# CENTER FOR DRUG EVALUATION AND RESEARCH

**ADVISORY COMMITTEE:** ONCOLOGIC DRUGS ADVISORY COMMITTEE

**DATE OF MEETING:** 12/18-19/97

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## AGENDA

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

***Oncologic Drugs Advisory Committee***
***55th Meeting***
***December 18-19, 1997***
***Holiday Inn Hotel - Bethesda***
***Versailles I , II & III***

# AGENDA

**Thursday, December 18, 1997** **Open Session**

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 Supplement 16-295/S-029 Droxia® (hydroxyurea capsules, USP) "indicated in the treatment of sickle cell anemia in adult patients to prevent painful crises and to reduce the need for blood transfusions."

| | |
|---|---|
| Bristol-Myers Squibb<br>Introduction | Collier A. Smyth, MD<br>Vice President, Medical Affairs |
| Disease | Martin H. Steinberg, MD<br>Director, DNA Laboratory, MSH<br>University of Mississippi |
| Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) | Samuel Charache, MD<br>Principal Investigator<br>Johns Hopkins University, School of Medicine |
| MSH follow-up study | Martin H. Steinberg, MD |

Summary Collier A. Smyth, MD

10:05 am- Committee Questions to Applicant

10:35 am- BREAK

10:50 am- FDA Presentation — Albert Lin, MD, Guest Speaker/ Reviewer

Paul Andrew, PhD
Pharmacologist

ODAC Discussants — James Krook, MD
Committee Member

David Johnson, MD
Committee Member

11:35 am- Committee Questions to FDA

12:05 pm- Committee Discussion

12:35 pm- Lunch Break

1:35 pm- Applicant's Presentation
NDA 20-798 Depocyt® (cytarabine lipid-particle injection) "indicated for the intrathecal treatment of neoplastic meningitis of patients with solid tumors, lymphoma, or leukemia."

DepoTech Corporation
Introduction — David B. Thomas, BA, MA
Senior Vice President, Quality Assurance & Regulatory Affairs

Disease Overview & Phase I Depocyte Trial — Marc V. Chamberline, MD
Staff Physician, Department of Neurology
Southern California Kaiser Permanente

| | |
|---|---|
| Efficacy of Depocyte | J. Wayne Cowens, MD<br>Division Vice President , Product Development |
| Safety of Depocyte | Michael Glantz, MD<br>Associate Professor of Neurology<br>University of Massachusetts, School of Public Health |
| Potential Advantage of Depocyte | Kurt A. Jaeckle, MD<br>Associate Professor, Department of Neurology<br>University of Texas M.D. Anderson Cancer Center |

| | | |
|---|---|---|
| 2:20 pm- | Committee Questions to Applicant | |
| 2:50 pm- | BREAK | |
| 3:05 pm- | FDA Presentation | Steve Hirschfeld, MD<br>FDA Reviewer |
| | ODAC Discussants | Victor Santana, MD<br>Committee Member |
| | | Kim Margolin, MD<br>Committee Member |
| 3:50 pm- | Committee Questions to FDA | |
| 4:20 pm- | Committee Discussion | |
| 4:50 pm- | Adjourn | |

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8:00 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

8:05 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.

8:35 am- Applicant's Presentation
BLA Supplement # 97-0501 Proleukin® (aldesleukin) (recombinant human interlukin-2) "indicated for the treatment of adult patients with metastatic melanoma."

| | |
|---|---|
| Chiron Corporation Introduction | Mary O'Hara, Associate Director Therapeutic Regulatory Affairs |
| Overview of Metastatic Melanoma | Michael Atkins, MD Beth Israel Deaconess Medical Center |
| Efficacy & Safety of Proleukin in Patients with Metastatic Melanoma | Lori Kunkel, MD, Associate Director Clinical Development |
| Conclusion | Mary O'Hara |

9:20 am- Committee Questions to Applicant

9:50 am- BREAK

10:05 am- FDA Presentation — Stephen Litwin, M.D. FDA Reviewer

ODAC Discussants — Derek Raghavan, MD Committee Member

Robert Ozols, MD Committee Member

10:50 am- Committee Questions to FDA

11:20 pm- Committee Discussion

11:50 pm- Lunch Break

1:00 pm- Applicant's Presentation
NDA 20-806 Neomark® (broxuridine for injection) "for use as a cell proliferation marker to determine the labeling index in breast cancer."

| | |
|---|---|
| NeoPharm Inc.<br>Introduction & Overview | William C. Govier, MD, PhD<br>President & CEO, NeoPharm, Inc. |
| Clinical Results | |
| Conclusions | |

1:40 pm- Committee Questions to Applicant

2:10 pm- BREAK

| | | |
|---|---|---|
| 2:25 pm- | FDA Presentation | Karen Johnson, MD,<br>FDA Reviewer |
| | ODAC Discussants | Sandra Swain, MD<br>Committee Member |
| | | Richard Simon, PhD<br>Committee Member |

3:10 pm- Committee Questions to FDA

3:40 pm- Committee Discussion

4:10 pm- Adjourn

**APPEARS THIS WAY**
**ON ORIGINAL**

# 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

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## MEMBERS

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Simon, Richard M., D.Sc. 6/30/01
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National Cancer Institute
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Bethesda, Maryland 20892

Schilsky, Richard L., M.D. 6/30/00
Director, University of Chicago
Cancer Research Center
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Chicago, Illinois 60637

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

## CONSULTANTS

Lawrence S. Lessin, M.D.
Medical Director , Washington Cancer Institute
Washington Hospital Center
Washington, D.C.

Julie M. Vose, MD
Associate Professor
University of Nebraska Medical Center
Omaha, NB

## GUEST EXPERT

Albert Lin, MD--------**Droxia®**
Santa Clara Valley Medical Center
San Jose, CA

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## QUESTIONS

QUESTIONS FOR THE ONCOLOGY DRUGS ADVISORY COMMITTEE

DROXIA NDA 16295 (S029)

DECEMBER 18, 1997

In the MSH Study Droxia appears to decrease the median annual sickle cell crisis rate by 46%, to decrease the number of patients transfused by approximately 30% and to decrease the number of transfusions by approximately 37%.

Although patients with 3 or more crises per year at baseline were eligible, most of the benefit in crisis reduction was restricted to the subgroups with 6 or more crises per year at baseline.

Considering the proposed patient population,

1. Does Droxia have a favorable risk/benefit ratio for the two year observation period in the MSH Study?

2. Does Droxia have a favorable risk/benefit ratio (especially regarding carcinogenicity) for adult life time use?

The Droxia capsules used in the MSH Study are a different formulation than the to be marketed Droxia capsules. The FDA will require verification of the relative bioavailability of the Droxia formulation used in the MSH Study and the to be marketed Droxia formulation. Providing this is satisfactorily accomplished,

3. Does the Committee recommend approval of this SNDA?

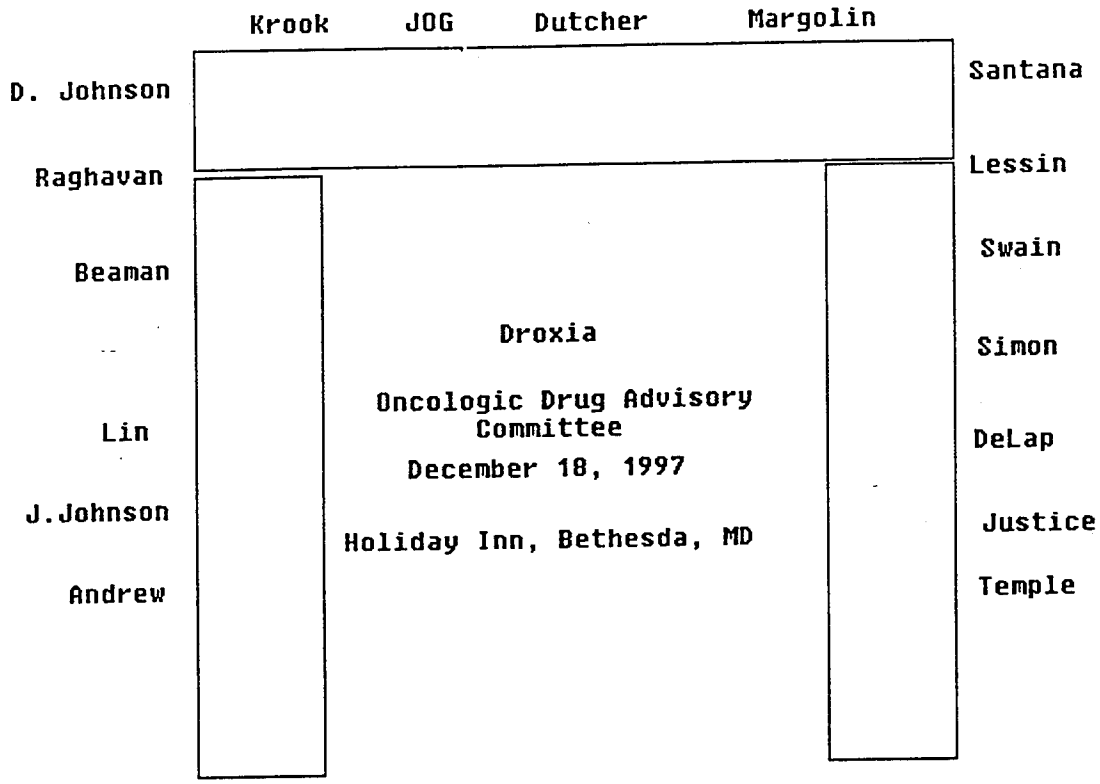
4. If so,

(a) Should the INDICATION be restricted to [redacted] adult patients with sickle cell anemia with moderate to severe recurrent painful crises[redacted]?

(b) Should the INDICATION be restricted to patients with [redacted]at least 3 crises during the last 12 months[redacted] (as per the MSH protocol eligibility requirement)? OR

(c) Should the INDICATION be restricted to patients with [redacted]at least 6 crises during the last 12 months[redacted] (as per the FDA subgroup analysis)?

5. Is the dosing regimen used in the MSH study appropriate for use in the labeling?

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# Questions for the Oncology Drugs Advisory Committee Regarding NDA 20-798 DepoCyt

Carcinomatous meningitis is a late stage complication of solid tumors for which there is no consensus treatment. There are two currently approved medications for intrathecal use, methotrexate and cytarabine. This NDA presents data from 3 small trials of patients with carcinomatous meningitis; 61 patients in a Phase III randomized comparative study, 4 patients in a pharmacokinetic study, and 9 patients in a Phase I study. The efficacy results are summarized in the following tables.

## SUMMARY OF RESPONSE IN SOLID TUMOR PATIENTS TREATED WITH DEPOCYT

| Study | Total # of Solid Tumor Patients | # of DepoCyt Responders | % Response |
|---|---|---|---|
| Phase III | 31 | 8 | ***26*** |
| PK | 4 | 2 | ***50*** |
| Phase I | 11 | 4 | ***36*** |
| Total | 44 | 14 | ***32*** |

## EFFICACY DATA FROM RANDOMIZED TRIAL

| | DepoCyt | Methotrexate | P value |
|---|---|---|---|
| Response Rate (cytologic response with no clinical progression) | 26% (8/31) | 20% (6/30) | ***0.76*** |
| Clinical Response Duration (median, days) | 39 | 26 | ***0.49*** |
| Cytologic Response Duration (median, days) | 39 | 34 | ***0.95*** |
| | | | |
| Clinical Time to Progression (median, days) | 166.5 | 66.5 | ***0.03*** |
| Cytologic Time to Progression (median, days) | 50.5 | 84 | ***0.49*** |
| | | | |
| Survival (median, days) | 421 | 132.5 | ***0.19*** |

1. Can the trials that produced these data be considered adequate and well controlled studies?

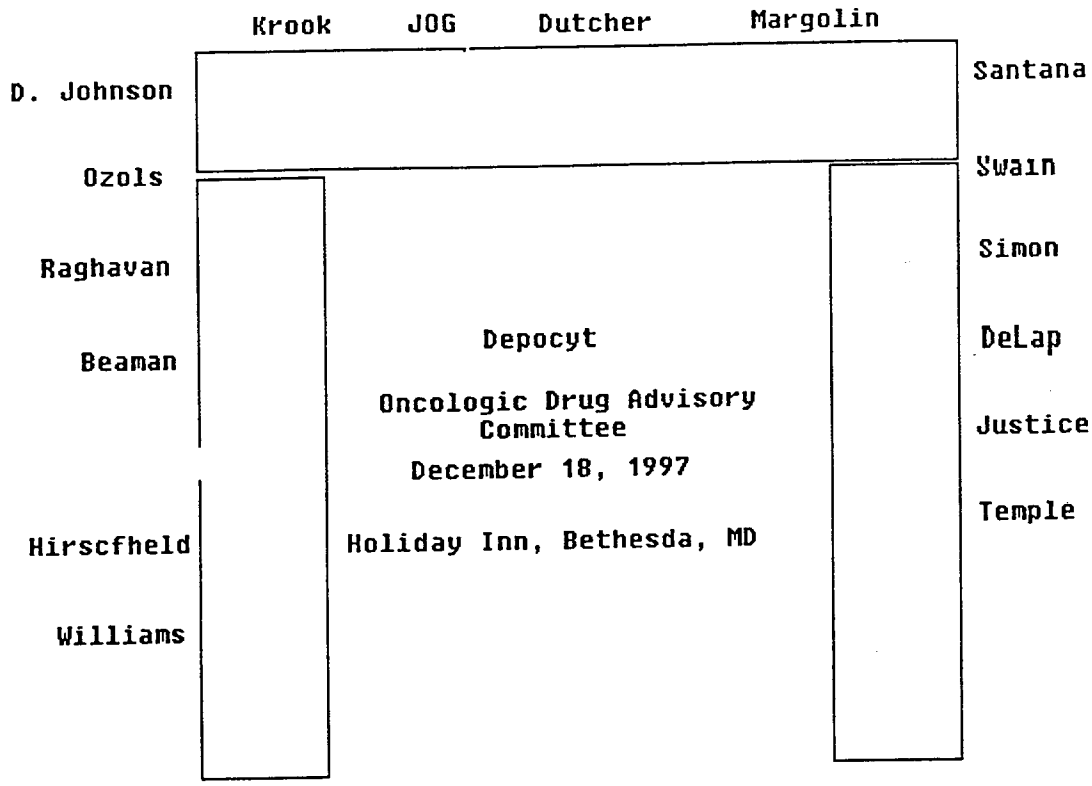
2. In patients with carcinomatous meningitis from solid tumors is the cytological response of the CSF sample in the absence of clinical progression a surrogate endpoint that predicts clinical benefit?

3. The results show a longer Clinical Time to Progression for Depocyt , together with evidence of cytologic responses in the controlled and two other very small trials. Is the clinical endpoint, together with evidence of cytologic response, substantial evidence of the efficacy of DepoCyt?

4. The following table summarizes the incidence of adverse reactions observed in patients from all trials of Depocyt for treatment of carcinomatous meningitis:

| Number (%) of Patients and Cycles | Patients n=59 | Cycles n= 208 |
|---|---|---|
| TOTAL CHEMICAL ARACHNOIDITIS | 38 (64%) | 59 (28%) |
| DEFINITE AND SERIOUS | 8 (14%) | 9 (4%) |
| POSSIBLE AND SERIOUS | 3 (5%) | 4 (2%) |
| DEFINITE | 13 (22%) | 20 (10%) |
| POSSIBLE | 14 (24%) | 26 (13%) |

Given the incidence and severity of chemical arachnoiditis seen with the use of DepoCyt , and considering the efficacy demonstrated by Depocyt (questions 1-3), do you recommend that Depocyt be approved for the treatment of carcinomatous meningitis ?



Questions for # 97-0501; IL-2 in metastatic melanoma

1. This license application describes the results of eight studies, enrolling a total of 270 patients, treated with a comparable dose and schedule of IL-2. Approximately 70% of the study population had visceral disease and more than one site of metastatic disease, 74% of the patients had ECOG PS 0 at baseline and all met stringent entry criteria regarding cardiac and pulmonary function. The pooled data revealed an ORR of 16% and CR rate of 6%. The median duration of response for patients achieving a PR was 8.3 months; 10 of 17 complete responders remain in remission for over 2 years. The ORR for other single agents in this disease ranges from 5-25%, with CR rates of 1-4.5%. Median response durations for CR patients treated with other single agent therapies has been up to 15 months.

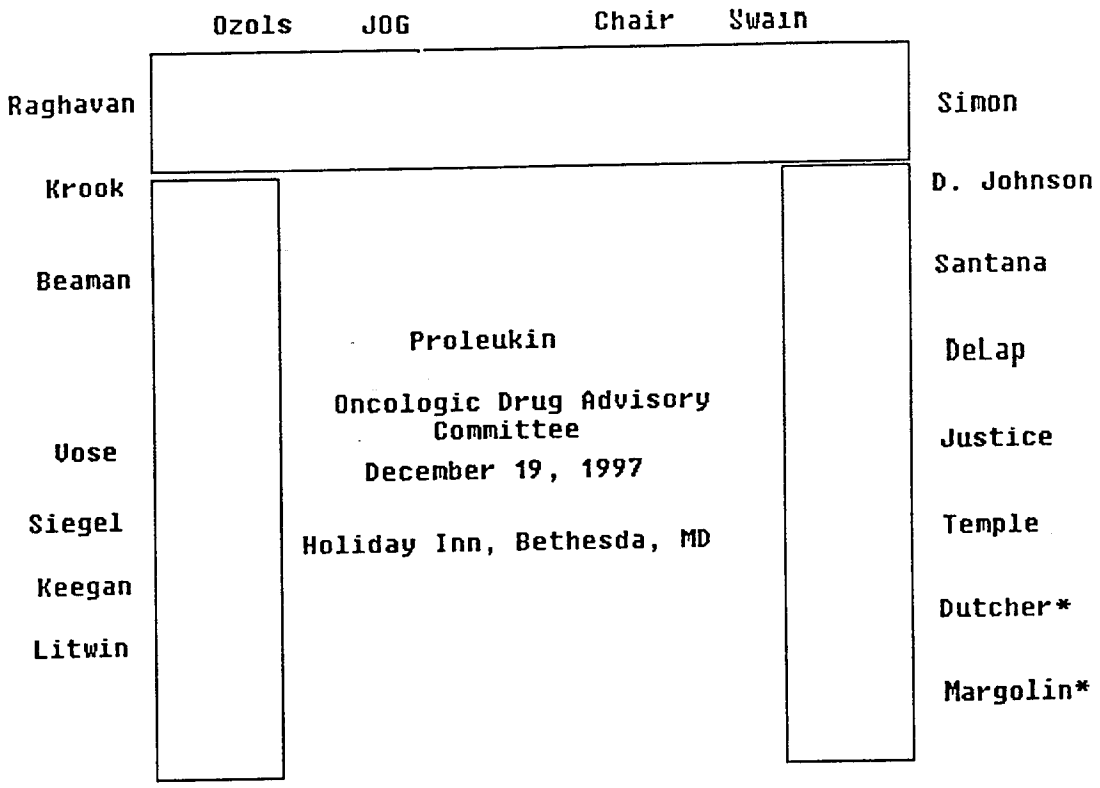
Please discuss: a) the type and quality of the responses observed and b) the population treated in this pooled dataset. Considering the rate, quality, and duration of response, can one conclude that IL-2 provides clinical benefit for patients with metastatic melanoma? If not, can one conclude that IL-2 has induced response which are reasonably likely to predict clinical benefit?

2. In these studies, 95% of the patients experienced grade 3 toxicity and 35% grade 4 toxicity. Treatment required hospitalization in an intensive care setting during the IL-2 administration and in the post-infusion period. The treatment related mortality, 6/270, was not dissimilar to the treatment related mortality of 11/259 observed in the renal cell studies. Mortality in the present dataset was disproportionately higher in patients with ECOG PS 1-2 (5/59) vs ECOG PS 0 (1/211). A logistic regression analysis indicated ECOG PS 0, lack of prior systemic therapy, and greater number of IL-2 courses administered correlated with a higher response rate. Current labeling for use in metastatic Renal Cell Cancer restricts use to intensive care facilities and to patients with normal cardiac and pulmonary function and notes that response rates were higher and mortality lower among patients with ECOG PS 0.

Please discuss the toxicities of IL-2. In view of the responses and the toxicities, should IL-2 be indicated for use in metastatic melanoma? If approved, should the label further restrict the use of IL-2 to specific populations, such as ECOG PS 0?

3. Under the accelerated approval mechanism, drugs and biologics that have been studied for serious and life threatening diseases and "that provide meaningful benefit to patients over existing treatments" may be approved based on a surrogate endpoint that is reasonably likely to predict benefit provided post marketing studies confirm net clinical benefit. Under standard approval, post marketing commitments can be required of the sponsor; e.g., for additional studies to optimize dosing regimen or the patient population.

If there is an accelerated approval, what studies would be appropriate to confirm clinical benefit? If there is a standard approval, what commitments for post marketing studies should be sought?



**Questions for Oncologic Drugs Advisory Committee**
**NDA 20-806: Broxuridine**

Two single-center, uncontrolled studies were submitted in support of using BUdR LI as an *in vivo* cell proliferation marker in patients with primary breast cancer. Protocol procedure involved the intravenous administration of a single dose of broxuridine during a period of 30 minutes in the hour before surgery to remove residual invasive breast cancer. Results in the table below were obtained from a Cox model with a single variable (dichotomized BUdR LI). The results show relative risk of death for patients with BUdR LI greater than, or less than, the breakpoint of 8.0.

## Relative Risk of Death by Study

| Study | n | Breakpoint | Relative Risk of Death (LI > 8.0 vs. ≤ 8.0) | p-value |
|---|---|---|---|---|
| T86-0217 | 163 | 8.0[1] | 13.9 | 0.0004 |
| CYL 93-02 | 28 | NA[2] | NA[2] | |

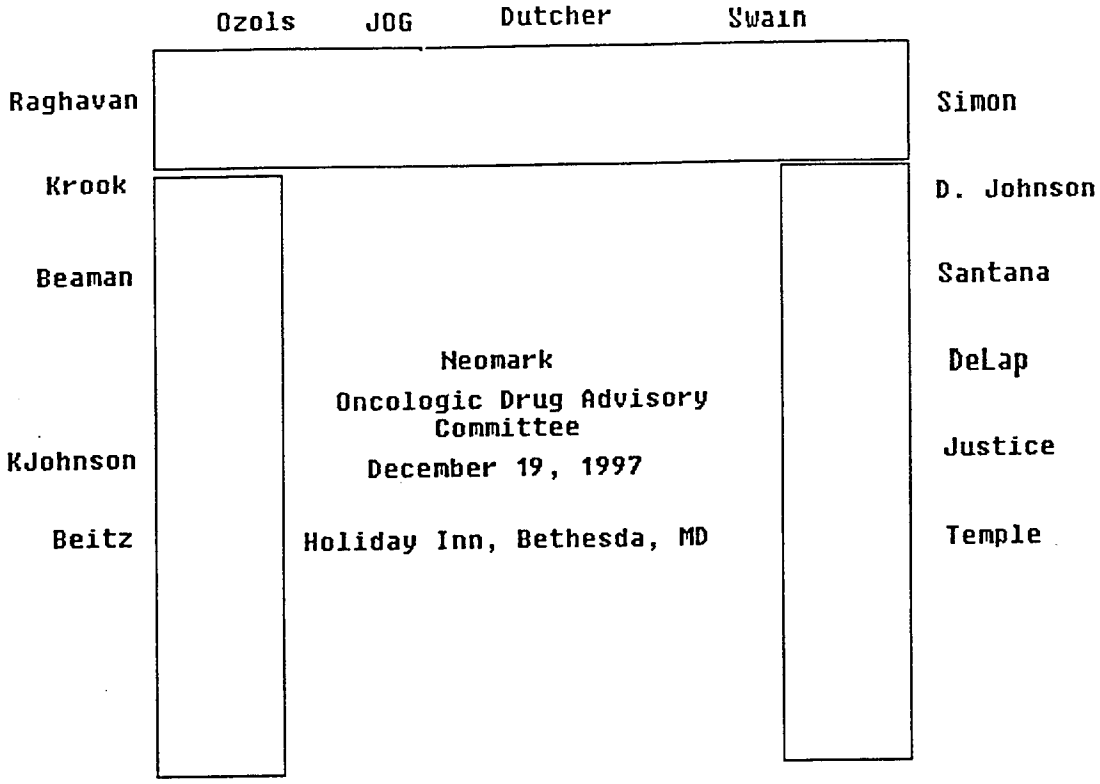
[1] - Based on median value of LI (163 patients in T86-0217
[2] - RR not obtainable from data set, model did not converge

1. The broxuridine labeling index (LI) breakpoint of 8.0 was based on the median value for 163 patients with primary breast cancer evaluated at a single institution (study T86-0217). There is no information in the NDA linking broxuridine LI with choice of therapy, nor is such information likely to be forthcoming. Does the broxuridine LI provide clinically meaningful information for physicians and breast cancer patients?

2. Is there sufficient evidence to conclude that a single, pre-surgical infusion of broxuridine at a dose of 200 mg/m$^2$ for *in vivo* tumor labeling is safe?

3. Do you recommend that broxuridine be approved as an infusion at surgery for LI determination to assign primary breast cancer patients to a higher versus a lower risk group? If not, what additional studies should be performed?

4. If approval for broxuridine is recommended, will a set of Kaplan-Meier survival plots for major prognostic groups (e.g., node-positive) be appropriate for presenting LI-related outcomes in product labeling?

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