CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ONCOLOGIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 03/19/98

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AGENDA

Food and Drug Administration
Center for Drug Evaluation and Research

Oncologic Drugs Advisory Committee
56th Meeting

Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

Proposed Agenda

March 19-20, 1998

8:00	Call to Order and Opening Remarks	Janice Dutcher, MD Chair, ODAC
	Introduction of Committee Conflict of Interest Statement	Karen M. Templeton-Somers, PhD Acting Executive Secretary, ODAC
8:10	Open Public Hearing I One half hour allocated unless public participation does not last that long.	
	Catherine Adelson Norma Broin - Alliance for Lung Cancer Advocacy, Support and Education	
	NDA 20-509/S-005 Gemzar® (gemcitabine HCl) - Eli Lilly and Company - indicated as a single agent or in combination with cisplatin for the first-line treatment of patients with locally advanced (Stage IIIA or Stage IIIB) or metastatic (Stage IV) non-small cancer of the lung.	
8:40	**Sponsor Presentation**	Eli Lilly and Company
	Introduction	Anders Pedersen, MD
	Overview of Chemotherapy in NSCLC	Larry Einhorn, MD
	Study JHEX	Alan Sandler, MD
	Studies JHBR and JHEZ	Rafael Rosell, MD, PhD
	Summary and Conclusions	Larry Einhorn, MD
9:40	Questions from the Committee	
10:10	Break	
10:30	**FDA Presentation**	Genevieve Schechter, MD FDA Reviewer
		Gang Chen, PhD Statistical Reviewer

11:30	Questions from the Committee	
12:00	Committee Discussion and Vote	
	ODAC Discussants	David H. Johnson, MD ODAC Member
		Kim A. Margolin, MD ODAC Member
12:30	Lunch	

March 19, 1998 - Afternoon Session

NDA 20-896 Xeloda™ (capecitabine) Tablets - Hoffman-LaRoche Inc.
- indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of paclitaxel and an anthracycline-containing chemotherapy.

1:30	**Sponsor Presentation**	Tom Griffin, MD
		Cindy Dinella, Pharm.D.
		Joyce O'Shaughnessy, MD
2:30	Questions from the Committee	
3:00	Break	
3:15	**FDA Presentation**	Alison Martin, MD FDA Reviewer
		Masahiro Takeuchi, Sc.D. Statistical Reviewer
4:15	Questions from the Committee	
4:45	Committee Discussion and Vote	
	ODAC Discussants	Sandra Swain, MD ODAC Member
		George Sledge, MD ODAC Consultant
5:15	Adjourn	

Friday, March 20, 1998 - Morning Session

8:00	Call to Order and Opening Remarks	Janice Dutcher, MD Chair, ODAC
	Introduction of Committee	
	Conflict of Interest Statement	Karen M. Templeton-Somers, PhD Acting Executive Secretary, ODAC
8:10	Open Public Hearing II	

One half hour allocated unless public participation does not last that long.

A. George Forbeck - Eastern Cooperative Oncology Group's Patient Representatives
Phyllis DeAngelis

NDA 20-262/S-026 Taxol® (pacletaxel) Injection
- Bristol-Myers Squibb Pharmaceutical Research Institute
- indicated as first-line therapy for the treatment of advanced carcinoma of the ovary.

8:40	**Sponsor Presentation**	Bristol-Myers Squibb
	Introduction	Dr. R. Canetta
	Chemotherapy in Ovarian Cancer	Dr. S. Williams
	BMS 139-022 GOG Study 111	Dr. D. Tuck
	Summary	Dr. B. Winograd
9:40	Questions from the Committee	
10:10	Break	
10:30	**FDA Presentation**	Susan Honig, MD FDA Reviewer
11:30	Questions from the Committee	
12:00	Committee Discussion and Vote	
	ODAC Discussants	James Krook, MD ODAC Member
12:30	Lunch	

NDA 20-262/S-026 Taxol® (pacletaxel) Injection
- Bristol-Myers Squibb Pharmaceutical Research Institute
- indicated for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative and/or radiation therapy.

1:30	**Sponsor Presentation**	Bristol-Myers Squibb
	Introduction	Dr. R. Canetta
	NSCLC	Dr. J. Ruckdeschel
	BMS 139-165 ECOG Study E5592	Dr. P. Bonomi
	BMS 139-103 ECOG Study 08925	Dr. G. Giaccone
	BMS 139-208	Dr. K. Ferrante
	Integrated Summary	Dr. B. Winograd
2:30	Questions from the Committee	
3:00	Break	
3:15	**FDA Presentation**	Isagani Chico, MD FDA Reviewer
4:15	Questions from the Committee	
4:45	Committee Discussion and Vote	
	ODAC Discussants	Kathy S. Albain, MD ODAC Consultant
		Richard L. Schilsky, MD ODAC Member
5:15	Adjourn	

CHAIRMAN

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March 17, 1998
KTS

Consultants (voting)

for Xeloda™ (capecitabine) Tablets for breast cancer

George Sledge, MD
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Indianapolis, IN 46202

for Taxol® (paclitaxel) Injection for non-small cell lung cancer

Kathy S. Albain, MD
Professor of Medicine
Division of Hematology/Oncology
Loyola University Medical Center
Cancer Center, Room 109
2160 South First Avenue
Maywood, IL 60153

Patient Representatives (voting)

for Gemzar® (gemcitabine HCl) for non-small cell lung cancer

Kenneth Giddes
Dunwoody, Georgia

for Xeloda™ (capecitabine) Tablets for breast cancer

Sandra Zook-Fischler
New York, New York

for Taxol® (paclitaxel) Injection for advanced carcinoma of the ovary

Martha Solonche
New York, New York

Guest Patient Representative (non-voting)

for Taxol® (paclitaxel) Injection for non-small cell lung cancer

Selma Rosen
East Norwich, New York

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ONCOLOGIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 03/19/98

QUESTIONS

Questions to the Committee

March 19, 1998

NDA 20-509/S-005: **Gemzar® (gemcitabine HCl)**
Eli Lilly and Company

Proposed Indication: as a single agent or in combination with cisplatin for the first-line treatment of patients with locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer

FDA Analysis

	JHEX		JHBR		JHEZ	
Treatment	**GP**	**P**	**GP**	**EP**	**G**	**EP**
# Patients	155	154	69	66	72	75
Response Complete	0	0	0	0	0	0
Response Partial	36	10	23	9	7	7
Response Rate	23.2	6.5	33.7	13.6	9.7	9.3
Fishers Exact	p=.0001		p=.012		p=1.0	
Med Resp Dur Mo	8	4.1	8.4	9.6	12.4	5.9
Log Rank	p=.013		p=0.71		p=0.16	
Med TTP Mo	5.5	3.5	5.7	4.2	2.8	3.0
Log Rank	p=.0045		p=.007		p=0.79	
Med Sur Time Mo*	8.7	7.5	8.7	7.0	6.0	7.3
Log Rank	p=.12		p=0.18		p=0.77	

*An updated survival analysis on 522 patients in study JHEX was submitted to the FDA. Complete data on other efficacy parameters, dosing and toxicity for the additional 213 patients was not submitted to the FDA. The MST was 9 months (GP) and 7.5 months (P) with p= .004LR.

Toxicity Study JHEX

	GP	P
Number Of Patients	155	154
Deaths On Drug All/Without Progression	13/5	12/3
Discontinue For ADR	35	23
Hospitalizations /Patients Hospitalized	109/71	74/35
Hb GIII-IV Toxicity	35.4%	4.9%
Neutrophil G III-IV Toxicity	58%	4.9%
Platelet G III-IV Toxicity	50.7%	3.5%
Pts With RBC Transfusions	34.2%	9.7%
# Units RBC Transfused	201	51
Pts With Platelet Transfusions	21.9%	0%
# Units Platelets Transfused	233	0
Pts Hospitalized for Febrile Neutropenia	3.9%	1.3%
Pts With G III-IV Infections	3.3%	0.7%
Renal Toxicity G III Creatinine	5.4%	2.1%
Neuromotor Toxicity G III	5.9%	4.2%
Neuro Hearing Toxicity G III	7.4%	5.6%

QUESTIONS:

1. In study JHEX, analysis of the 309 patients for whom full data has been submitted to the FDA shows no statistically significant difference in survival between the Gemzar/cisplatin and the cisplatin treatment groups (p=0.12 LR).

   In study JHEX, an updated survival analysis on 522 patients shows the Gemzar/cisplatin treatment group has a better MST by 1.5 months (p=0.004). Complete data was not submitted on the 213 additional patients for other efficacy parameters, dosing and toxicity. Thus, the FDA analysis of this study is not complete.

   In the updated survival analysis of study JHEX, there is an unexplained disparity between Europe and North America. In Europe (192 total study patients) the Gemzar/cisplatin regimen MST is 3.1 months better (p=0.0025 LR) and in North America (330 total study patients) the Gemzar/cisplatin regimen MST is 0.7 months better (p=0.157 LR).

   Should this disparity impact our interpretation of the study survival results? If so, how?

2. In the RCT JHEX, does the better efficacy on the Gemzar/ cisplatin treatment arm (especially the 1.5 month longer MST) outweigh the increased toxicity of this regimen?

3. Is Gemzar approvable for use in combination with cisplatin for the palliative treatment of Stage III and Stage IV NSCLC?

4. Is the RCT JHEZ a well controlled clinical trial demonstrating that Gemzar as a single agent is safe and effective for the palliative treatment of NSCLC?

5. Is Gemzar approvable for use as a single agent for the palliative treatment of NSCLC?

Questions to the Committee

March 19, 1998

NDA 20-896: **Xeloda™ (capecitabine)**
Hoffman-LaRoche, Inc.

Proposed Indication: for treatment of patients with metastatic breast cancer after failure of paclitaxel and an anthracycline-containing chemotherapy regimen.

Traditional New Drug Approval

Since the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, sponsors have been required to provide "substantial evidence" that new drugs were not only safe but also effective for the proposed indication. Such evidence must come from "adequate and well-controlled" clinical trials. For traditional new drug approval, efficacy must represent clear patient benefit. For oncology drug approvals, such evidence might include improvement compared to a control (or equivalence to a known effective treatment) in survival, time to progression, tumor-related symptoms, or a valid measure of quality of life. Durable complete responses would also have been an established basis for approval as their correlation with real benefit appears well-established. Partial response rates, however, would not generally be considered an adequate endpoint for demonstrating efficacy because their relationship to clinical benefit is far less clear.

Accelerated Approval

Drugs for serious or life-threatening illnesses may also be approved on the basis of improvement in a surrogate endpoint such as response rate under the Accelerated Approval regulations (21 CFR 314.500, Subpart H). Accelerated Approval may be granted "on the basis of adequate and well-controlled trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely... to predict clinical benefit..." To be eligible for Accelerated Approval, the treatment must represent a therapeutic gain. It must be expected to "provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."

Accelerated Approval comes with a condition: "Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit..." For oncology drugs, this would generally mean committing to perform a Phase 4 comparative study that would provide data on endpoints such as survival, time to progression, and/or tumor-related symptoms. We have allowed this study to be in a phase of disease other than the one for which the drug was approved.

Study SO 14697

Study SO 14697 was a non-comparative, multicenter trial in 162 women with metastatic breast cancer who had progressive disease despite treatment with paclitaxel. The primary efficacy endpoint was the objective response rate in patients with measurable disease. In the 135 women with measurable disease, the response rate was 18.5% (95% C.I.: 12.4%, 26.1%) with a median duration of 154 days (range 63-233)*. The response rate in the 43 patients who had disease resistant to both paclitaxel and an anthracycline was 25.6% (11/43; 95% C.I.: 13.5%, 41.2%), with a median duration of response of 154 days (range 63-233)*.

*Response duration by WHO criteria starts on the first day of treatment. The Agency's analysis dates the onset of response to the first day of documented response.

Questions to the Committee

1. Of the 162 women entered into the pivotal trial, 43 had disease that was resistant to both paclitaxel and an anthracycline.

    a. In the 43 women with breast cancer resistant to both paclitaxel and an anthracycline, is an objective tumor response rate of 25.6% with a median duration of 154 days evidence of meaningful therapeutic benefit over existing treatments?

    b. Are the other patients in the trial supportive of the response rate in this doubly resistant population?

2. Patients who have received certain cumulative doses of anthracyclines and/or anthracenediones could be considered to be intolerant of or poor candidates for further therapy with these agents because of the risk of cardiotoxicity with additional treatment. On 3/17/98, we received data on cumulative doses of anthracyclines and/or anthracenediones received by each patient. In addition to the 43 patients above, there are 48 patients in the paclitaxel resistant and anthracycline exposed group, some of whom could potentially meet this criteria. We are currently analyzing the number of patients and objective response rates in the following groups:

    a. In patients whose breast cancer is resistant to paclitaxel and who have received a minimum cumulative dose of 400 mg/m^2 of doxorubicin equivalents, would Xeloda™ represent a meaningful therapeutic gain over additional treatment with an anthracycline, assuming an overall response rate of 20% when these patients are added to the 43 resistant patients?

    b. In patients whose breast cancer is resistant to paclitaxel and who have received a standard adjuvant regimen resulting in a minimum cumulative dose of 240 mg/m^2 of doxorubicin equivalents, would Xeloda™ represent a meaningful therapeutic gain over additional treatment with an anthracycline, assuming an overall response rate of 20% when these patients are added to the 43 resistant patients and those described in 2a?

3. Is the overall toxicity profile acceptable for women who have resistant disease after treatment with both paclitaxel and an anthracycline?

4. Assuming an overall response rate of 20%, should Xeloda™ receive accelerated approval for the treatment of women with metastatic breast cancer:

   a) resistant to paclitaxel and an anthracycline-containing chemotherapy regimen?

   b) resistant to paclitaxel and who have received a minimum cumulative dose of 400 mg/m^2 of doxorubicin equivalents?

   c) resistant to paclitaxel and who have received a standard adjuvant regimen resulting in a minimum cumulative dose of 240 mg/m^2 of doxorubicin equivalents?

5. The sponsor has submitted a protocol for a randomized trial, "An open-label randomized Phase 3 study of capecitabine in combination with docetaxel (Taxotere) versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer." Eligible patients would be resistant to or have recurrent disease after an anthracycline-containing therapy or have relapsed during or within 6 weeks of an adjuvant anthracycline-containing therapy. A total of 454 patients would be randomized to one of two arms. The primary endpoint is to demonstrate superiority in time to progression in favor of the capecitabine-docetaxel combination arm.

   Would a favorable result with combination therapy in this study confirm the clinical benefit of Xeloda™ in patients with prior chemotherapy?

Questions to the Committee

March 20, 1998

NDA 20-262/SE1-026: **Taxol® (paclitaxel)**
Bristol-Myers Squibb Pharmaceutical Research Institute

Proposed Indication: First-line or second-line therapy for the treatment of advanced carcinoma of the ovary

Study Design:

Data for one multicenter trial, GOG 111 (CA139-022), and literature for two additional trials (EORTC and GOG 132) were submitted for review. GOG 111 was a prospective, randomized comparison of cyclophosphamide and cisplatin versus paclitaxel and cisplatin as first-line therapy of patients with suboptimal Stage III and Stage IV ovarian cancer. The primary endpoint was progression-free survival; survival was the secondary endpoint; response was a tertiary endpoint. The efficacy findings from the study report and from the FDA analysis are presented below:

Table 1. GOG 111 Efficacy

Efficacy Parameter	BMS Analysis			FDA Analysis		
	Cisplatin-paclitaxel	**Cisplatin-CTX**	**p-value**	**Cisplatin-paclitaxel**	**Cisplatin-CTX**	**p-value**
Median survival	35.5 mo	24.2 mo	0.0002	35.5 mo	24.2 mo	0.0002
Median progression-free survival	16.6 mo	13.0 mo	0.0008	15.7 mo	12.6 mo	0.002
Overall clinical response rate	68/113 (60%)	64/127 (50%)	0.153	70/113 (62%)	61/127 (48%)	0.04

QUESTIONS:

1. Is trial GOG 111 an adequate and well-controlled trial demonstrating the efficacy and safety of paclitaxel in combination with cisplatin in patients with advanced stage ovarian cancer?

2. Should paclitaxel in combination with cisplatin be approved for the first-line treatment of patients with advanced ovarian cancer?

Questions to the Committee

March 20, 1998

NDA 20-262/SE1-024: **Taxol® (paclitaxel)** Injection
Bristol-Myers Squibb Pharmaceutical Research Institute

Proposed Indication: Treatment of non-small cell lung cancer in patients who are not candidates for potentially curative and/or radiation therapy

Study Design:

Three randomized, prospective, multicenter clinical trials in more than 1300 patients compared taxol in combination with cisplatin to cisplatin/etoposide in study 165, cisplatin/teniposide in study 103, and a higher dose of cisplatin alone in study 208 with the following efficacy results:

Efficacy Results/FDA Analysis- Taxol Pivotal Studies[a]

	Number of Patients (%)						
	Study 165 (24-hr taxol infusion)			Study 103 (3-hr taxol infusion)		Study 208 (3-hr taxol infusion)	
	T/C (n=198)	HD-T/C (n=201)	C/E (n=200)	T/ C (n=166)	Ten/C (n=166)	T/C (n=190)	C (n=197)
Response rate (p-value)	21% **p=.01[b]**	24% **p=.001[b]**	12% α=.0125	33% **p=.02**	21% α=.05	26% **p=.04**	17% α=.05
Time to Progression Median (months) (p-value)	4.3 p=.05[b]	4.9 **p=.004[b]**	2.7	5.1 p=.72	5.0	4.3 p=.08	3.2
Survival Median (months) (p-value)	9.3 p=.13[b]	10.0 p=.08[b]	7.4	9.5	9.9 p=.80	8.1	8.6 p=.86

T= taxol, C= cisplatin, E= etoposide, Ten= teniposide
[a] areas shaded show statistical significance
[b] versus cisplatin/etoposide, α= .0125

The taxol combination arms in the three trials showed superior response rates compared to the control arms. A significant increase in time to tumor progression was shown only in the HD-taxol/cisplatin arm in study 165. There was no statistically significant difference in overall survival between treatment arms in any of the studies.

The taxol combination arms were more toxic than the cisplatin/etoposide arm in study 165; and compared to a higher dose of cisplatin in study 208. In study 103, the teniposide/cisplatin arm had significantly more hematologic toxicities while the taxol/cisplatin arm had more arthralgia, myalgia and neurosensory events. Adverse events with statistically significant differences are shaded in the following table:

Safety Results- Taxol Pivotal Studies

	Number of Patients (%)						
	Study 165 (24-hr taxol infusion)			Study 103 (3-hr taxol infusion)		Study 208 (3-hr taxol infusion)	
Toxicity	T/C (n=195)	HD-T/C (n=197)	C/E (n=196)	T/ C (n=159)	Ten/C (n=163)	T/C (n=200)	C (n=204)
Neutropenia [a]	144 (74) p=.001	128 (65) p=.06	108 (55)	44 (28)	108 (69) p<.001	90 (46) p<.0001	34 (17)
Fever/Neutropenia	NS	NS	NS	8 (5)	60 (36) p<.0001	8 (4) p=.02	1 (<1)
Thrombocytopenia[a]	1 (1)	9 (5)	9 (5) p=.02	2 (1)	30 (18) p<.0001	1 (<1)	1 (<1)
Hypersensitivity[b]	1 (1)	8 (4) p=.01	1 (1)	2 (1)	1 (1)	15 (7) p=.02	5 (2)
Neurosensory[b]	25 (13)	55 (28) p=.04	15 (8)	14 (9) p=.0003	1 (1)	8 (4)	2 (1)
Arthralgia/Myalgia[c]	40 (21) p=.001	83 (43) p<.001	17 (9)	79 (49) p<.001	28 (17)	92 (46) p<.0001	41 (20)
Diarrhea[c]	67 (34) p=.04	94 (48) p=.005	48 (24)	49 (30)	50 (29)	40 (20) p=.01	22 (11)
Alopecia[b]	128 (66)	151 (77)	130 (67)	143 (90)	144 (88)	174 (87) p<.0001	39 (19)
Ototoxicity[b]	--	--	--	7 (5)	7 (11)	9 (4)	33 (16) p=.0001

T= taxol, C= Cisplatin, E= etoposide, Ten= teniposide, NS= data not submitted

[a] grade IV only
[b] grades III-IV
[c] grades I-IV