitaxel's antiangiogenic activity also contributes to its anti-tumor activity.

Paclitaxel inhibits angiogenesis by at least three mechanisms: (1) it inhibits endothelial cell proliferation; (2) it inhibits endothelial cell locomotion; and (3) it inhibits protease production by endothelial cells, including the production of collagenase, which dissolves the extracellular matrix surrounding new blood vessels. Paclitaxel inhibits angiogenesis in experimental systems such as the chicken chorioallantoic membrane and *in vitro* cultures of capillary endothelial cells. Studies by Ernest Brahn at UCLA also show that paclitaxel can inhibit angiogenesis in an animal model of collagen-induced arthritis. Companies such as Bristol-Myers Squibb and Angiotech Inc. have specifically referred to antiangiogenesis as one activity of paclitaxel.

The Angiogenesis Foundation, Inc.
P.O Box 383011
Cambridge, MA 02238
617.644.3564 tel

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How might this information influence the Committee's views of Paxene?

First, Paxene's antiangiogenic activity lends validity to its rationale for treating Kaposi's sarcoma. KS lesions are angiogenic, composed of vascular-like spindle cells and secrete at least 6 angiogenic cytokines, including basic fibroblast growth factor, vascular endothelial growth factor, platelet-derived growth factor, interleukin-6, transforming growth factor-b, GM-CSF, and the HIV-Tat protein. Therefore, antiangiogenesis is a rational approach to treating KS.

Second, because of its antiangiogenic activity, Paxene may have promise for treating other angiogenesis-dependent diseases, including rheumatoid arthritis, diabetic retinopathy, psoriasis, and solid tumors. Further studies need to be conducted. Until such studies are completed, we believe that appropriate cautions for the off-label use of Paxene should be developed.

Third, there may be valuable lessons to be learned from other angiogenesis-inhibitor drugs, such as TNP-470, thalidomide, marimastat, and interferon-alpha. With these drugs we are learning that: (1) long-term therapy is needed for efficacy; (2) the optimal biological dose may be lower than the maximal tolerated dose; and (3) the detection of angiogenic cytokines in blood, urine and cerebrospinal fluid may serve as useful surrogate markers to moniter therapy.

Fourth, if approval is given, during the post-marketing surveillance period for Paxene, we encourage physicians to be alert to possible unanticipated, beneficial antiangiogenic effects, such as the inhibition of diabetic retinopathy or psoriasis in Paxene-treated AIDS patients with these co-morbid conditions. There may also be unanticipated adverse effects due to antiangiogenesis, such as the inhibition of collateral formation in coronary artery disease or the delay of wound healing after surgery.

In summary: we wish to emphasize to the Committee that Paxene's effects include the inhibition of angiogenesis. This lends validity to its use for treating Kaposi's sarcoma, opens up new potential applications of this drug, and merits further specific examination for its effects as an antiangiogenic agent.

PRESENTED BY: William W. Li, M.D. (9/19/97)
Medical Director, the Angiogenesis Foundation
Tel: (617) 644-3564
Fax: (617) 576-2728

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DATE OF MEETING: 09/18-19/97

QUESTIONS

Questions for the ODAC

NDA 20-451 /SE1-002
Photofrin® (porfirmer sodium) for Injection
September 18, 1997

Obstructing Lung Cancer Indication

1. Two prospective, randomized trials (P503 with 141 patients and P17 with 70 patients) compared Photodynamic Therapy with Photofrin® (PDT) to Nd:YAG laser therapy in patients with obstructing non-small cell lung cancer (NSCLC). The Applicant's analysis of 'month 1 response rate' (the rate of increasing the diameter of the obstructed lumen by at least 50% from baseline on days 18-45) for Photofrin® was 42% in Trial P503 and 61% in trial P17. In each trial the numerical response rate was higher on the PDT arm than on the Nd:YAG arm. This analysis and the FDA analysis of response, which included all data on or after day 18, are summarized in the table below. Whether statistical comparisons between the arms of these trials would be appropriate is debatable: the endpoints and analysis plans were retrospectively determined, follow-up was asymmetric on the study arms in Trial P503, and Trial P17 was stopped prematurely.

LUMINAL RESPONSE
Applicant 'Month 1' and FDA 'Day 18 and after' analyses

	APPLICANT ANALYSIS Response on days[a] 18-45 (Month 1)		FDA ANALYSIS Best response on days[b] ≥ 18	
	PDT	**YAG**	**PDT**	**YAG**
Trial P503	61% (42/69) p = 0.002[c]	35% (25/72)	64% (44/69) p = 0.09[c]	49% (35/72)
Trial P17	42% (14/33) p = 0.04[c]	19% (7/37)	52% (17/33) p = 0.01[c]	22% (8/37)

[a] Day measured from day of last laser administration on both arms; includes course 1 data only.

[b] Day measured from day of first laser administration on both arms; includes data from all courses.

[c] Fisher's exact test.

A third to a fifth of the patients reported an improvement in dyspnea, cough, and/or hemoptysis at one month. The Applicant also performed an evaluation of individual patient records for evidence of significant clinical benefit from therapy. Patients must have demonstrated either marked symptom improvement on some occasion, or sustained improvement of symptoms or sustained objective response. In these two trials the Applicant found that in 36 of the 102 patients randomized to PDT (and also in 23 of 109 patients randomized to Nd:YAG) such clinical benefit could be demonstrated. After review of the 36 individual cases on the PDT arm, the FDA reviewer agreed that in 33 cases (32%) clinical benefit could be demonstrated.

Do these 2 trials serve as adequate and well controlled trials demonstrating the efficacy of Photofrin® for treatment of patients with partially or completely obstructing endobronchial non-small cell lung cancer?

2. There was more toxicity on the PDT arm; in the combined database from the two trials, photosensitivity, psychiatric symptoms, bronchitis and dyspnea were significantly more common on PDT. There were more life-threatening events on PDT (19 vs. 8), mostly pulmonary events (predominantly hemoptysis and respiratory insufficiency). The rate of Fatal Massive Hemoptysis (FMH) in the PDT group was about twice that of the control group in studies of PDT versus Nd:YAG (10% for PDT vs. 6% for Nd:YAG) and in studies comparing PDT plus Radiation Therapy (XRT) versus Radiation Therapy alone (17% for PDT plus XRT versus 9% for XRT alone). These differences were not statistically significant, but the studies were not large. Despite these findings there was no difference between the PDT arm and the Nd:YAG arm in either survival or in the number of deaths within 30 days of a procedure (16% on PDT versus 17% on Nd:YAG).

Considering the balance of efficacy and toxicity demonstrated in these trials, should Photofrin® by approved for: <u>reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small cell lung cancer (NSCLC)</u>?

Superficial Lung Cancer Indication

1. The Applicant submitted data on 100 patients treated with Photofrin® in 3 single-arm trials in early lung cancer (P505, P506, and P507). The Applicant determined that in 24 of these patients (designated INDICATION patients) both surgery and radiation therapy were contraindicated.[1] In this INDICATION group, the reasons for the inoperable status included prior resection (14 patients), poor pulmonary function (11 patients), and inability to resect due tumor location (12 patients). Eighteen patients had more than one reason for inoperable status. Median FEV1 in the INDICATION group was 1.0 L. Reasons for not receiving Radiation Therapy included having previously received high-dose XRT (9 patients), poor pulmonary function (FEV1<0.8L) (7 patients), multifocal disease (8 patients) and poor medical condition (1 patient).

The Applicant has selected a group of patients with early lung cancer in whom surgery and radiation therapy are said to be contraindicated. Do the 24 INDICATION patients represent a group of patients with no standard therapeutic option ? If not, can you recommend criteria for selecting such a group?

2. Thirty-five (44%) patients in the overall population developed recurrence. Median TTR was 2.8 years in the study population and 2.7 years in the INDICATION group. Median survival was 3.5 years (3.4 years in the INDICATION group). Thirty-one percent of the study population and 29% of the INDICATION group were documented to have died of cancer. Median disease-specific survival was 5.7 years for the group overall, and could not be calculated for the INDICATION group. Eight percent of patients experienced severe and 6% life-threatening adverse events. Most were either from photosensitivity or from pulmonary events.

Should Photofrin be approved for <u>treatment of endobronchial carcinoma *in situ* or microinvasive NSCLC in patients for whom surgery and radiotherapy are not indicated</u> ?

[1] Sum of numbers exceeds number of patients; some patients had multiple reasons for not being candidates for surgery and/or radiation therapy.

Questions for the ODAC

Paxene®
NDA 20-826
September 19, 1997

1. **Is the Paxene® study size of 89 patients adequate for approval of a drug for use "after failure of first line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related Kaposi's sarcoma"?**

2. The Paxene® study resulted in a 42% objective response rate in 89 patients (ITT analysis), using the protocol-specified criteria (Table 1). In an analysis including only eligible patients, the objective response rate was 46% (Table 2). Median response duration was 128 days, and median time to progression was 164 days (Table 3). The reviewer's assessment of photographic data is shown in Table 4.

Table 1. Intent to treat analysis of overall response in cutaneous lesions

response	FDA		applicant (9/16/97)	
	count	%	count	%
complete response	0	0	2	2
partial response	37	42	39	44
stable disease	16	18	29	33
progressive disease	22	25	5	6
not evaluable	14	16	14	16
total	89	100	89	100

Table 2. FDA eligible patients analysis

response	count	%
complete response	0	0
partial response	36	46
stable disease	13	16
progressive disease	20	25
not evaluable	10	13
total	79	100

Table 3. Longitudinal response parameters (n=89)

	FDA	applicant	
parameter	median	median	95% c.i.
duration of response, days	128		
time to response, days	34	60	50-105
time to progression, days	164	231	293-inestimable

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Table 4. Reviewers' assessment of photographic data

	improved		no improvement		total identified
lesion	count	%	count	%	count
facial lesions	6	24	19	76	25
foot lesions	1	8	12	88	13
lower extremity lymphedema	6	12	45	88	51

Does the Paxene® study show patient benefit based on the 42% cutaneous tumor response rate, the clinical benefit assessments and the QOL assessments?

3. **Is the Paxene® safety acceptable in view of the efficacy results and results available with alternative therapy?**

4. **Is the Paxene® NDA approvable for the indication of use "after failure of first line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related Kaposi's sarcoma"?**