REVISED

CLINICAL DATA REVIEW OF NDA 20-798 DepoCyt (liposomal cytarabine)

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Scope of Presentation

- Statement of proposed major issues for discussion
- Brief review of current literature
- Review of selected aspects of current submission
- Summary

Proposed Major Issues for Discussion

- Interpretation of conclusions that can be derived from small datasets
- The value of using cytological response of the cerebrospinal fluid (CSF) as a surrogate endpoint for patients with solid tumors and carcinomatous meningitis (CM)

Review of Literature

- Carcinomatous meningitis (CM), also known as leptomeningeal meningitis (LM) or neoplastic meningitis (CM) is considered a late stage and ominous complication of solid tumors
- Median survival is usually about 3 months following diagnosis
- About 50% of patients die from other causes including systemic disease
- Prognosis dependent upon initial staging and perhaps independent of intervention
- Value of intrathecal therapy is questioned

Estimated Number of Patients ~ 2500 year

Tumor Type	Cases per yr.	Est. cases CM
Breast	180 000	1800
SCLC	34 000	340
Intracranial	17 000	170

Current Therapy

- Radiation
- Systemic chemotherapy
- Intrathecal chemotherapy
  - methotrexate, cytarabine, thiotepa
- Surgical resection for solitary lesions
- Combinations

Clinical Background

There is no consensus on management due to :

- most published series including

  –patients with varying tumor types

  –patients with and without brain parenchymal disease

- difficulties in interpreting studies due to alterations in cerebrospinal fluid (CSF) flow caused by CM

Clinical Background-cont'd

There is no consensus on management due to:

- absence of uniform criteria on how to address clinical or laboratory endpoints

- a reliance on surrogate markers rather than neurologic improvement or survival as study endpoints

Brief Regulatory History

October 1992: A meeting between the sponsor and the FDA proposed a controlled study design that :

- had three separate trials, termed arms, for solid tumors, lymphoma, and leukemia
- primary brain tumor patients were allowed in the solid tumor arm
- in each trial or arm patients to be randomized to one of two treatment groups- DepoCyt or an active control
- the solid tumor control group was IT methotrexate

Regulatory History- cont'd

- response determined by CSF cytology
- quality of life assessment component necessary
- stratification according to tumor type
- minimum of 20 patients per group and 10 in each strata per group

Critical Assumption #1

Intrathecal therapy(IT), and in particular IT therapy with methotrexate at a dose of 10 mg IT 2 x week, is of benefit to patients with carcinomatous meningitis secondary to solid tumors

Primary Endpoint- Cytological Response Defined

- After week 4 (~day 29) CSF pathology negative at single site of choice previously documented to be positive and no clinical evidence of progressive disease.
- Confirmatory sample(s) taken from all previously positive sites between weeks 4 and 5 (~day 32) that is negative
- The definition of positive is cells that are positive for malignancy or suspicious

Primary Endpoint- cont'd Response Defined

- The definition of negative is cells that are atypical or absent
- If a patient meets the above criteria, the patient will be ruled a complete responder and receive study drug for 12 more weeks
- If any CSF sample is positive or if there is clinical progression, the patient will be considered a non-responder and will discontinue study treatment, but will be followed clinically

Critical Assumption # 2

Cytological response is a surrogate marker for patient benefit. In order to validate this assumption, other measures of patient benefit were incorporated into the study design

Study Regimen

- All patients to receive dexamethasone prophylaxis
- Methotrexate group- 10 mg IT 2 x week
- DepoCyt group- 50 mg IT q 14 days
- Assessment at 30 days to determine response
- Continue if response detected or if patient wishes to cross over to other study group

Current Submission- Phase III Study

Proposed	Submitted
• controlled randomized trial	• controlled randomized trial
• 20 patients in each treatment group	• 30 patients in each treatment group
• 10 patients in each strata in each group	• > 10 patients in each strata in each group

Characteristics of 61 Patients Randomized to Treatment

Variable	Values
Age	Median 49 range (20-74)
Gender	44 female, 17 male
Race	52 Caucasians, 5 African-American, 3 Asian, 1 Hispanic
Tumor Types	22 breast, 14 CNS primary, 6 NSCLC, 5 melanoma, 4 SCLC, 10 other
Karnovsky status	median 70 range (50-100)
Geography	31 % from 1 of the 17 study sites

Concomitant Therapy

Patients that received chemotherapy n = 7

Patients that received radiotherapy n = 18

Patients that received concomitant therapy by study drug DepoCyt = 10 methotrexate = 15

Patients that crossed over

Assigned to DepoCyt n = 2

Assigned to methotrexate n = 4

Efficacy

Primary Endpoint-Cytological Response

n = 14/61 (23%)

- 8/44 (18%) females, 6/17 (35%) males
- 4/26 (15%) breast or SCLC, 10/ 35 (29%) other tumor types
- 4/7 (57%) who received concomitant chemotherapy
  - 3 of the 4 were assigned to methotrexate
- 5/18 (28%) who received concomitant radiation
  - 3 of the 5 were assigned to DepoCyt
- 6/19 (32%) from a single study site
- 8/31(26%) randomized to DepoCyt (6/8 female)
- 6/30 (20%) randomized to methotrexate (4/6 male)

Statistical Analysis of Primary Endpoint

- No difference in response rates according to
  - study medication
    - DepoCyt = 26 %, MTX = 20%
  - gender
    - females = 18 %, males = 35 %
      - 4/8 (50%) men and 2/22 (9%) females assigned to MTX were responders (p = 0.029)
  - geography
    - single site = 32 %, all others = 19%
  - tumor strata
    - breast/SCLC = 13 %, all others = 27%

Statistical Analysis of Secondary Endpoints

- No differences in overall survival or clinical duration of response between medication groups or groups based on other variables
- Statistically significant difference in duration of cytological response based on geography (p = < 0.01)
- Statistically significant difference in time to clinical progression based on medication group (p= <0.01) but also gender, race and concomitant treatment effects

Survival Data for All Patients

DepoCyt- Median = 107 days

Methotrexate-Median = 82.5 days

No statistically significant difference

by log-rank test

There were no significant differences in Karnofsky Performance Status, Mental Status, or Quality of Life between treatment groups

Efficacy conclusion

DepoCyt showed activity in patients with carcinomatous meningitis associated with solid tumors and had a response rate that did not statistically differ from a methotrexate based regimen. There was a difference in clinical time to progression, but due to the small sample size and multiple analyses, this cannot necessarily be ascribed to study medication.

Safety

There were significant differences in several types of adverse events

COSTART Term	# of DTC 101 pts.	% of DTC 101 pts.	% of MTX pts.	# of MTX pts.	p-value
ASTHENIA	25	86%	87%	26	
NAUSEA	23	79%	63%	19	0.25
PAIN	20	69%	53%	16	0.28
CONFUSION	16	55%	57%	17	
GAIT ABNORM	16	55%	53%	16	
VOMIT	16	55%	60%	18	
ANOREXIA	13	45%	30%	9	0.29
CONSTIPATION	12	41%	47%	14	
DEATH	12	41%	23%	7	0.17
HYPESTHESIA	12	41%	27%	8	0.26
PAIN CHEST	10	34%	17%	5	0.14
SOMNOLENCE	10	34%	23%	7	
REFLEXES DEC	9	31%	53%	16	0.11
DIZZINESS	8	28%	27%	8	
DYSPNEA	8	28%	13%	4	
ALOPECIA	7	24%	27%	8	
CONVULSION	7	24%	27%	8	
EDEMA PERIPH	7	24%	7%	2	0.079
INCONTIN URIN	7	24%	10%	3	0.18

There was a significantly higher rate of serious adverse events in patients that received DepoCyt compared to methotrexate

Patients with SAE by Study Medication

Study Medication	# of Patients with SAE	# of Patients without SAE	Rate
DepoCyt	24	5	82.7 %
Methotrexate	15	15	50 %

p = 0.013 using Fisher's exact test

There was a trend for more drug related SAEs with DepoCyt

Rate of Patients with a Drug Related SAE by Medication

Study Medication	Drug Related SAE	No Drug Related SAE	Rate
DepoCyt	10	19	34.5 %
Methotrexate	5	26	16.7 %

p = 0.14 using Fisher's exact test

Incidence of Chemical Arachnoiditis

- DepoCyt = 20/29 patients that received medication (69%) or 23/104 (22 %) of total cycles.
  - 6/9 (67%) of cycles without dexamethasone, 17/95 (18%) cycles with dexamethasone ($p < 0.01$)
- Methotrexate = 10/30 patients (33 %) or 13/69.5 (19%) of total cycles
  - 63 % of cycles without dexamethasone, 12% of cycles with dexamethasone ($p < 0.01$)

On a per patient basis the difference between treatment groups was statistically significant favoring methotrexate ($p < 0.01$), but <u>not</u> on a per cycle basis

Analgesic use

- 100 % of the DepoCyt patients and 83% of the methotrexate patients used analgesics while on study. The difference is not statistically significant ($p = 0.1$)
- There was no statistical difference in analgesic use for the the first 60 days on study in total analgesic use or opiate use

Safety Summary

•There were significantly ($p = 0.013$) more serious adverse events per patient with DepoCyt (83%) than with MTX (50%)

•35% of SAEs were thought by investigators to be medication related for DepoCyt while 17% were thought to be medication related for methotrexate ($p = 0.14$).

Safety Summary- cont'd

•The profiles of adverse events were similar for the two treatment groups; however, DepoCyt had a significantly higher incidence of headache, back pain, fever, neck rigidity and chemical arachnoiditis on a per patient basis.

•Treatment with dexamethasone, which was used in both study arms, significantly ameliorated the incidence and severity of chemical arachnoiditis.

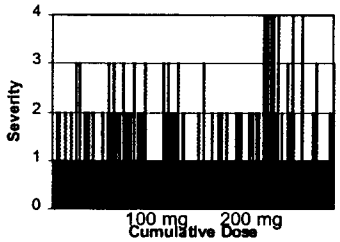
Supporting Study PK

- Study Design
- Patient Population Characteristics
- Efficacy Data
- Safety Data
- Conclusions

Supporting Study Phase I

- Study Design
- Patient Population Characteristics
- Efficacy Data
- Safety Data
- Conclusions

Dose versus Severity in Phase I Patients



Although SAEs could occur at any dose, the highest grade SAEs occurred at a cumulative dose above 200 mg

Efficacy Summary

Study	Total # of Solid Tumor Patients	# of DepoCyt Responders	% Response
Phase III	29	8	*28*
PK	4	2	*50*
Phase I	11	4	*36*
Total	44	14	32

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Integrated Summary of Safety

Frequency of Adverse Events per Patient

	% of Patients
HEADACHE	95%
VOMIT	84%
ASTHENIA	79%
NAUSEA	68%
PAIN BACK	64%
FEVER	63%
PAIN	48%
CONFUS	45%
ANOREXIA	43%
GAIT ABNORM	41%
CONSTIP	38%
PAIN CHEST	34%
ANEMIA	34%
THROMBOCYTOPENIA	30%
HYPESTHESIA	29%
DIZZINESS	29%
DYSPNEA	29%
REFLEXES DEC	27%
DEATH	25%
SOMNOLENCE	25%
CONVULS	25%
DIARRHEA	25%

Integrated Summary of Safety

Frequency of Serious Adverse Events per Patient

COSTART Term	% of Patients
DEATH	35%
HEADACHE	24%
CONVULS	13%
FEVER	13%
NEUTROPENIA	13%
ASTHENIA	11%
CONFUS	9%
NAUSEA	9%
THROMBOCYTOPENIA	9%
VOMIT	9%
DEHYDRAT	7%
MENINGISM	7%
PAIN BACK	7%
DIARRHEA	6%
INTRACRAN HYPERTENS	6%
MENINGITIS	6%
PAIN	6%
PNEUMONIA	6%
SOMNOLENCE	6%

Frequency of Chemical Arachnoiditis

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%)

Summary of Risks and Benefits

- DepoCyt has activity that is not statistically different from methotrexate in patients with solid tumors who have carcinomatous meningitis
- DepoCyt has a statistically significant higher incidence per patient of adverse events and SAEs than methotrexate
- The dosing schedule of DepoCyt is more convenient than that of methotrexate

Summary of Risks and Benefits- cont'd

- The types of adverse events that occurred were similar to those seen with other intrathecal medication
- The adverse events are generally amenable to treatment
- Dexamethasone will significantly decrease, but not prevent, the incidence of chemical arachnoiditis
- Dexamethasone prophylaxis, and careful observation must be employed when using DepoCyt

Comments on Cytological Response

Using the study data for all patients, it was not possible to demonstrate a correlation between :

- cytological time to progression or
- duration of cytological response

and overall survival.

In addition, it was not possible to demonstrate a correlation between :

- cytological time to progression and
- clinical time to progression.

Conclusion: There was insufficient data in this study to provide definitive comment on the utility of cytological response as a marker of patient benefit for patients with solid tumors who have carcinomatous meningitis.

Comment on Clinical Time to Progression following Cytological Response

Examining the relationship for all patients between time to clinical progression (median = 100 days) and overall survival (median = 279 days) shows that :

they differ significantly ($p = 0.027$) but

- there is a significant correlation between them with a correlation coefficient $r = 0.6$ and $p = 0.024$

Consideration for Future Studies

Time to clinical progression should be considered as a potential endpoint for future studies

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Phase III Randomized Trial: Effect of Dexamethasone on Chemical Arachnoiditis

No Cycles No Cycles w/ w/o DEX	DepoCyt n=159 w/ DEX (n=145) No. (%)	DepoCyt n=159 w/o DEX (n=14) No. (%)	MTX n=69.5 w/ DEX (n=60) No. (%)	MTX n=69.5 w/o DEX (n=9.5) No. (%)	Ara-C n=44 w/ DEX (n=37) No. (%)	Ara-C n=44 w/o DEX (n=7) No. (%)
Total Episodes	35 (24)	9 (64)	7 (12)	6 (63)	5 (14)	1 (14)
Mild	10 (7)	2 (20)	2 (3)	1 (11)	1 (3)	0
Moderate	16 (10)	4 (29)	3 (5)	5 (53)	3 (8)	0
Severe	7 (5)	3 (21)	2 (3)	0	1 (3)	1 (14)
Life-Threatening	2 (2)	0	0	0	0	0

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Phase III: Solid Tumor Arm Patient Demographics (3 of 3)

Characteristic	DepoCyt (n=31)	MTX (n=30)
Progressive Systemic Disease	10	11
Number of Extraneural Metastatic Sites		
0	6	8
1-3	22	19
>3	3	3
Previous IT Therapy	2	2
Previous RT	28	28
Concurrent RT	4	8
Concurrent Systemic Chemotherapy	8	5

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Phase III: Solid Tumor Arm - DepoCyt Patients Without Positive CSF at Baseline or Adequate CSF Follow-up

Patient ID	Time to Clinical Progression (Days)	Survival (Days)
15-SB-010	105	105
01-SO-052	354	354
17-SO-055	237	237
19-SO-062	96	96
Responders* (median)	100	279
Non-Responders (median)	28	73

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* Unadjusted Medians

Phase III: Response by Tumor Type No. Responders (No. Evaluable)

Tumor Type	DepoCyt	MTX
Primary Brain	5 (7)	2 (7)
Breast Carcinoma	2 (8)	0 (10)
Melanoma	0 (1)	1 (3)
NSCLC	0 (2)	1 (3)
Other Solid Tumor	1 (4)	0 (4)
SCLC	0 (0)	2 (2)

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Other Tumor Types: Unknown Primary, Gall Bladder, Renal, Cervical (2), Colorectal, Ovarian, Lymph nodes

Phase III Trial: Solid Tumor Arm Incidence of Chemical Arachnoiditis Across Cycles

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle ≥5
No. Patients Receiving this Cycle of Treatment	N=29	N=23	N=19	N=12	N=19
No. CA Episodes (%)	15 (52)	4 (17)	4 (17)	0	0

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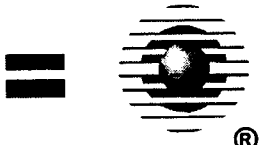
Phase III Randomized Trial: Clinical Disease Progression CRF

Neurological Assessment

Do NOT complete at Baseline or during Induction. This section should ONLY be completed at End of Induction (Visit 6, onwards)

Is there evidence of neurological disease progression relevant to leptomeningeal metastasis sufficient to contemplate a change in Intra-CSF chemotherapy?

- ☐ **NO (continue with study protocol)**
- ☐ **YES (disease progression: patient should discontinue study treatment after discussion with medical monitor)**



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DepoCyt™ (Cytarabine Liposome Injection)

NDA 20-798

Oncologic Drugs Advisory Committee
December 18, 1997

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Introduction and Indication

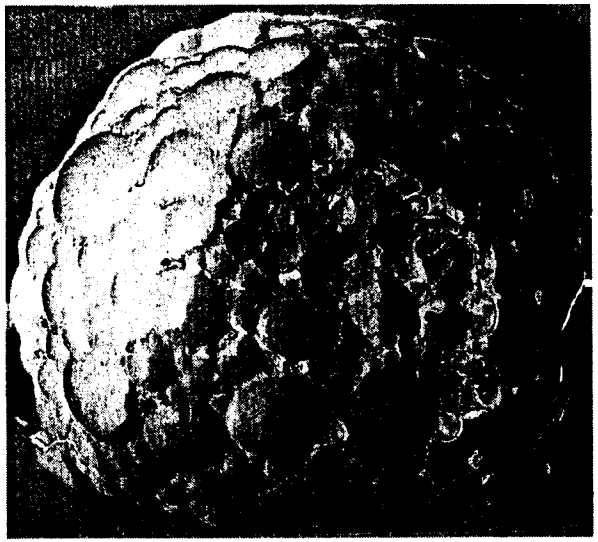
David B. Thomas, M.A.
Senior Vice President
Quality Assurance & Regulatory Affairs

DepoTech Corporation

Indication

DepoCyt is indicated for treatment of Neoplastic Meningitis from Solid Tumors

DepoCyt



- Sustained release suspension of cytarabine
- Cytarabine is encapsulated in multivesicular lipid particles
- Cytarabine is released by erosion or reorganization of chamber walls
- DepoCyt particles are phospholipids and cholesterol and cleared by lipid pathway
- DepoCyt is formulated for intrathecal injection

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Development Background

- **Development work was carried out by DepoTech Corporation and Chiron Corporation**

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DepoCyt Regulatory History

- Phase I IT trial of NM completed 1/93
- Agreement on Phase III trial
  - Trial Size
  - Filing strategy
- Phase III trial 3/94 - ongoing
- Phase IV trial opened 6/96

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Agenda

Topic	Presenter
I. Introduction and Indication	David B. Thomas, M.A. Senior Vice President Quality Assurance and Regulatory Affairs DepoTech Corporation
II. Background of Neoplastic Meningitis: Prior Randomized Trials, Phase I Trial, Pharmacology, and Safety	Marc C. Chamberlain, M.D. Department of Neurology Southern California Kaiser Permanente
III. Efficacy of DepoCyt (Phase I and III Trial Results)	J. Wayne Cowens, M.D. Division Vice President Product Development Chiron Corporation

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Agenda

Topic	Presenter
IV. Safety of DepoCyt (Phase III Trial)	Michael J. Glantz, M.D. Department of Medicine Brown University School of Medicine
V. Potential Advantages of DepoCyt	Kurt A. Jaeckle, M.D. Associate Professor Department of Neuro-Oncology University of Texas M.D. Anderson Cancer Center

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Disease Overview and Phase I DepoCyt Trial

Marc C. Chamberlain, M.D.
Department of Neurology

Southern California Kaiser Permanente

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Topics

- **Neoplastic Meningitis (NM) Overview**
- **Review of Prior Randomized Trials**
- **Pharmacokinetic and Safety Results of DepoCyt Phase I Trial**

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Leptomeningeal Metastases: Epidemiology

Incidence	
Overall (autopsy)	5%
Leukemia	8-12%
Lymphoma (AIDS-related)	7-15% (30-40%)
Solid Tumor	1-5%

7,000 to 9,000 newly diagnosed patients in the U.S.

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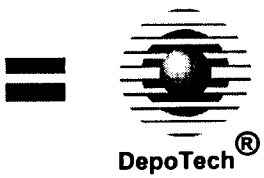
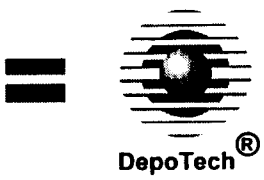
Neoplastic Meningitis: Tumor Burden

- **Status systemic disease**
  - **Progressive disease** **70%**
  - **Remission** **20%**
  - **Initial presentation** **5-10%**
- **Concurrent CNS disease**
  - **Brain parenchymal metastases** **18%**
  - **Epidural spinal cord metastases** **16%**
  - **Brain and epidural metastases** **1%**



Neoplastic Meningitis: Neurologic Presentation

• Spinal cord dysfunction	60%
• Cranial neuropathies	36%
• Multilevel dysfunction	25%
• Hemispheric dysfunction	16%
• Nonfocal	12%



Neoplastic Meningitis: Methods of Evaluation

- CSF Analysis
- Brain Imaging
- Spine Imaging
- Radioisotope CSF Flow Study

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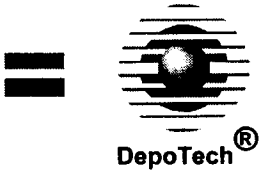
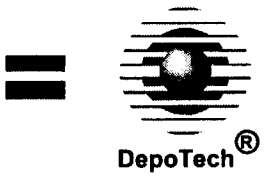


Neoplastic Meningitis: Standard Therapy

- Radiotherapy
  - Symptomatic or bulky disease
  - CSF flow obstruction
- Intra-CSF chemotherapy
  - Methotrexate
  - Cytarabine
  - Thiotepa
- Concurrent systemic chemotherapy



Neoplastic Meningitis: Prior Randomized Trials

- **Hitchens RN et al**
  - **Comparison MTX vs MTX + Ara-C**
  - **44 patients enrolled**
- **Definition of Response**
  - **Complete**
    - » **Negative CSF cytology (1 site)**
    - » **Normal CSF glucose, protein**
    - » **Improved neurological examination**

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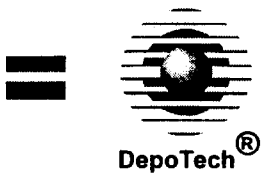
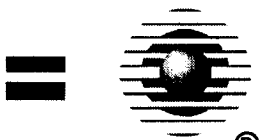
Neoplastic Meningitis: Prior Randomized Trials
Results: Hitchens Study

- Complete response 17%
- Cytologic response 50%
- Median survival
  - MTX 84 days
  - MTX + Ara-C 49 days
  - Responders 133 days
  - Non-responders 49 days



Neoplastic Meningitis: Prior Randomized Trials

- **Grossman SA et al**
  - **Comparison of MTX vs Thiotepa**
  - **59 patients enrolled**
- **Definition of Response**
  - **Complete**
    - » **Negative CSF cytology (2 sites)**
    - » **Normal CSF glucose, protein**
    - » **Normal neurological examination**
    - » **Normal brain and spine imaging**



Neoplastic Meningitis: Prior Randomized Trials
Results: Grossman study

● Complete response	0%
● Cytologic response	
– Overall	31%
– Solid Tumors	21%
● Time to tumor progression	
– Overall	75% @ 8 wks
● Median survival	
– MTX	111 days
– Thiotepa	99 days

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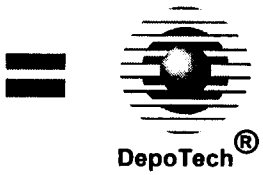
Neoplastic Meningitis: Prior Randomized Trials
Conclusions

- Treatment is palliative
  - Neurological deficits rarely improve
  - Intent is stabilization of neurologic function
- Results of treatment comparable
- Chemical meningitis is the primary toxicity



DepoCyt Phase I Trial: Patient Demographics

Variable	Parameter	Total
Sex	Male	12
	Female	7
Age (years)	Median	41
Primary Cancer	Solid Tumor	11
	Lymphoma	6
	Leukemia	2
ECOG Performance Status	Median	1.0
Previous intra-CSF Treatment		18
Baseline CSF Cytology (Solid Tumor)	Positive	16 (8)

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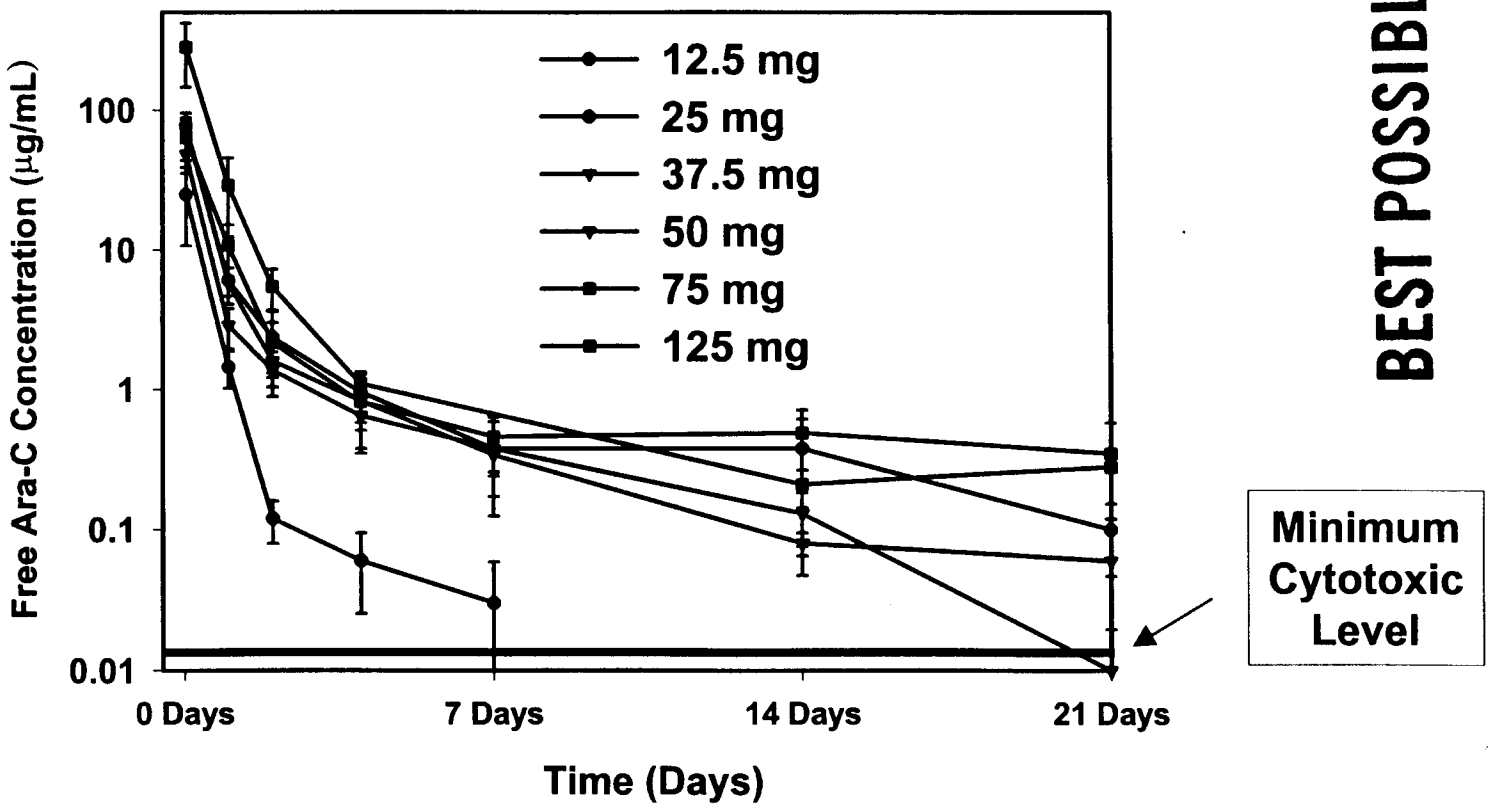
DepoCyt Ventricular CSF Pharmacokinetics: Free Ara-C



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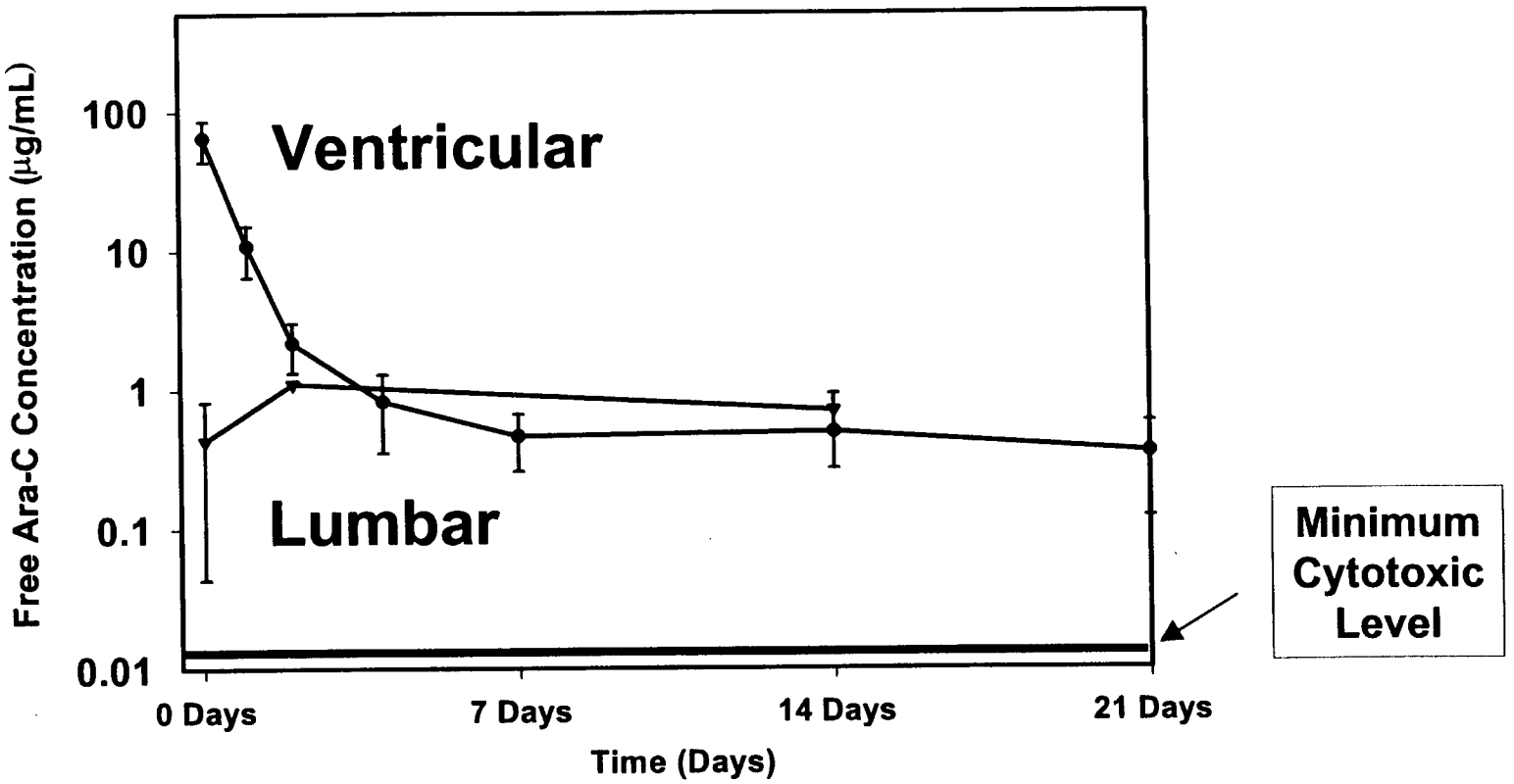
DepoCyt 75 mg: Ventricular vs Lumbar CSF Pharmacokinetics Following Intraventricular Administration



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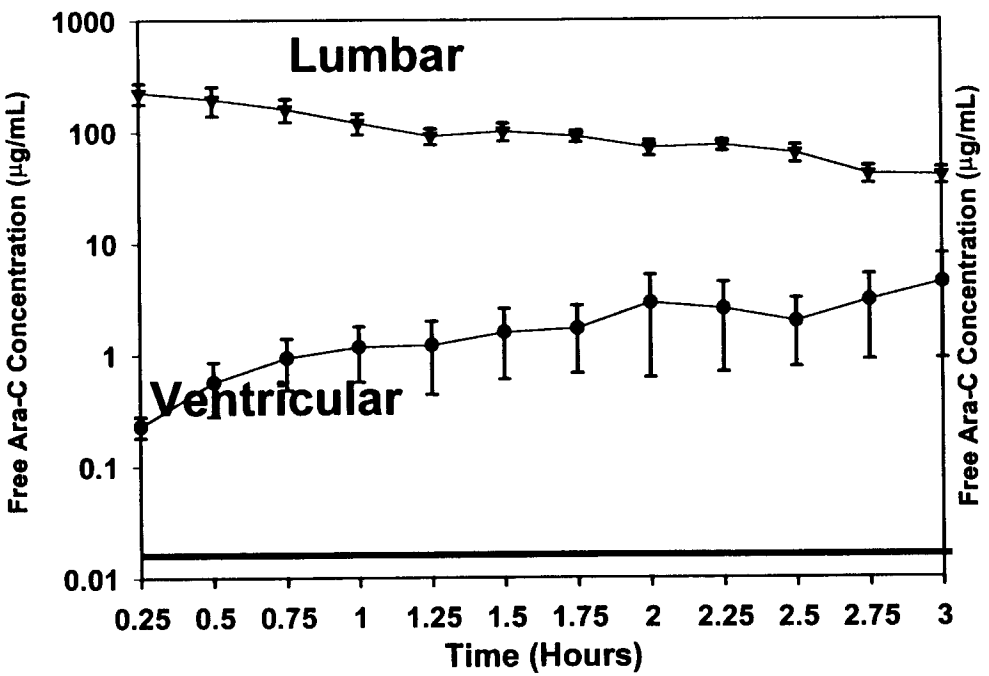
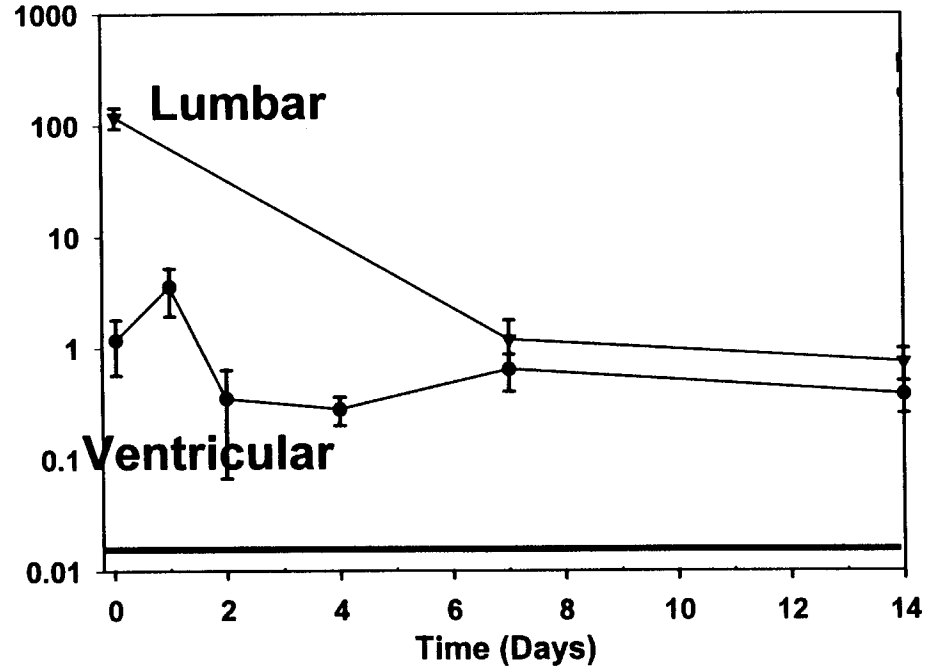
DepoCyt 75 mg: Ventricular vs Lumbar CSF Pharmacokinetics Following Intralumbar Administration



Free Ara-C



Free Ara-C

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DepoCyt Phase I Trial: Drug-Related Grade ≥ 3 Toxicity

	Percent of Cycles					
Dose	**12.5 mg**	**25 mg**	**37.5 mg**	**50 mg**	**75 mg**	**125 mg**
No. of patients	2	6	5	10	14	4
No. of cycles	3	7	7	15	40	4
Fever	33%	0	0	0	0	25%
Headache	0	0	0	13%	0	0
Nausea/Vomiting	0	14%	14%	0	5%	25%
Pain (neck/back)	0	0	0	0	0	0
Encephalopathy	0	29%	14%	20%	13%	25%

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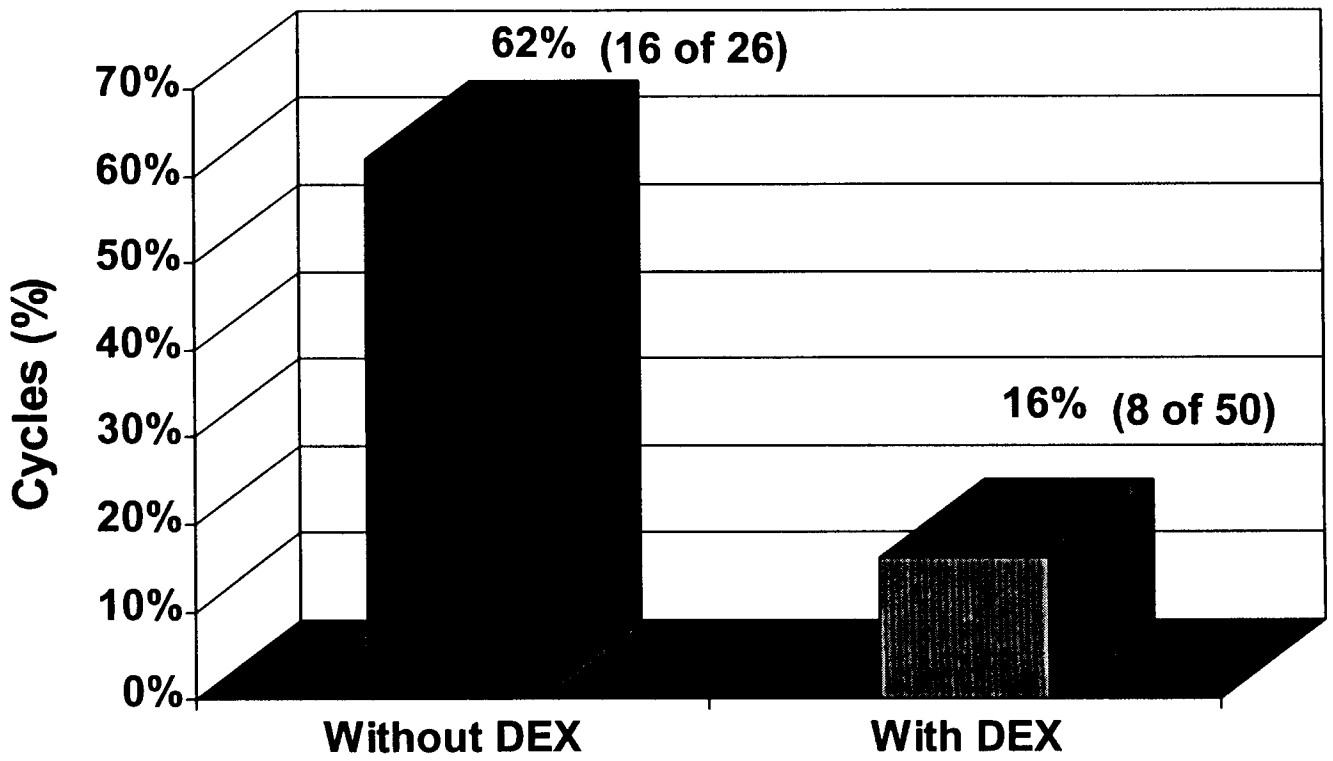
DepoCyt Phase I Trial: Chemical Arachnoiditis by Dexamethasone Use



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DepoCyt Phase I Trial: Conclusions

- Increased half-life 42 fold
- Maintained cytotoxic levels for $\geq$ 14 days
- Rationale for dose of 50 mg every 14 days
- Achieved cytotoxic levels irrespective of site of administration
- Concurrent steroids mitigate toxicity

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Efficacy of DepoCyt

J. Wayne Cowens, M.D.

Division Vice President

Product Development

Chiron Corporation

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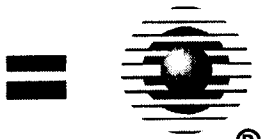
Introduction

- **Treatment with DepoCyt more convenient**
- **Trends in all measures of efficacy favor DepoCyt**
- **Efficacy results consistent across studies**



Clinical Studies in the NDA

Protocol	Design	# of Patients in NDA
Phase III (Solid Tumor Arm)	Comparison of the efficacy/safety of DepoCyt to MTX	61
Phase III (PK Patients)	Pharmacokinetics of DepoCyt	9
Phase III Lymphoma Arm/ Leukemia Arm)	Comparison of the efficacy/safety of DepoCyt to Ara-C	18/5
Phase I	MTD and pharmacokinetics of DepoCyt	19

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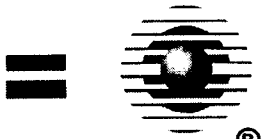
Phase III: Study Design

- Open-label, randomized, multi-center
- 3 arms: solid tumor, lymphoma, leukemia
- Control Treatments: MTX, Ara-C
- Positive CSF cytology at entry
- CSF cytologies reviewed independently (blinded)



Phase III: Solid Tumor Arm Study Design

- **Induction (4 weeks)**
  - **2 doses of 50 mg DepoCyt given every 2 weeks**

    -- or --
  - **8 doses of 10 mg MTX given twice weekly**
  - **Concurrent dexamethasone**
- **Consolidation (12 weeks)**
  - **4 doses of 50 mg DepoCyt**

    -- or --
  - **8 doses of 10 mg MTX**
  - **Concurrent dexamethasone**
- **Follow-up (3 months)**

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Phase III: Solid Tumor Arm Patient Demographics

- **Treatment groups balanced for prognostic characteristics**
  - **Age**
  - **Karnofsky Performance Score**
  - **Tumor histology**
  - **Neurologic deficits**

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Phase III: Prospective Efficacy Measures

- **Primary Measure**
  - **Complete Response**
- **Secondary Measures**
  - **Clinical Progression**
  - **Survival**
  - **Quality of Life**

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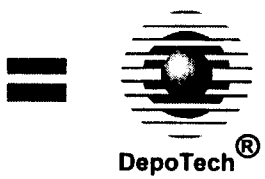
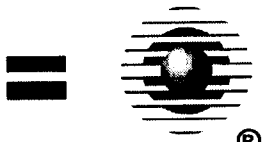
Phase III and Phase I: Definition of Complete Response

- **At anytime following induction**
  - **Negative CSF cytology by all sites positive at baseline**
  - **No evidence of clinical (leptomeningeal) disease progression**



Phase III: Prospective Patient Population Definitions

- **Intent to Treat - ITT**
  - **All patients randomized**
- **Evaluable**
  - **On study ≥ 12 days**
  - **Received study drug**
  - **Positive CSF cytology at baseline**
  - **Follow-up CSF cytology from all sites positive at baseline**



Phase III: Solid Tumor Arm Evaluable Population

Treatment Group	Randomized Patients	Patients who did not Receive Drug	Patients without Adequate Time on Study	Patients without Adequate Cytologic Follow-up	Evaluable Patients
MTX	30	0	1	0	29
DepoCyt	31	2	3	4	22

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Phase III: Solid Tumor Arm Complete Response

	DepoCyt		MTX	
	ITT	Evaluable	ITT	Evaluable
No. Patients	31	22	30	29
Complete Response (%) (w/confirmation)	3 (10)	3 (14)	1 (3)	1 (3)
All Complete Responses (%)	8 (26)	8 (36)	6 (20)	6 (21)

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Phase III: Solid Tumor Arm Complete Response

	DepoCyt		MTX	
	ITT	Evaluable	ITT	Evaluable
No. Patients	31	22	30	29
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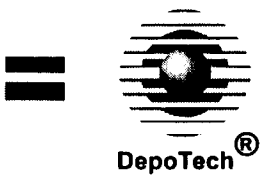
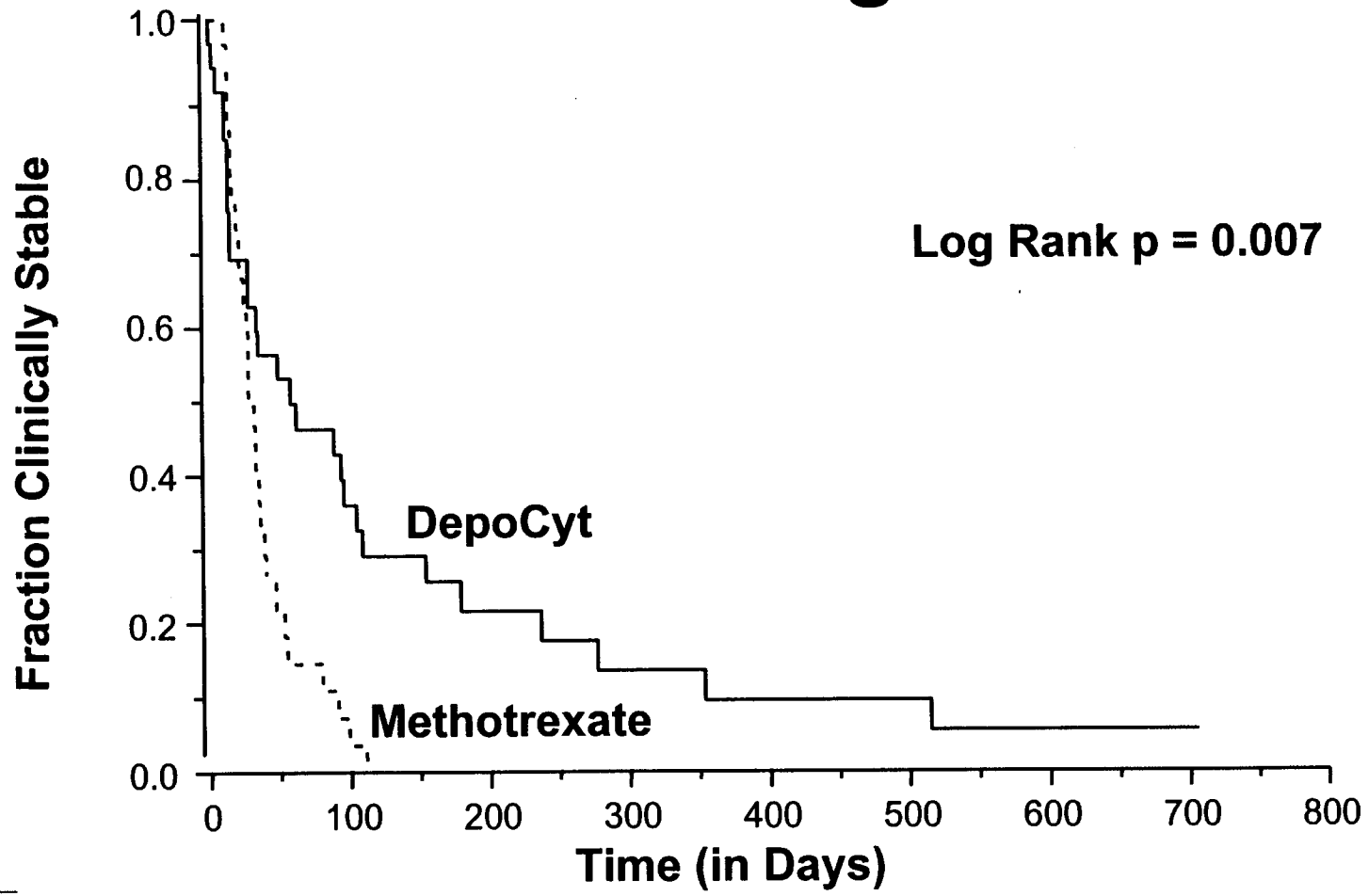
Phase III and Phase I: Definition of Clinical Progression

- **Attributable to neoplastic meningitis**
  - **Appearance of new neurological findings**
  - **Worsening of existing neurological findings**

- **Other Events (Death)**



Phase III: Solid Tumor Arm Time to Clinical Progression



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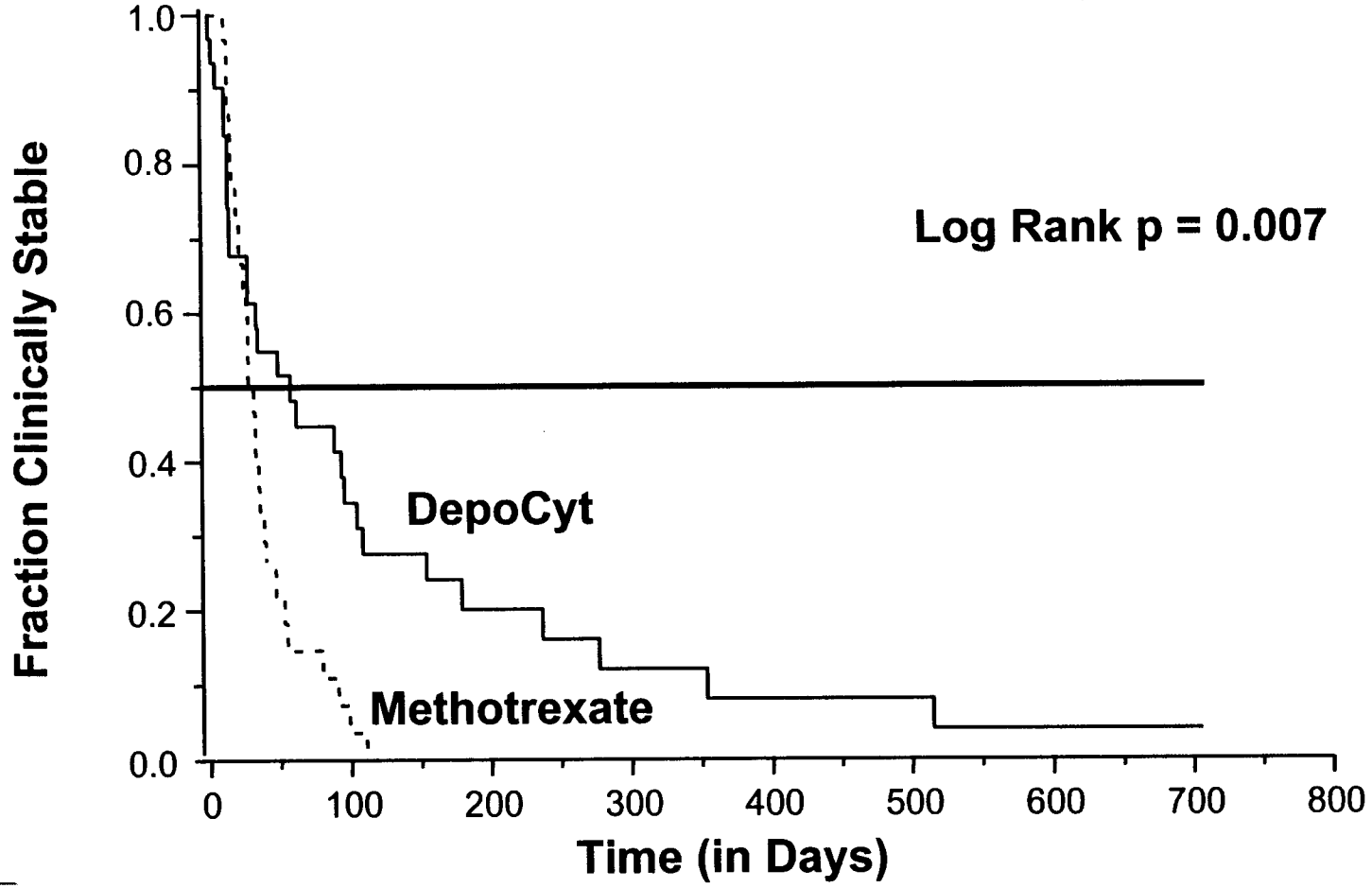
Phase III: Solid Tumor Arm Time to Clinical Progression



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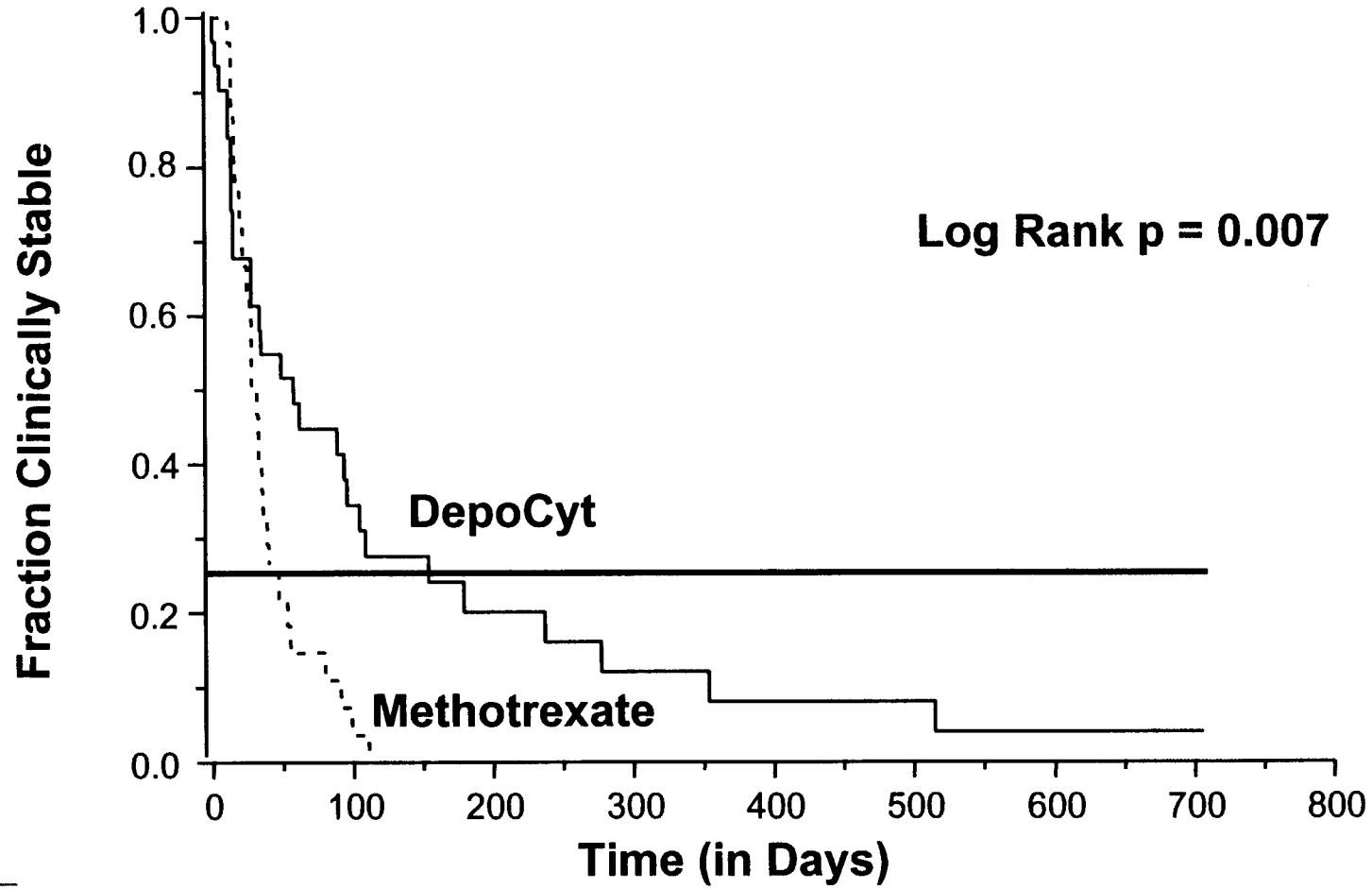
Phase III: Solid Tumor Arm Time to Clinical Progression



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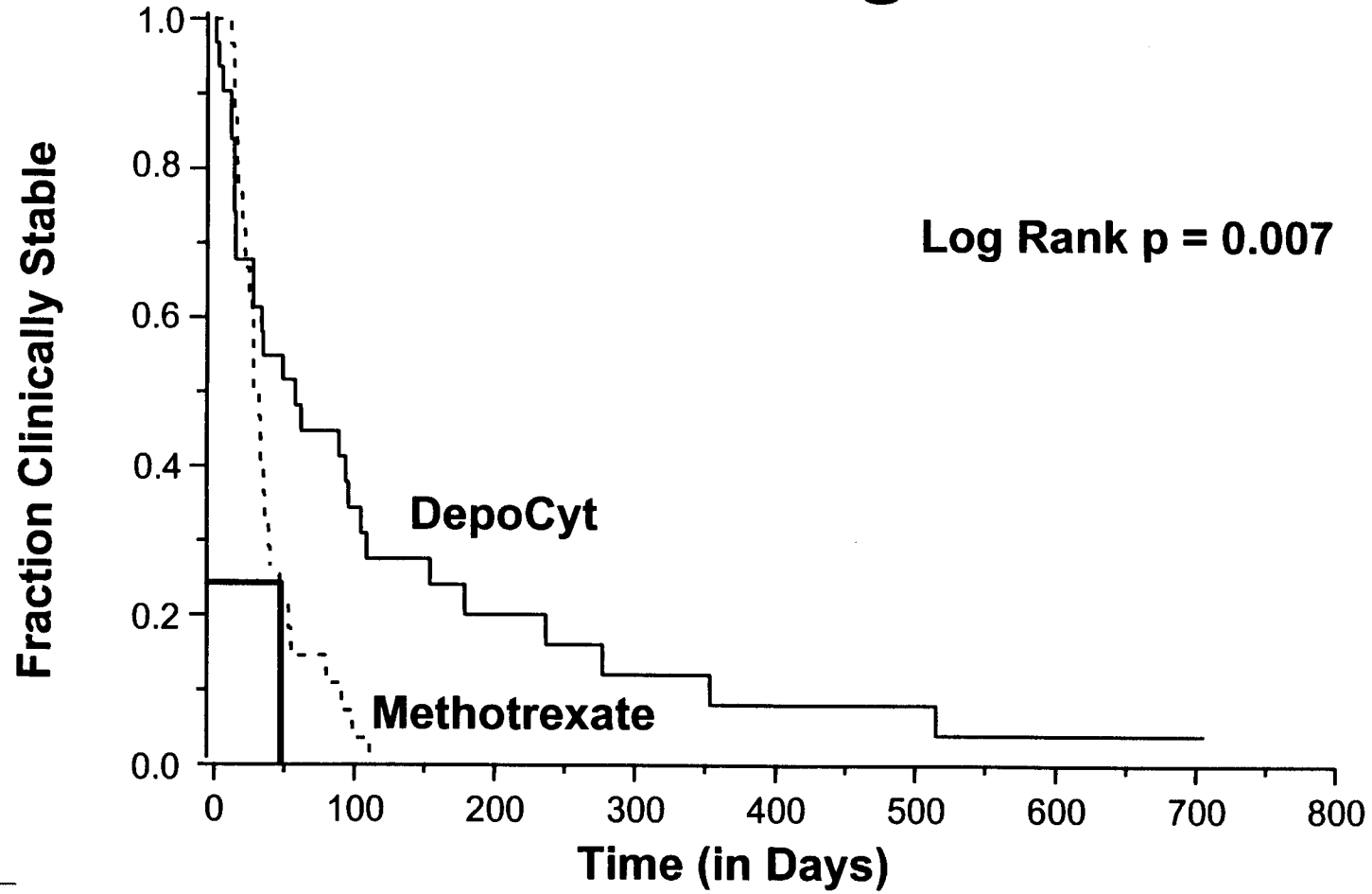
Phase III: Solid Tumor Arm Time to Clinical Progression



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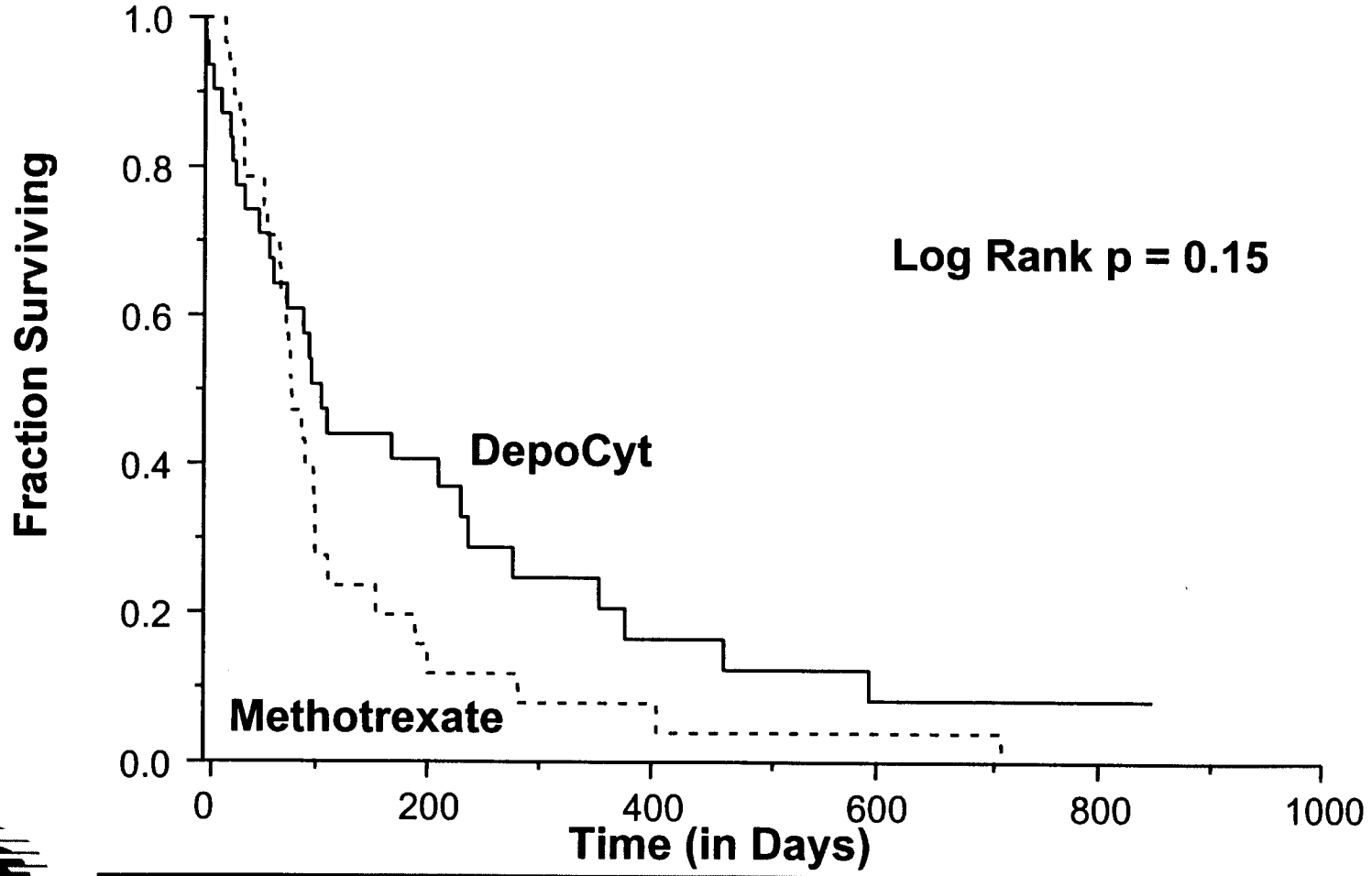
Phase III: Solid Tumor Arm Survival



Log Rank p = 0.15

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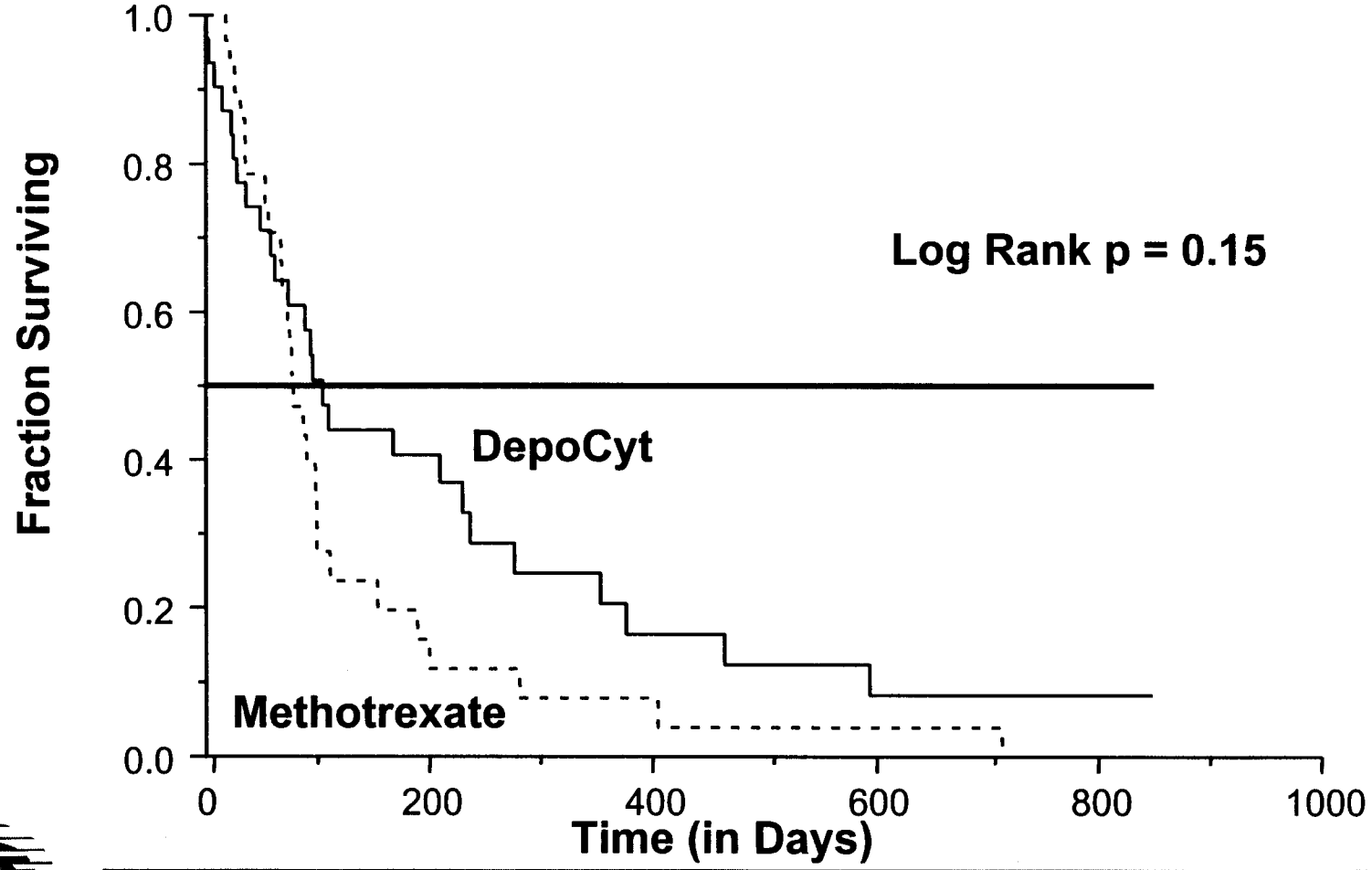
Phase III: Solid Tumor Arm Survival



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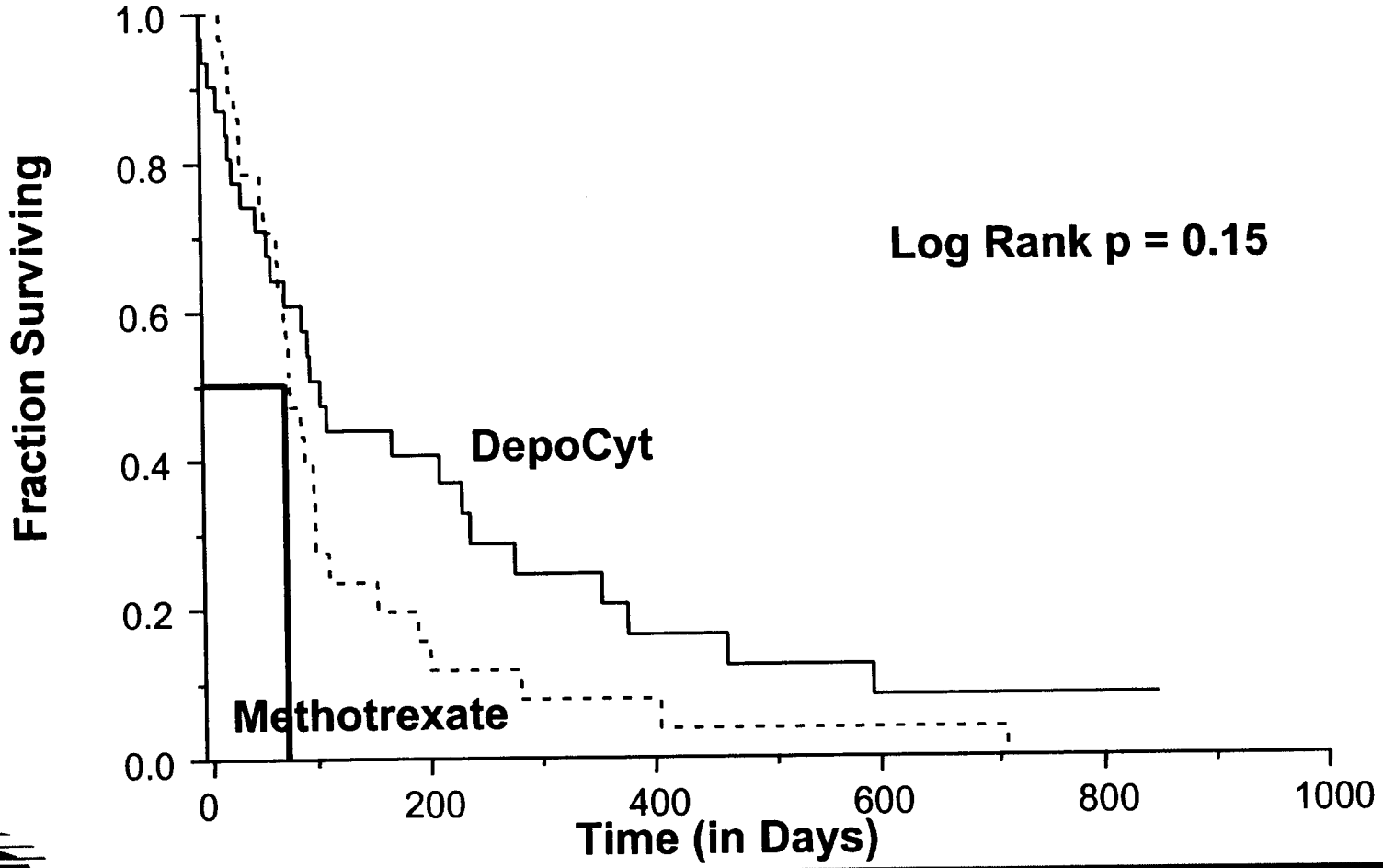
Phase III: Solid Tumor Arm Survival



Log Rank p = 0.15

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Phase III: Solid Tumor Arm Quality of Life: FACT-CNS Change from Baseline

- **Treatment Groups**

	DepoCyt (n=14)	MTX (n=11)
Median	0.50	0.47

- **Responders vs Non-Responders**

	Complete Responders (n=10)	Non-Responders (n=15)
Median	1.5	0.0

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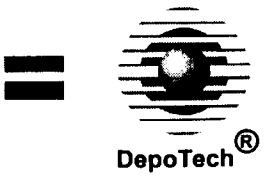
Phase III: Solid Tumor Arm Outcome Comparing Responders vs Non-Responders (28 Day Landmark)

	Time to Clinical Progression Median (days)	Survival Median (days)
Responders	**66**	**251**
Non-Responders	**34**	**63**



All DepoCyt Studies: Solid Tumor Patients Consistency of Response

	Phase I	Phase III PK	Phase III	Total DepoCyt	MTX
No. Patients	11	5	31	47	30
CR	36%	40%	26%	30%	20%
% CR with Duration >60 Days	60%	50%	38%	47%	17%

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All DepoCyt Studies: Solid Tumor Patients Consistency of Response

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% CR with Duration >60 Days	60%	50%	38%	47%	17%

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All DepoCyt Studies: Lymphoma Patients Consistency of Response

	Phase I	Phase III PK	Phase III	Total DepoCyt	Ara-C
No. Patients	6	2	9	17	9
CR	50%	50%	67%	59%	11%
% CR with Duration >60 Days	67%	100%	17%	40%	0

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All DepoCyt Studies: Lymphoma Patients Consistency of Response

	Phase I	Phase III PK	Phase III	Total DepoCyt	Ara-C
No. Patients	6	2	9	17	9
CR	50%	50%	67%	59%	11%
% CR with Duration >60 Days	67%	100%	17%	40%	0

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All DepoCyt Studies: Lymphoma Patients Consistency of Response

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No. Patients	6	2	9	17	9
CR	50%	50%	67%	59%	11%
% CR with Duration >60 Days	67%	100%	17%	40%	0

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Conclusions

With a more convenient dosing schedule:

- **Trends in all efficacy measures favor DepoCyt over methotrexate**
- **Efficacy results are consistent across all DepoCyt studies**

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Safety of DepoCyt

Michael J. Glantz, M.D.

Department of Medicine

Brown University
School of Medicine

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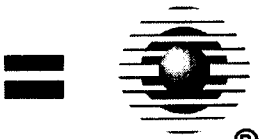
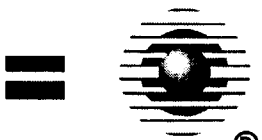
Preview: Side Effects of IT Chemotherapy

- DepoCyt toxicity is qualitatively similar to that of methotrexate
- The most common toxicity is chemical arachnoiditis
- Concurrent use of oral dexamethasone mitigates chemical arachnoiditis



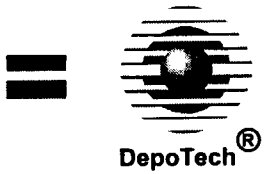
Probability of Drug-Relatedness

- **Definite**
- **Probable**
- **Possible**
- **Unable to determine**

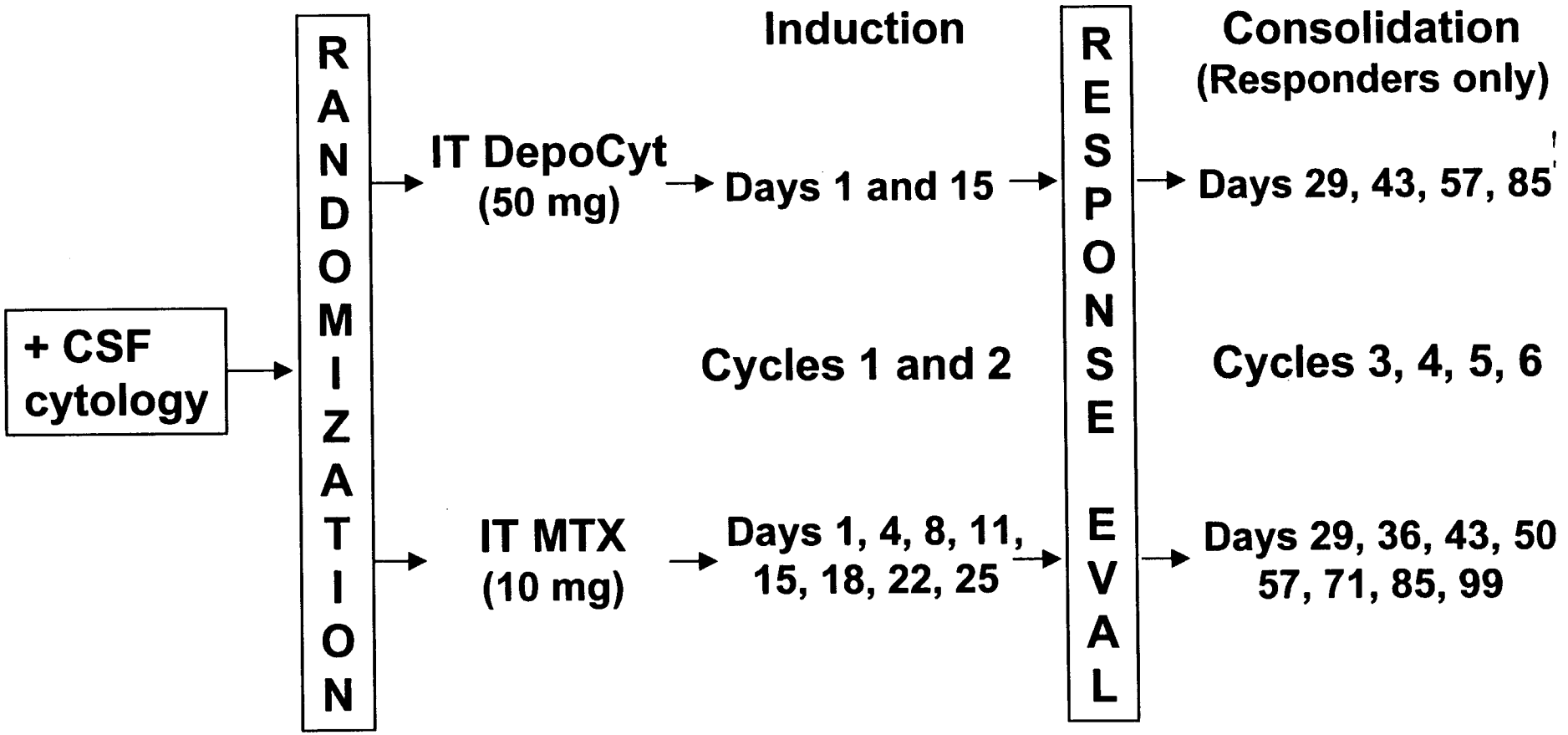


Drug-Relatedness:
Phase III Randomized Trial: Solid Tumor Arm

No. Events	DepoCyt n=437	MTX n=457
Definite	6%	0
Probable	7%	2%
Possible	17%	19%
Unable to Determine	5%	2%
Not Related	65%	77%



Treatment Plan:
Phase III Randomized Trial: Solid Tumor Arm



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Cycles and Length of Therapy:
Phase III Randomized Trial: Solid Tumor Arm

	DepoCyt	MTX
No. Patients	29	30
Total Cycles	102	69.5
Mean No. Cycles	3.5	2.3
Mean Days on Study	56	31

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Expected Complications of IT Chemotherapy

- Acute Neurotoxicity
- Subacute Neurotoxicity
- Chronic Neurotoxicity
- CNS Infection
- Myelosuppression

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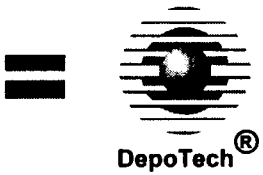
Definition of Chemical Arachnoiditis

- **Signs and symptoms**

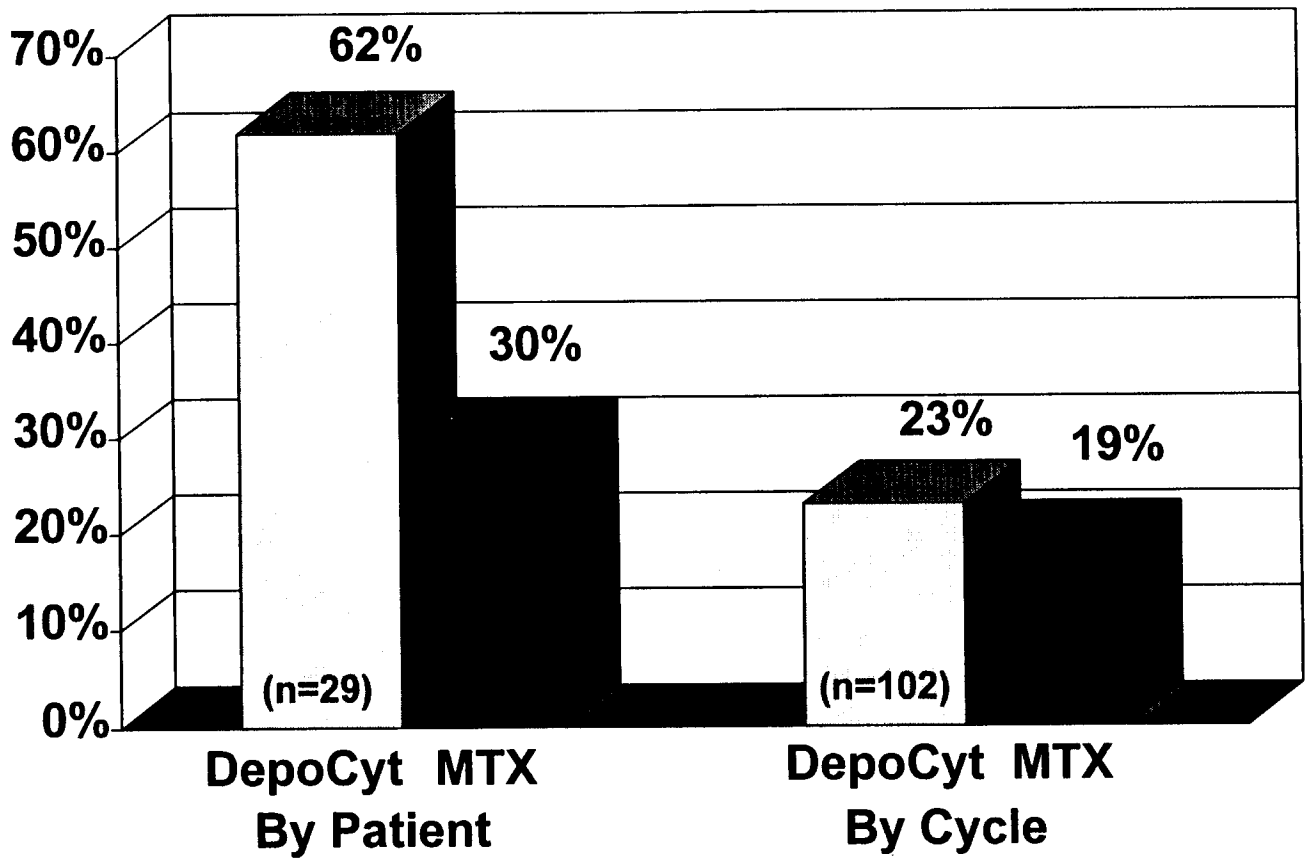
Major	Minor	
neck rigidity	nausea/vomiting	back pain
neck pain	headache	pleocytosis
meningismus	fever	

- **Categories**
  - **Definite**
  - **Possible**
  - **Serious**

APPEARS THIS WAY
ON ORIGINAL



Incidence of Chemical Arachnoiditis:
Phase III Randomized Trial: Solid Tumor Arm



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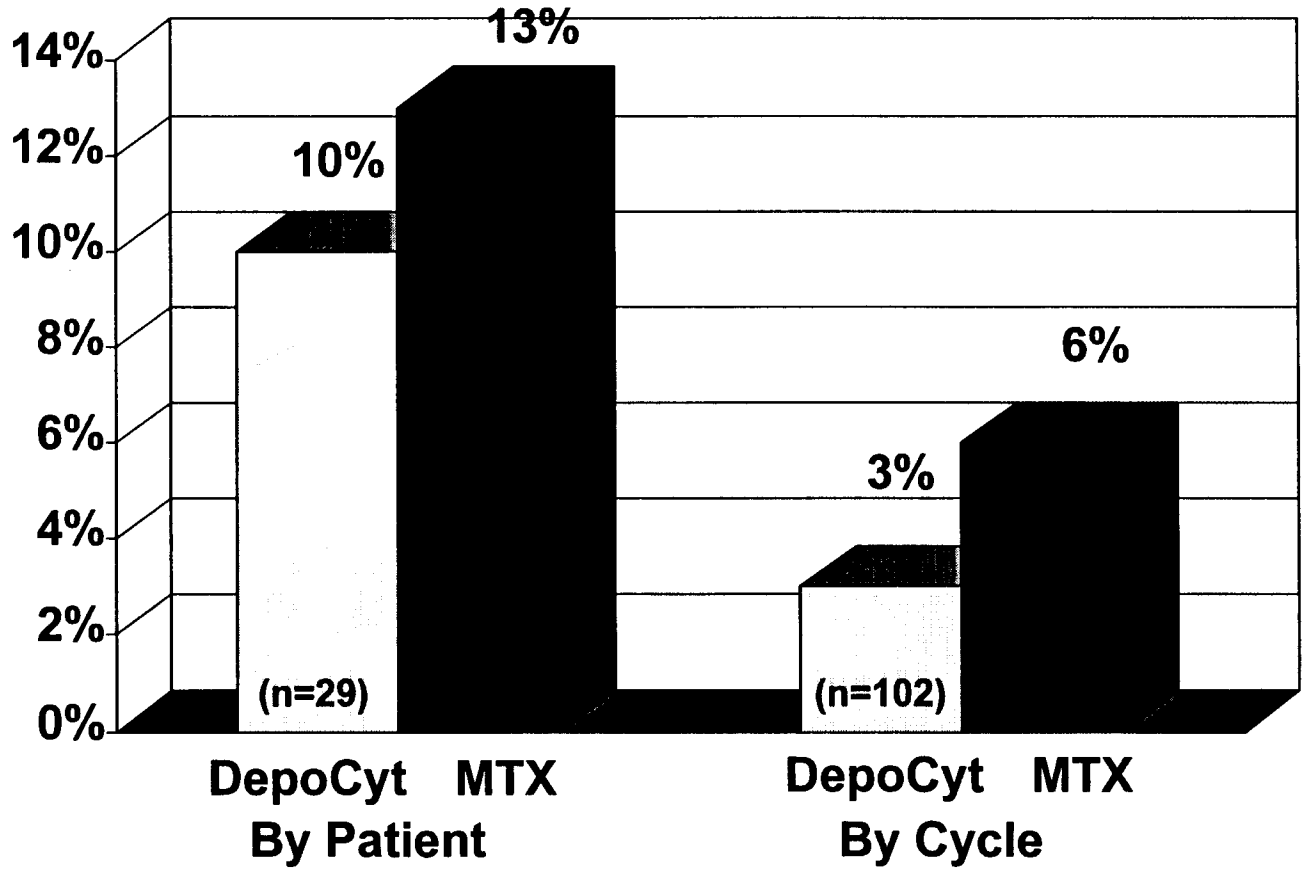
Incidence of Serious Chemical Arachnoiditis:

Phase III Randomized Trial: Solid Tumor Arm



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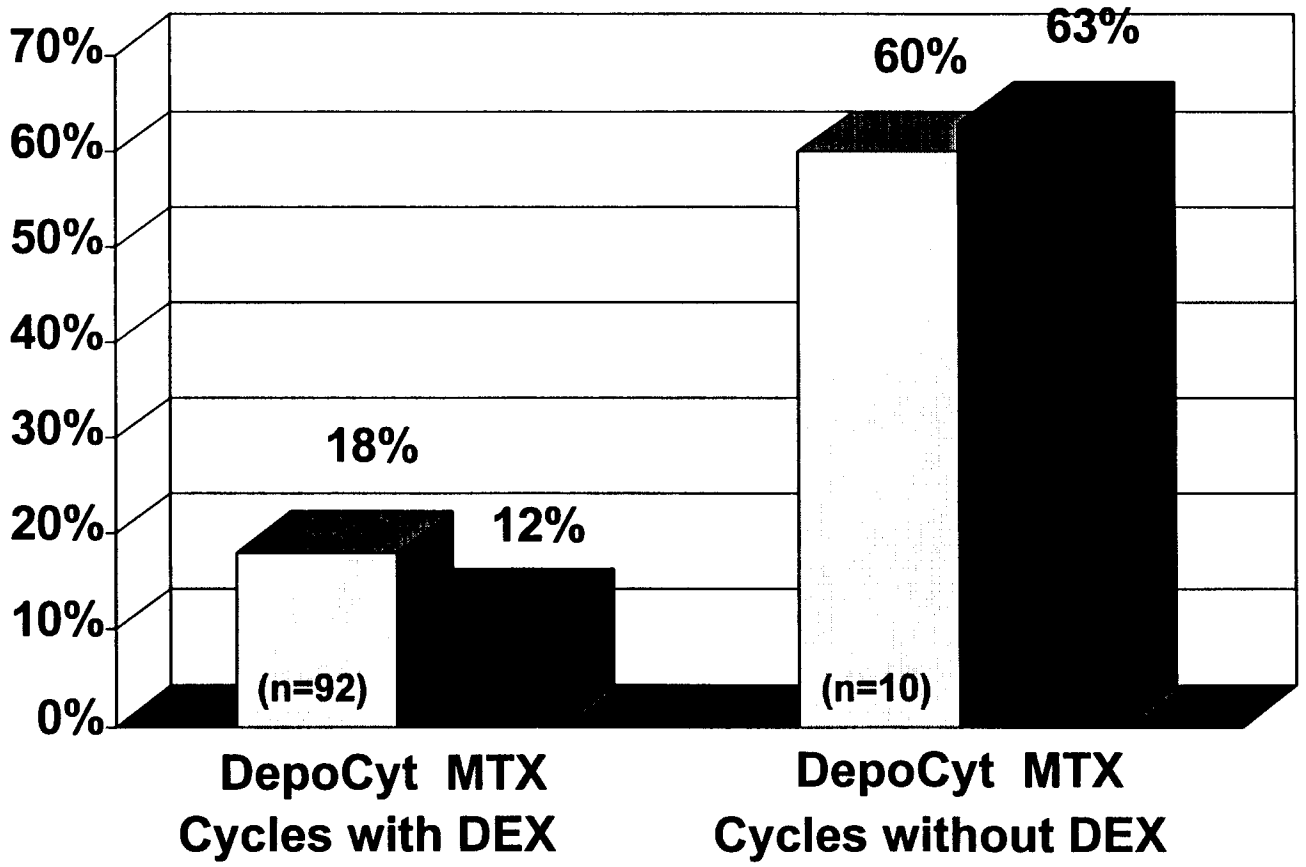
Effect of Dexamethasone on Chemical Arachnoiditis:

Phase III Randomized Trial: Solid Tumor Arm



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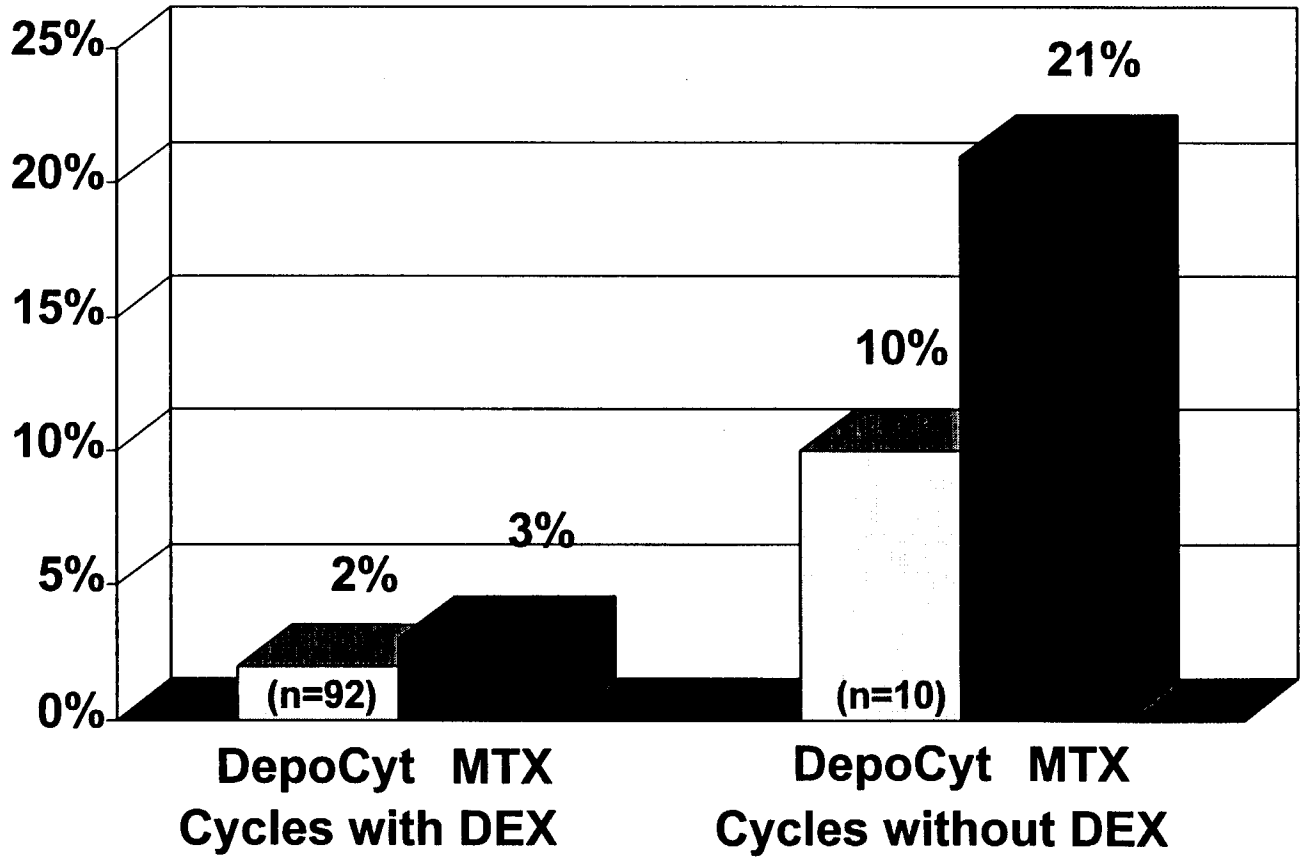
Effect of Dexamethasone on Serious Chemical Arachnoiditis:

Phase III Randomized Trial: Solid Tumor Arm



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Drug-Related Grade 3/4 Neurologic Adverse Events:
Phase III Randomized Trial: Solid Tumor Arm

No. Patients	DepoCyt n=29 No. (%)	MTX n=30 No. (%)
Sensory Deficit	0	2 (7)
Motor Deficit	0	2 (7)
Visual Disturbance	1 (3)	0
Ataxia/Abnormal Gait	0	0
Seizure	1 (3)	0
Encephalopathy	1 (3)	0
Myelopathy	0	0
Total Patients Reporting	3 (10)	3 (10)

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Culture-Confirmed CNS Infection:
Phase III Randomized Trial: Solid Tumor Arm

	DepoCyt n=29	MTX n=30
Cases (%)	0	1 (3)

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Drug Related Grade 3/4 Hematologic Adverse Events Phase III Randomized Trial: Solid Tumor Arm

	DepoCyt		MTX	
	Patients (n=29) No. (%)	Cycles (n=102) No. (%)	Patients (n=30) No. (%)	Cycles (n=69.5) No. (%)
Neutropenia	3 (10)	3 (3)	2 (7)	2 (3)
Thrombocytopenia	0	0	2 (7)	3 (4)
Anemia	0	0	0	0
Total Patients Reporting	3 (10)		3 (10)	

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Drug-Related Deaths and Discontinuations Phase III Randomized Trial: Solid Tumor Arm

No. Patients	DepoCyt n=29 No. (%)	MTX n = 30 No. (%)
Deaths	0	1 (3%)
Discontinuations	1 (3%)	1 (3%)

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Conclusions

- DepoCyt toxicity is qualitatively similar to that of methotrexate
- The most common toxicity is chemical arachnoiditis
- Concurrent use of oral dexamethasone mitigates chemical arachnoiditis

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Potential Advantages of DepoCyt

Kurt A. Jaeckle, M.D.
Associate Professor,
Department of Neuro-Oncology

University of Texas
M.D. Anderson Cancer Center

Comparison of DepoCyt to Standard Therapy in NM

- **DepoCyt addresses pharmacologic limitations of intrathecal therapy**
- **More convenient dosing schedule**
- **Comparable toxicity**
- **Equivalent efficacy with trends favoring DepoCyt**

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Pharmacologic Limitations to Effective IT Therapy

- Standard agents have short $T_{1/2}$
- Few cycling CSF tumor cells
- Inconsistent levels after lumbar dosing

DepoCyt Addresses these Pharmacologic Limitations

- **Sustains cytotoxic CSF concentrations**
- **Even distribution with intralumbar or intraventricular administration**

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DepoCyt Dosing Schedule Advantages

- More convenient than twice weekly therapy
- Less patient discomfort
- Patients spend more time at home
- More patients can receive treatment

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Comparable Toxicities of DepoCyt to Standard Therapy

- **Comparable to MTX, except chemical arachnoiditis**
- **Arachnoiditis manageable with oral dexamethasone**

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Efficacy of DepoCyt Equivalent to Standard Therapy

- **Equivalence, with trend favoring DepoCyt in:**
  - **CR rate**
  - **Overall survival**
  - **Death due to neoplastic meningitis**
- **First IT agent significantly prolonging time to clinical progression**

APPEARS THIS WAY
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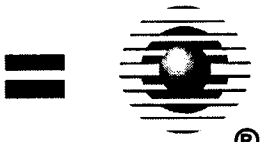
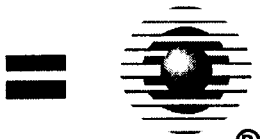


Conclusions About DepoCyt

- **Addresses pharmacologic limitations of IT therapy**
- **Personal experience consistent with clinical trial data**
- **Risk/Benefit favorable:**
  - **Toxicity and efficacy comparable**
  - **More convenient for patients and physicians**



DepoTech®

NDA 20-806: Bromodeoxyuridine for Labeling Index Determination

Oncologic Drugs Advisory Committee
December 19, 1997

REVIEW TEAM: NDA 20-806

	PRIMARY REVIEWER	SECONDARY REVIEWER
MEDICAL	Karen Johnson	John Bertz
STATISTICS	Antonia Kontsevaya	George Chi
PHARM/TOX	Paul Andrews	Wendolyn Schmidt
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PROPOSED INDICATION

Broxuridine is indicated as a "cell proliferation marker for the estimation of the Labeling Index (LI) of breast tumors."

PROPOSED MEASURES OF CLINICAL BENEFIT (Primary Breast Cancer)

- Correlation of survival with BUdR LI
- Clinically relevant separation of patients into prognostic groups based on BUdR LI

Regulatory History

- 1979: Investigational study of intravenous broxuridine for this indication began (IND 2197)
- 8/86 - 3/95: Accrual period for T86-0217 at UCSF
- 5/91 - 4/95: Accrual period for CYL 93-02 at Syracuse
- 7/96: Pre-NDA meeting
- 12/96: NDA submission
- 8/97: Updated data set, extended follow-up
- 10/97: Updated analysis

Studies Submitted for Review

	T86-0217	CYL 93-02
Site:	UCSF	Syracuse
Design:	Single Arm	Single Arm
Endpoints:	Survival	Survival
N:	163	28
Dose:	200 mg/m^2	100 mg/m^2
Timing:	Over 30 min, about 1 hr before surgery	Over 30 min (post IUdR), about 30 min before surgery

T86-0217 Study Objectives

- "To label primary female breast cancer in vivo with BUdR prior to tumor removal ..."
- "These data will be analyzed for extent of heterogeneity within patient subsets, and correlated with standard histological criteria and with patient outcome (i.e., rate of recurrence and time to recurrence in individual patients)."

T86-0217: Primary Protocol Endpoint

- Protocol did not specify the primary endpoints for analysis
- Protocol did not specify a methodical process for assessing recurrent disease status
- Clinical documentation of recurrence has not been provided

Conclusion: A recurrence endpoint cannot be verified, so survival was used as the primary endpoint.

Eligibility for T86-0217

- Female
- Karnofsky of 90% or better
- Normal bone marrow, renal and hepatic function
- Cytologically or histologically confirmed diagnosis of resectable stage 1, 2, or 3 breast cancer

T 86-0217: Patient Population

207 BUdR LI patients were identified in the UCSF investigational database

- 5 did not receive intravenous BUdR, but tumor samples were sent for *in vitro* determination of BUdR LI
- 3 patients received intravenous BUdR as part of another protocol: T94-0071
- A single patient was assigned two study accession numbers

Conclusion: 198 patients had an intravenous infusion of BUdR for LI determination as part of T86-0217

Excluded Patients: T86-0217

35 patients (of 198) excluded by the sponsor:

- 13 patients with no LI (8: samples not sent, 4: insufficient specimen, 1: no residual tumor)
- 11* patients with recurrent disease
- 7* stage 0
- 3* samples from lymph nodes
- 1* sarcoma

* Did not meet protocol eligibility criteria (22)

Excluded Patients: T86-0217

- 3 additional patients have been excluded by the FDA
  - 2 without residual invasive cancer
  - 1* stage 4
- 3* protocol violations not leading to exclusion: male breast cancer

* Did not meet protocol eligibility criteria (4)

Excluded Patients: T86-0217

Conclusions:

- 38 patients were excluded
- % excluded: 19% (38/198)
- 26 of the 38 excluded patients did not meet eligibility criteria
- % ineligible: 13% (26/198)

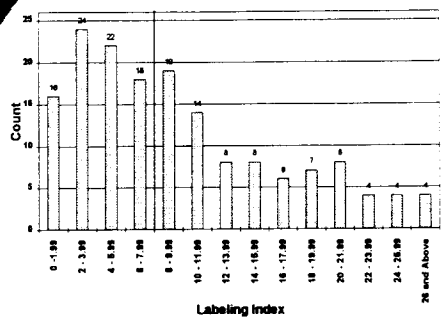
T86-0217: Status of Patient Follow-up

- No follow-up data for at least one year prior to data cut-off were available for 30/163 patients (18%)
- These 30 patients were not distinguishable from other patients on the basis of known characteristics or outcomes (e.g., BUdR LI)

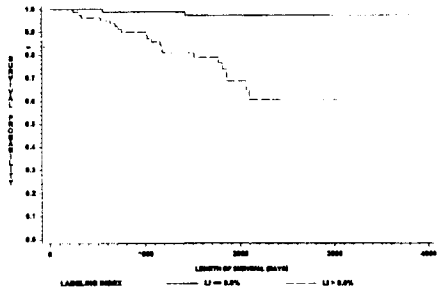
Patient Characteristics: T86-0217

Number	163 (Sponsor)
Median age	50.7 years
Stage 1	36/% (59/163)
2	49% (80/163)
3	13% (22/163)
Receipt of systemic therapy	~78%
Median duration of follow-up	4.8 years
Range	0.2 to 10.9 years
Median value of BUdR LI	7.9
Range	0.1 to 34.5

T86-0217: Distribution of Labeling Index



T86-0217: Overall Survival



T86-0217: Breakpoint at the Median LI

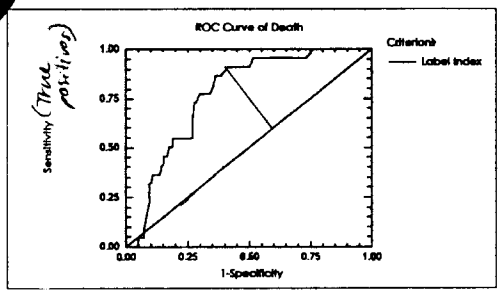
Outcome	Breakpoint	Relative Risk (> 8 vs. < 8)	p-value*
Overall survival	8.0	13.9	0.0004

* Log-rank

Receiver Operating Characteristic Analysis

- Sensitivity: deaths occuring with LI > cut-off divided by total dead
- Specificity: number of patients alive with LI ⩽ cut-off divided by total living
- Point coordinates: sensitivity vs. 1- specificity or a comparison of the true vs. false positives
- Curve: each point represents one of the possible cut-off scores
- Informative breakpoint: the odds of correctly predicting an event exceeds the odds of incorrect prediction

Breakpoint ROC Curve



T86-0217 Breakpoints

Outcome	Breakpoint	Relative Risk (Above breakpoint versus breakpoint or less)	p-value[3]
Overall survival	8.0[1]	13.9	0.0004
	9.1[2]	7.7	0.0002

[1] Based on median
[2] Optimal value from FDA ROC analysis
[3] Log-rank

Clinical Use of Prognostic Factors

- Historically, adjuvant therapy has been used ever more widely
- Theoretically, prognostic factors could be used in the following circumstances:
  - To identify a subgroup of good prognosis patients who could be spared uncessarily harsh therapy
  - To identify a poor prognosis subgroup that required more agressive therapy
  - To confirm that there is no group of patients who do not benefit from adjuvant therapy
- Increasing the number of available prognostic factors may lead to a wider range of estimates of prognosis (more uncertainty)

Pitfalls in the Evaluation of New Prognostic Factors

- Univariate analyses
  - No single prognostic factor is sufficiently correlated with outcome
  - Individual factors "may be alternative representations of the same biologic phenomenon"*
  - Integrated prognostic models adjust for correlations
- Small studies
- Heterogeneous treatments

*Clark, 1996

Optimizing Prognostic Models

- Values of LI at the borderline between dichotomized prognostic groups carry the most uncertainty
- An alternative method of selecting breakpoints or prognostic groups may be preferable, such as focusing on specific segments of the prognostic factor distribution

Studies Submitted for Review

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Endpoints:	Survival	Survival
N:	163	28
Dose:	200 mg/m^2	100 mg/m^2
Timing:	Over 30 min, about 1 hr before surgery	Over 30 min (post IUdR), about 30 min before surgery

Patient Characteristics: CYL 93-02

Number in analysis	28 (Sponsor)
Median age	52.5
Stage 1	25% (7/28)
2	68% (19/28)
3	7% (2/28)
Median value of BUdR LI	6.35
Range	0.4 to 22.0
Median duration of follow-up	2.3 years
Range	0.3 to 5.2 years
Receipt of systemic therapy	~57%

CYL 93-02: Results

- 5/33 patients were inevaluable
  - 1 benign tissue
  - 2 cancers, not breast
  - 1 unreadable LI
  - 1 specimen, no residual tumor
- 6 events among 28 evaluable patients: 3 deaths, 3 recurrences
- Univariate Cox models attempted
  - Survival: insufficient data, model did not converge

CYL 93-02: Conclusions

Conclusions:

- Data set from CYL 93-02 is uninformative
  - population too small
  - events too few
- Size of CYL 93-02 does not allow a determination that results from the two studies can be justifiably merged
- Data from T86-0217 must stand on its own

Intravenous Broxuridine: Single-dose Safety

- 231 patients in T86-0217 and CYL 93-02 received a single dose of broxuridine by intravenous infusion
  - 198 patients: 200 mg/m^2
  - 33 patients: 100 mg/m^2
  - No adverse events reported
- Around 5,000 patients have received 50 to 500 mg/m^2 in single dose studies resulting in 3 mild adverse events
  - Mild hypotension
  - Mild headache
  - Vomiting

NDA 20-806: Conclusions

- Survival of a group of stage 1, 2, and 3 breast cancer patients from T86-0217 was related to BUdR LI
- Study procedures for assessing relapse-free survival were not sufficiently defined to warrant the use of BUdR LI for prognostication of relapse
- A multivariate prognostic model with an optimized breakpoint has not been defined
- Potential usefulness of this test in treatment planning has not been established

Source: Clark GM: Prognostic and Predictive Factors, p 478; in Diseases of the Breast, Eds: Harris JR, Lippman ME, Morrow M and Hellman S; Lippincott-Raven, Philadelphia, 1996

Prognostic Factor Models

Given the number and diversity of the potential prognostic factors, physicians and patients have difficulty synthesizing and integrating the information that they provide. A special issue of the journal *Breast Cancer Research and Treatment* (volume 22, no. 3, 1992) was devoted to prognostic factor integration. Factor integration techniques include simply adding points for each adverse factor (eg, histologic grading systems), multiple regression equations usually from Cox survival models (eg, the Nottingham Prognostic Index), decision trees,[249] and neural networks.[250] No matter how sophisticated the model might be, however, it is only as good as the data used to construct and validate it.

Most of the information in this chapter is derived from retrospective studies that have included relatively few factors. Some of these studies involved large numbers of patients, but most had small to modest sample sizes with relatively short follow-up. Small studies that include patients who have received heterogeneous treatments are unlikely to answer any of the questions about new prognostic factors. Definitive studies in node-negative breast cancer, in which only about 30% of patients have a recurrence, require large numbers of patients followed for long periods to evaluate new prognostic factors adequately. Each study has its own particular selection biases, and all the usual precautions concerning the interpretation of retrospective analyses pertain to most of these studies. A particular concern is the lack of multivariate analyses in the evaluation of potential prognostic factors. Many of these factors are related to each other and may in fact be alternative representations of the same biologic phenomena. Without adjustments for these statistical correlations, the results of univariate correlative analyses may be misleading. One should always ask whether the new factor adds any information to what can be learned from the standard prognostic factors.

Another problem is lack of standardization of assay methods, scoring systems, and antibodies used to measure new biomarkers. Even though many of the new, potential prognostic factors have been evaluated in several studies, few have been conducted under standardized conditions that would permit a true validation of previous results. Particularly worrisome is the use of different cutpoints to define assay positivity, especially when these cutpoints are derived from the same patients used to evaluate the new factor. Hilsenbeck and associates[251] demonstrated that performing multiple analyses on the same data set to find the optimal cutpoint for a new prognostic factor results in substantial type I errors. Validation of results on a truly independent, external population of patients using standardized methods is a necessity before any new factor can be considered ready for clinical use.

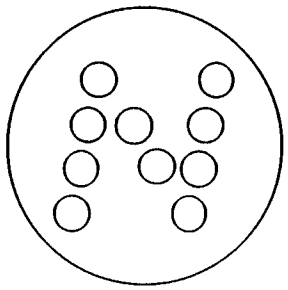
NDA 20-806

BROXURIDINE

(NEOMARK®-BU)

PRESENTATION SLIDES

NeoPharm, Inc.
ODAC Meeting
December 19, 1997



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NEOMARK®-BU (broxuridine)

NeoPharm Representatives

- **William C. Govier, M.D., Ph.D., President, CEO**

Consulting Attendees

- Tony Dritschilo, M.D., Georgetown University, Washington, D.C.
- William Goodson, M.D., University of California, San Francisco, CA
- Seema Khan, M.D., State University of New York, Syracuse, NY
- Tim Kinsella, M.D., University of Wisconsin, Madison, WI
- Ted Lawrence, M.D., Ph.D., University of Michigan, Ann Arbor, MI
- Jaye Thompson, Ph.D., Synergos, Inc., Houston, TX
- Fred Waldman, M.D., Ph.D., University of California, San Francisco, CA

NEOMARK®-BU (broxuridine)

Cell Proliferation Marker to Determine the Labeling Index in Breast Carcinoma

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NEOMARK®-BU (broxuridine)

What is it?

- **A tool to rapidly obtain prognostic information about a breast carcinoma.**

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NEOMARK®-BU (broxuridine)

What it is not.

- Not a therapeutic agent for this indication.
- Not a diagnostic agent.
- Does not indicate which specific therapy to use.
  - Other prognostic factors that do not specify therapy:
    - Blood Pressure 150/95
    - Cholesterol 290
    - PSA 300
    - Contrast media

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NEOMARK®-BU (broxuridine)

Structural Formula

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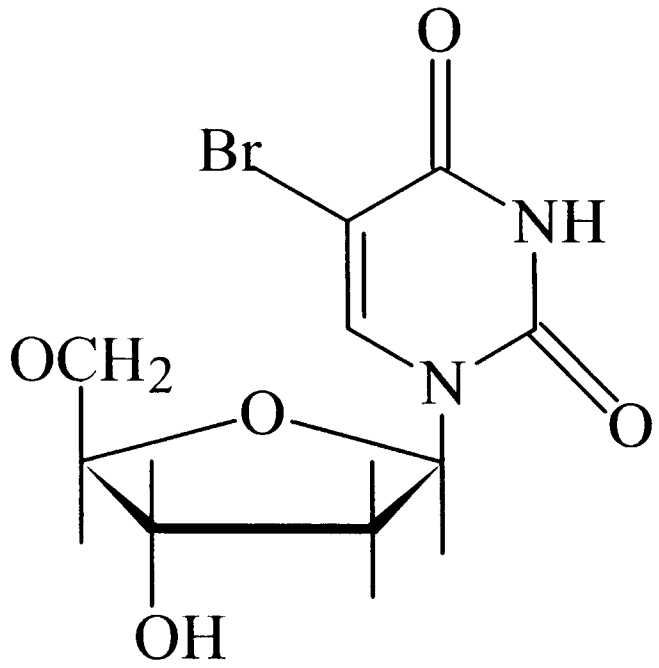

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NEOMARK®-BU (broxuridine)

What Does It Do?

- Incorporates into DNA of actively dividing cells (S-phase).
- Permits identification of those actively dividing cells by means of immunohistochemical techniques.
- This information permits calculation of the tumor Labeling Index.
- Labeling Index is the percentage of actively dividing cells in the tumor.

General Concept of Labeling Index Utility

- Malignant tumors have actively dividing cells.
- The more active cells there are, the more malignant the tumor and the higher the Labeling Index.
- Highly malignant tumors are more likely to kill the patient.
- General Principle
  - The higher the Labeling Index, the more aggressive the tumor, and the more likely it is to kill the patient.

How is it used?

- Lesion first identified as malignant by FNA or other technique.
- Small dose by intravenous infusion just before surgical removal of tumor.
- Small piece of tumor, now labeled, undergoes immunohistochemical analysis.
- Labeled cells are counted under a microscope to determine the Labeling Index.

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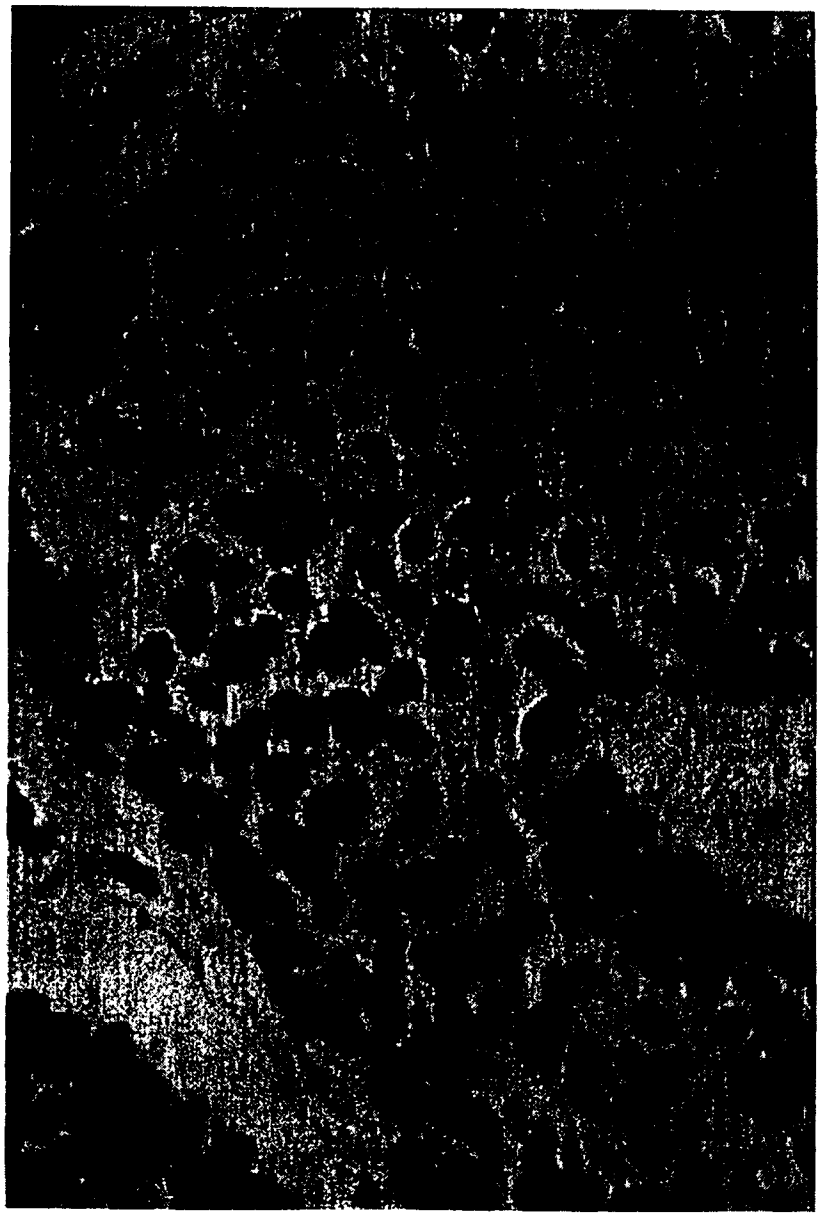

NEOMARK®-BU Labeled Breast Cancer Cells

- **A section of invasive ductal carcinoma.**
- **Tumor cells that are actively dividing show a brown positive stain.**

Correlation of Labeling Index with Survival

Concept of Correlation with Survival is Not New

- Early labeling work using ^{3}H-Thymidine began in 1967.
- More than 10,000 breast cancer cases using ^{3}H Thymidine technique in literature.
- The data show a strong positive correlation with high Labeling Index and decreased survival.
- The higher the Labeling Index, the less likely is survival.

^{3}H-Thymidine Has Significant Disadvantages

- Radioactive.
- Can only be done on *in vitro* specimens.
- Results are obtained by radioautography.
  - Typically requires weeks or months.
  - Results are not available when needed by the patient.

Background

- NEOMARK® shown to replace thymidine in DNA in 1957.
- Availability of specific antibody in 1982 accelerated work.
- More than 5,000 patients with many types of tumors have had their Labeling Index determined using NEOMARK®.
- Approximately 240 patients with breast cancer have been studied using NEOMARK®.
- NEOMARK® results correlate well with ^{3}H Thymidine results - both show correlation with survival and recurrence-free survival.

Advantages

Advantages of NEOMARK® Over ^{3}H-Thymidine

- **Not radioactive.**
- **Permits *in vivo* Labeling Index determination.**
- **Results available in 1 to 2 days.**

Advantages of *In Vivo* Determination

- Labels entire tumor rather than just surface layers.
- Provides homogeneous distribution of label.
- Can be used with very small tumors.
- Permits Labeling Index of worst regions of tumor.
- Eliminates non-viable cell problems.
- Eliminates slice penetration problems.
- Samples can be stored, re-cut and the test redone.

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ON ORIGINAL

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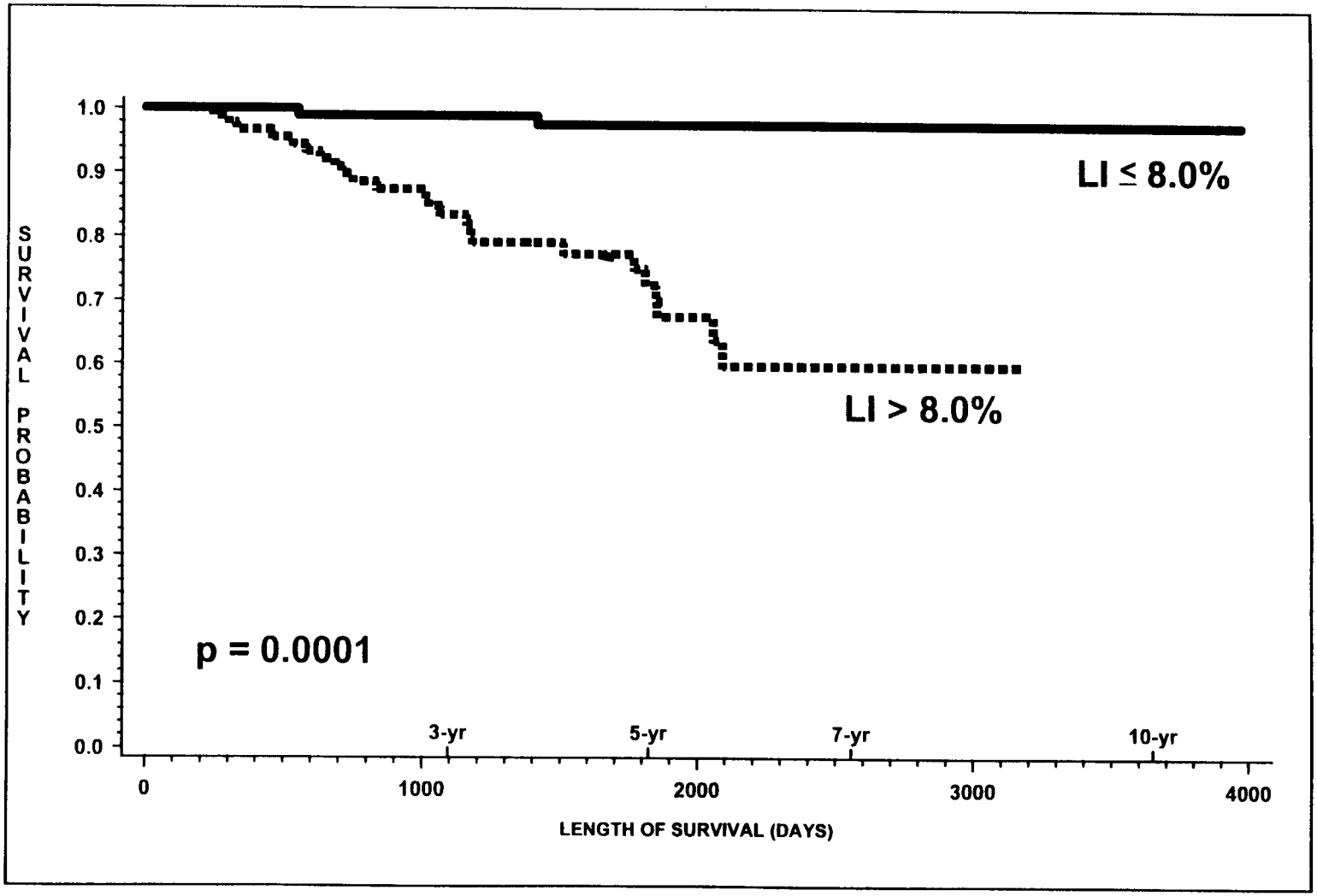
Kaplan-Meier Curves - Survival



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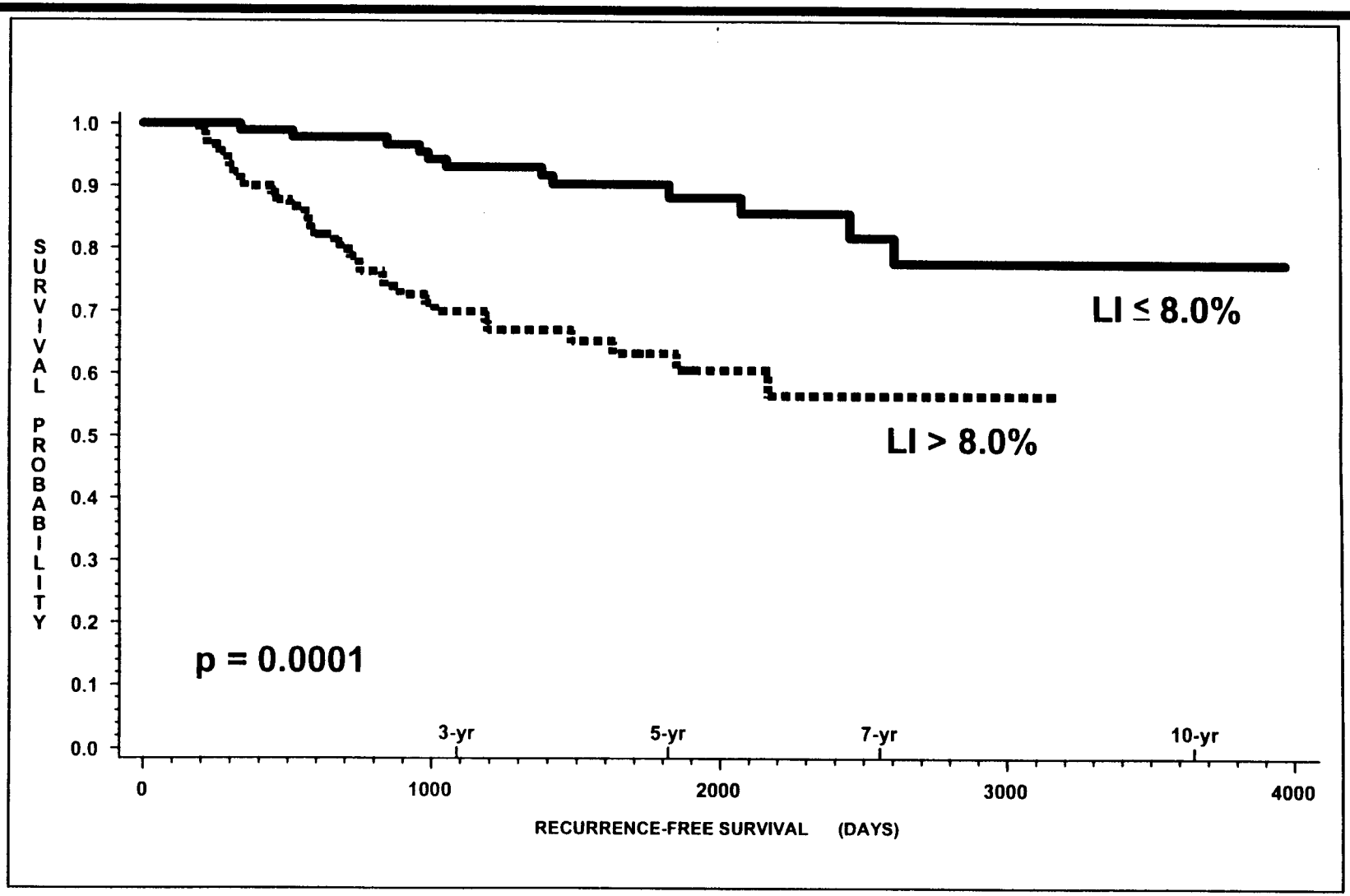
Kaplan-Meier - Recurrence-Free Survival



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Risk Ratios

Cox Proportional Hazards Increased Risk When LI > 8	Risk Ratio	95% Confidence Interval
Survival	16	(3.8, 68.0)
Recurrence-Free Survival	4	(2.0, 7.7)

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Survival Rates by Labeling Index

Labeling Index	3 Year Survival	5 Year Survival	7 Year Survival
≤ 8%	98.9%	97.6%	97.6%
> 8%	84.8%	72.5%	59.7%
Difference	14.1%	25.1%	37.9%

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ON ORIGINAL

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Safety

- Over 5,000 Labeling Index cases with many tumors.
- Only 3 adverse events:
  - 1 mild hypotension
  - 1 mild headache
  - 1 vomiting

Value of Labeling Index

- Useful to both physician and patient.
- Labeling Index describes how aggressive the tumor is.
- Analysis shows it adds prognostic information to the standard indicators such as node status, ER, PR, or any other commonly used indicator.

Value of Labeling Index

- Can separate traditional prognostic factors into good or poor prognosis groups.
- A high LI identifies patients who do poorly with standard therapy and may be candidates for innovative therapy.
- A low LI identifies patients who would be expected to do well with standard therapy despite poor traditional prognostic factors.
- Information describes characteristic of the tumor. It does not suggest a therapy.

Patient Example 1

- Patients with small tumors, 0 or 1 positive node and high LI.

LI	Tumor Size (cm)	Positive Nodes	Months to Death
17.2	2.0	0 / 17	34
19.6	1.6	1 / 8	18
21.4	1.0	0 / 16	38
16.8	1.9	1 / 15	69
15.0	2.0	0 / 2	15

Patient Example 2

- Patients with large tumors, positive nodes and low LI.

LI	Tumor Size (cm)	Positive Nodes	Months to Death
4.3	12.0	12 / 15	93+
3.7	4.0	26 / 38	90+
3.0	4.0	6 / 20	92+
4.6	4.5	7 / 13	85+

+ All patients still alive at time of last audit 7/97.

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Patient Considerations

- Patients want to know as much as possible about their own tumors.
- NEOMARK® Labeling Index provides information about the specific individual's tumor.
- Helps patient to intelligently participate in therapeutic decisions.

Study Parameters

- Prospective studies.
- Investigator offered study participation to each patient meeting entry criteria.
  - 7 patients refused to participate.
- No therapy decisions were based on the Labeling Index.
- Patient population similar to published literature and SEER population.
- No evidence that a patient selection bias could alter correlation between Labeling Index and Survival/RFS.
  - No significant interactions with other factors and LI.
- Patients were actively followed at 3, 6 and 12 month intervals via office visits, tumor registry and telephone contacts.

Demographics/Disease Characteristics

	Study 1 (UCSF)	Study 2 (SUNY)	Combined
Total N	207	33	240
Eligible	163	28	191
Ductal Invasive	137 (84%)	25 (89%)	162 (85%)
Stage 1	59 (36%)	7 (25%)	66 (35%)
Stage 2	80 (49%)	19 (68%)	99 (52%)
Stage 3	23 (14%)	2 (7%)	25 (13%)
Median Age	51	52	52
Pre-Menopausal	65 (40%)	12 (43%)	77 (40%)
Post-Menopausal	88 (54%)	16 (57%)	104 (54%)

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Demographics/Disease Characteristics

	Study 1 (UCSF)	Study 2 (SUNY)	Combined
Node Status			
Negative	85 (52%)	14 (50%)	99 (52%)
1-3 Positive	35 (22%)	8 (29%)	43 (23%)
4 or more Positive	41 (25%)	5 (18%)	46 (24%)
ER Positive	106 (65%)	15 (54%)	121 (63%)
PR Positive	99 (61%)	14 (50%)	113 (59%)
Most Extensive Surgery			
Lumpectomy/Biopsy	13 (8%)	16 (57%)	29 (15%)
Mastectomy	150 (92%)	11 (39%)	161 (84%)
Adjuvant Therapy			
Radiation	95 (58%)	16 (57%)	111 (58%)
Tamoxifen Alone	50 (32%)	14 (50%)	64 (34%)
Adriamycin Combination	43 (26%)	10 (36%)	53 (28%)

Summary of Therapy by Menopausal Status and Node Status

	Node Status			
	Negative		Positive	
Pre-Menopausal	H	8.8%	H	2.3%
	C	55.8%	C	97.6%
Post-Menopausal	H	39.3%	H	67.5%
	C	19.7%	C	32.5%

H = Hormonal Therapy C = Chemotherapy

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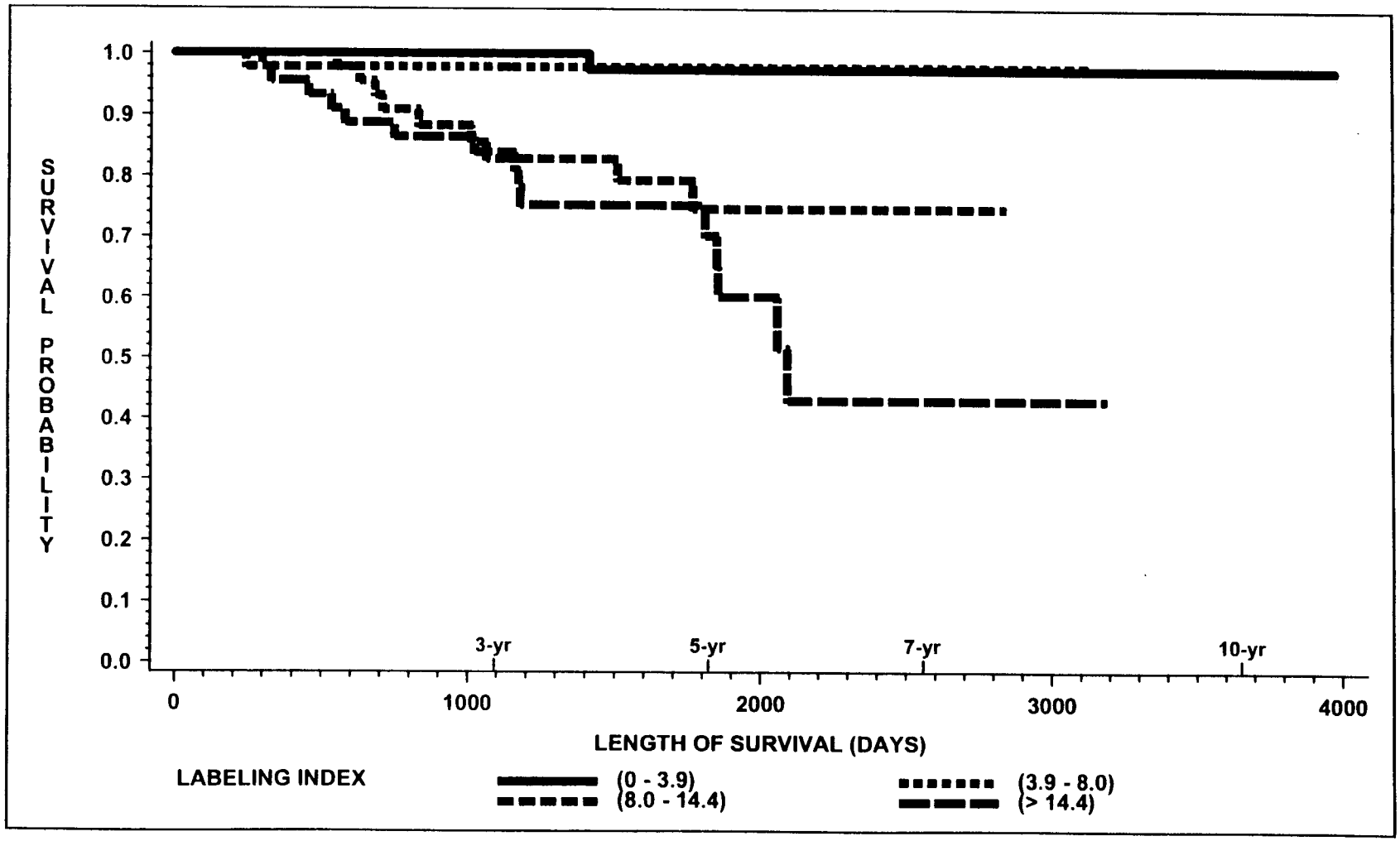
Kaplan-Meier by LI Quartile - Survival



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Cutpoint Determination - Survival

LI Cutpoint	-2 Log Likelihood	Risk Ratio	P- value
6	230.885	22.4	0.0023
7	231.886	13.2	0.0005
8 (near median)	225.914	16.7	0.0001
9	225.130	13.5	0.0001
10	233.649	7.1	0.0001
continuous	239.454	1.1	0.0001

Results generated from pooled studies univariate Cox models.
The smallest -2 Log Likelihood notes the best model fit.

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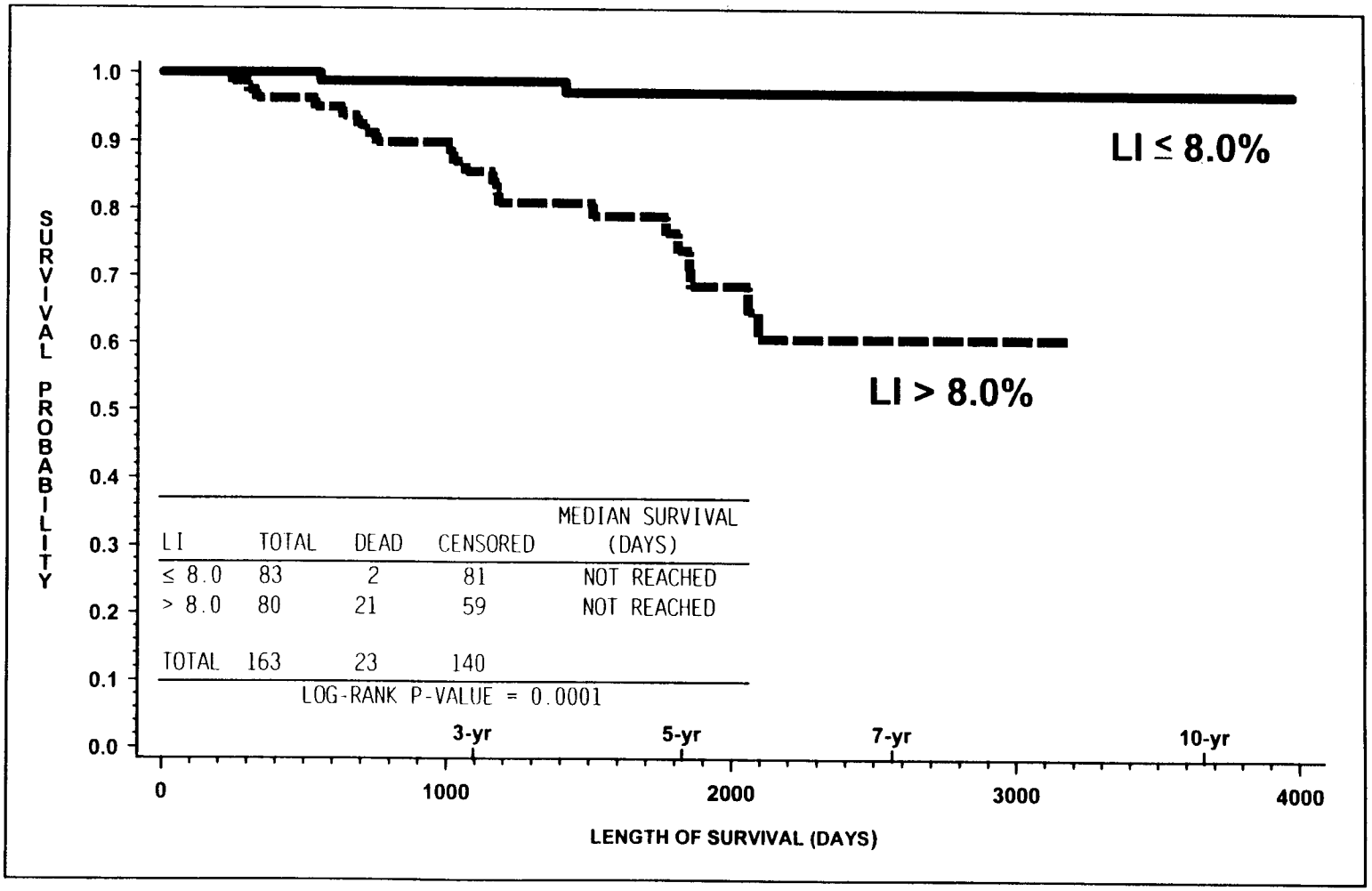
Study 1 Kaplan-Meier - Survival



LI	TOTAL	DEAD	CENSORED	MEDIAN SURVIVAL (DAYS)
≤ 8.0	83	2	81	NOT REACHED
> 8.0	80	21	59	NOT REACHED
TOTAL	163	23	140	

LOG-RANK P-VALUE = 0.0001

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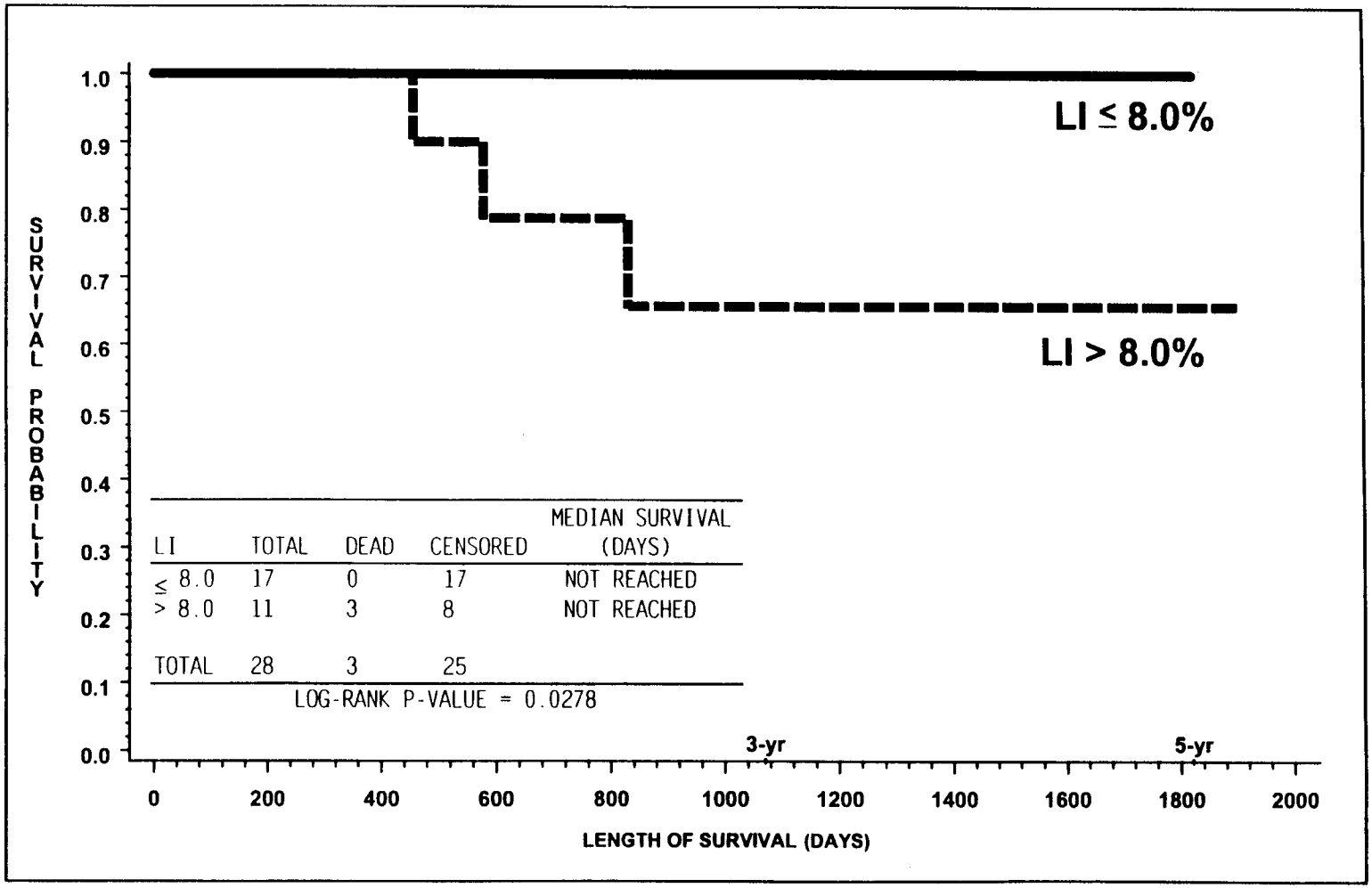
Study 2 Kaplan-Meier - Survival



LI	TOTAL	DEAD	CENSORED	MEDIAN SURVIVAL (DAYS)
≤ 8.0	17	0	17	NOT REACHED
> 8.0	11	3	8	NOT REACHED
TOTAL	28	3	25	

LOG-RANK P-VALUE = 0.0278

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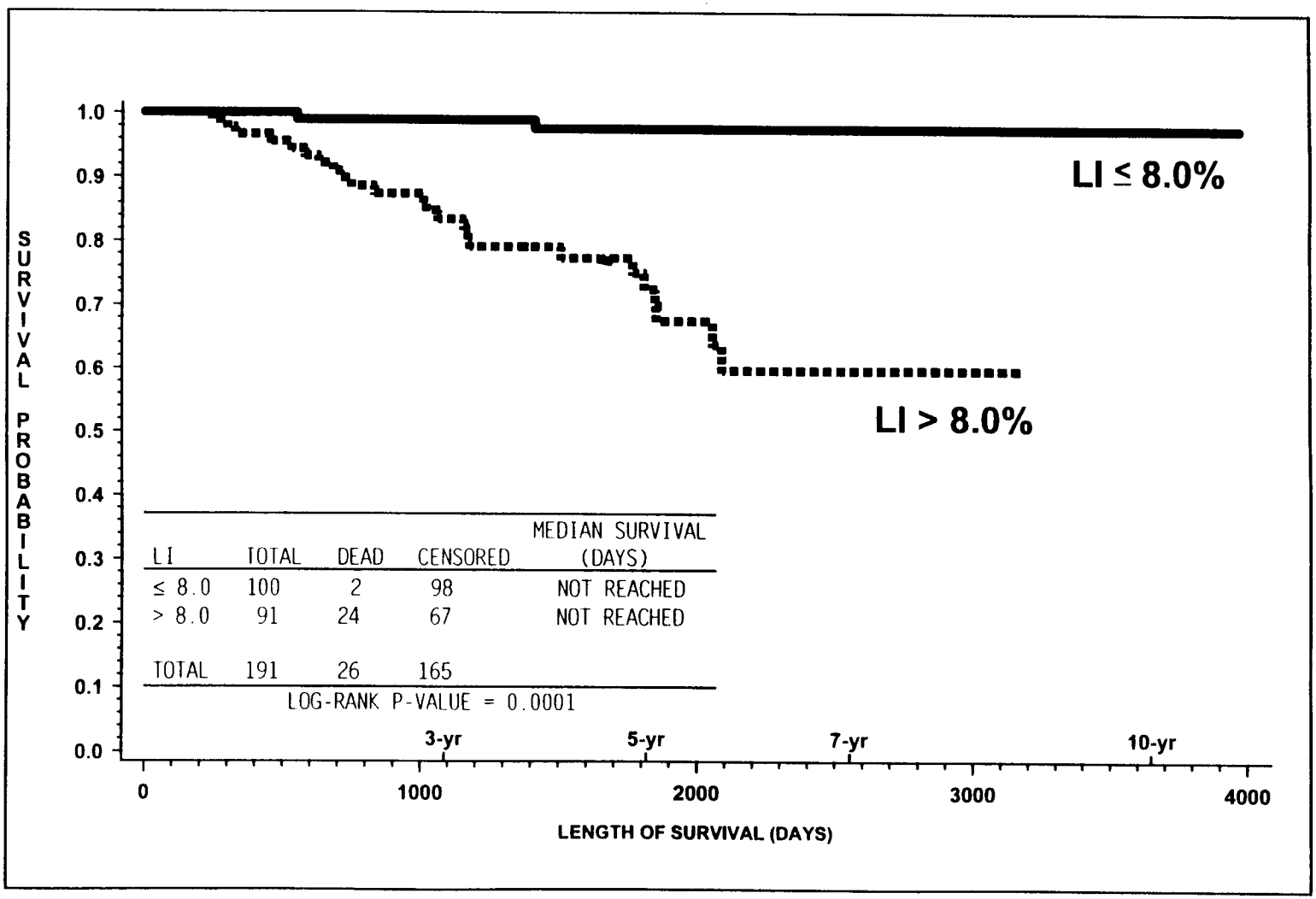
Kaplan-Meier Curves - Survival



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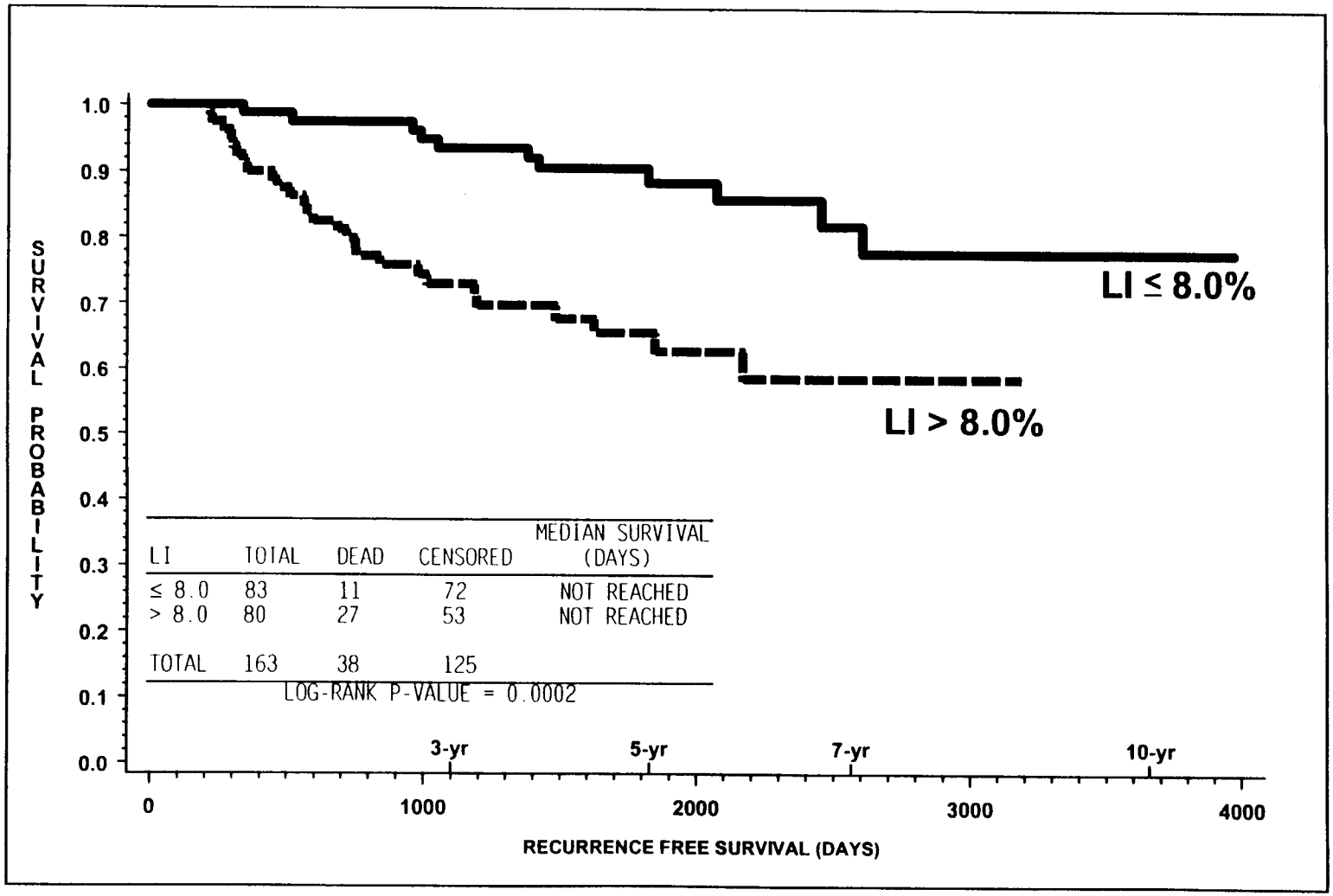
Study 1 Kaplan-Meier - RFS



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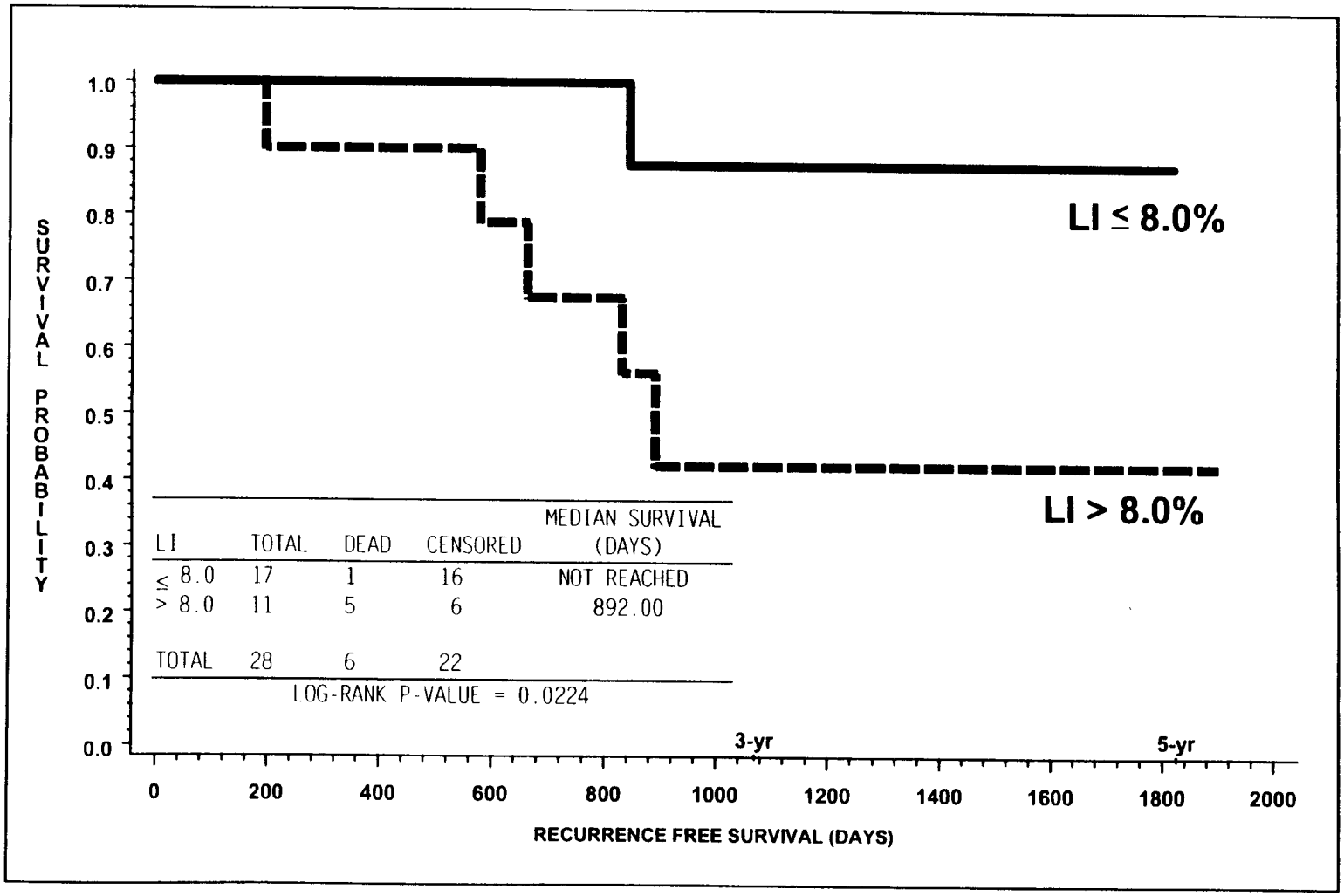
Study 2 Kaplan-Meier - RFS



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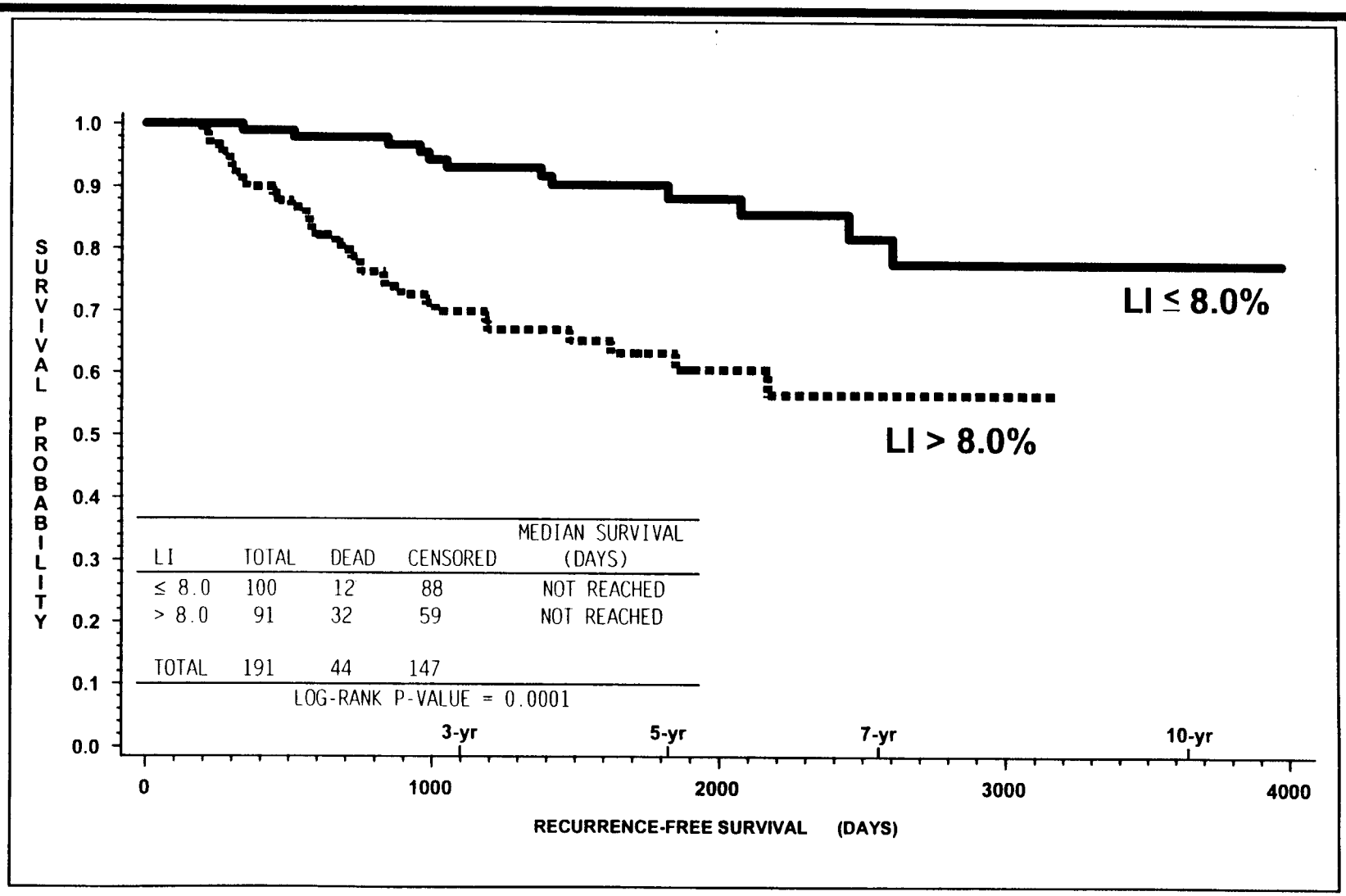
Kaplan-Meier - Recurrence-Free Survival



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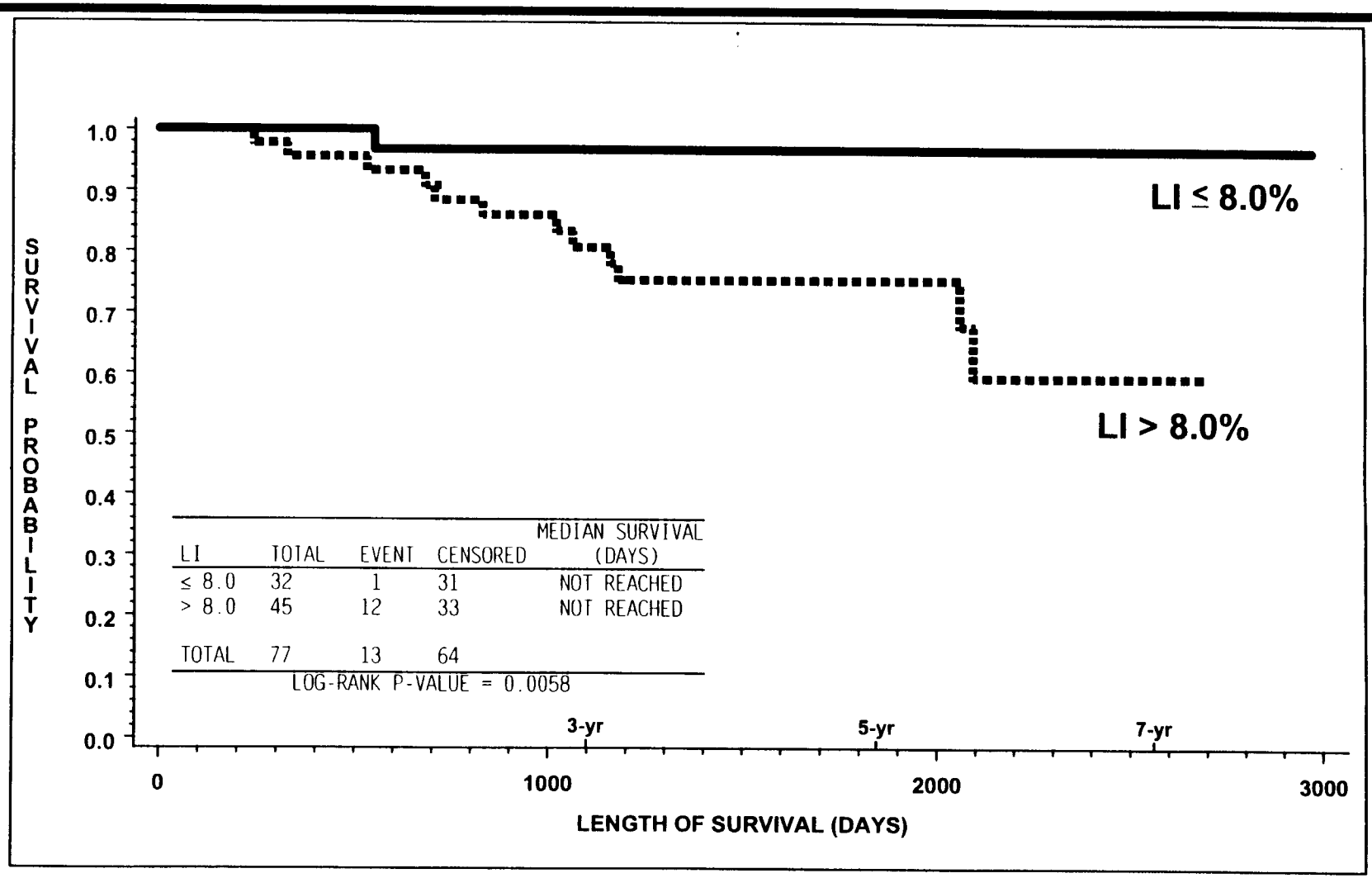
Pre-Menopausal Kaplan-Meier - Survival



LI	TOTAL	EVENT	CENSORED	MEDIAN SURVIVAL (DAYS)
≤ 8.0	32	1	31	NOT REACHED
> 8.0	45	12	33	NOT REACHED
TOTAL	77	13	64	

LOG-RANK P-VALUE = 0.0058

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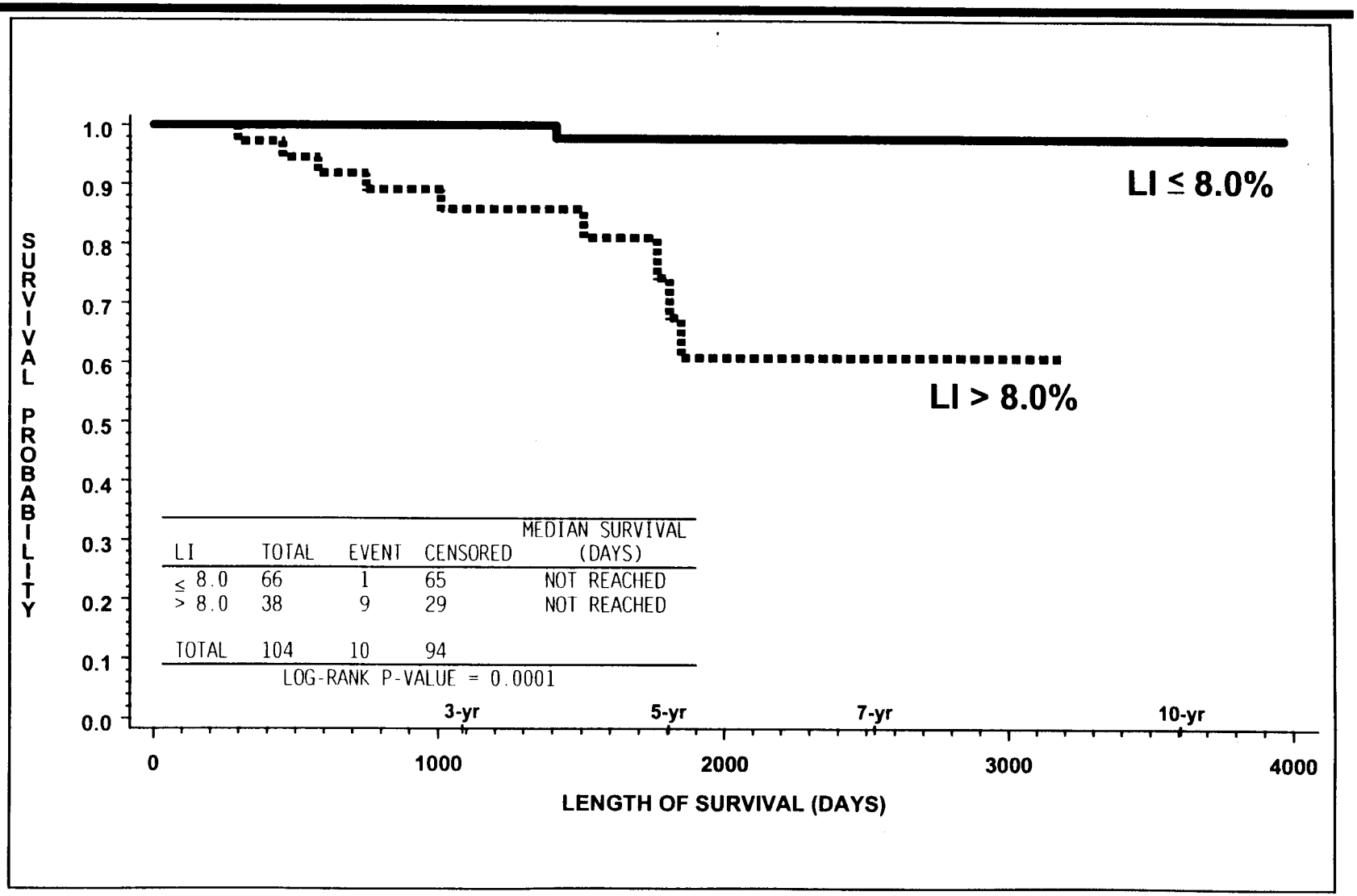
Post-Menopausal Kaplan-Meier - Survival



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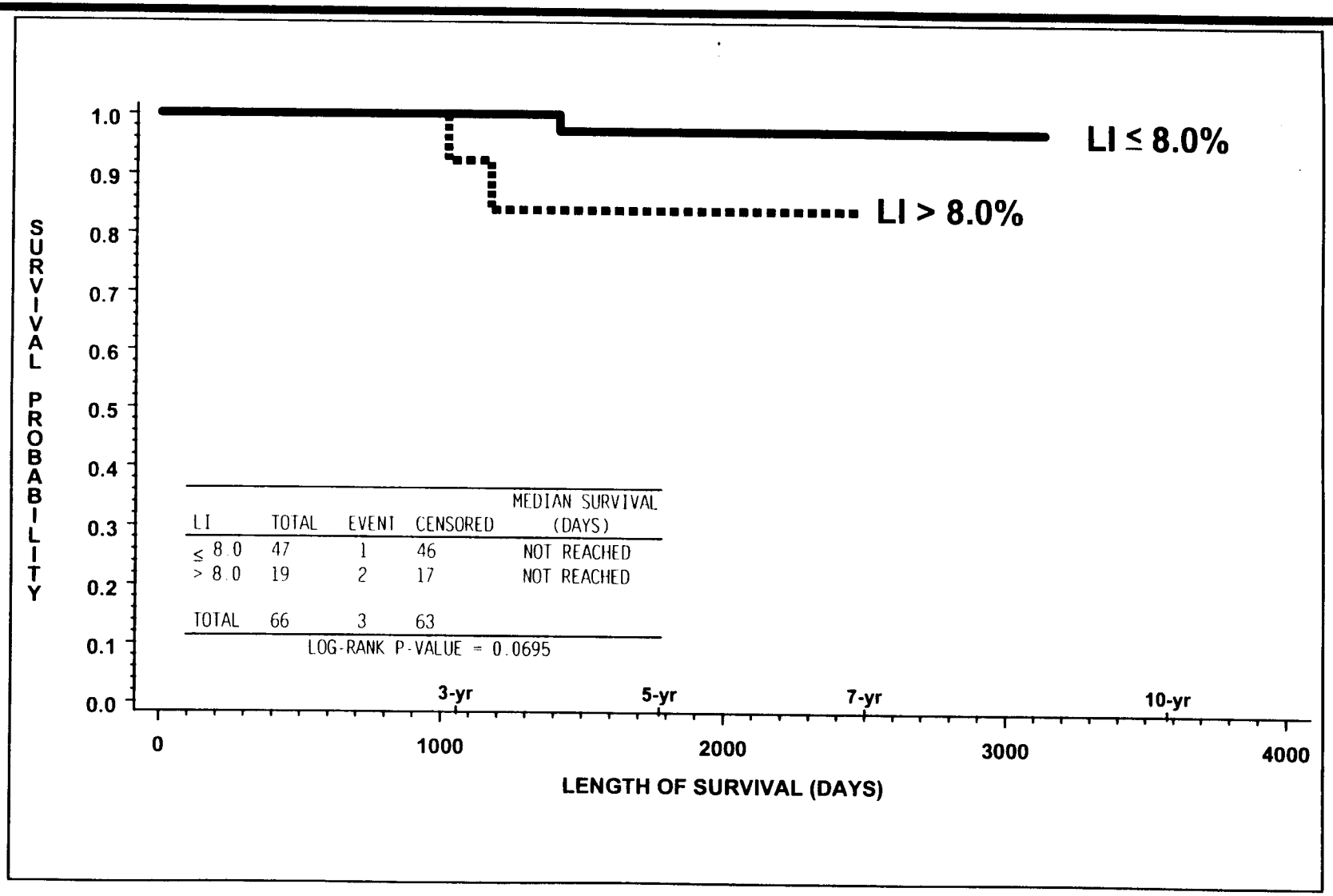
Stage I Kaplan-Meier - Survival



LI	TOTAL	EVENT	CENSORED	MEDIAN SURVIVAL (DAYS)
≤ 8.0	47	1	46	NOT REACHED
> 8.0	19	2	17	NOT REACHED
TOTAL	66	3	63	

LOG-RANK P-VALUE = 0.0695

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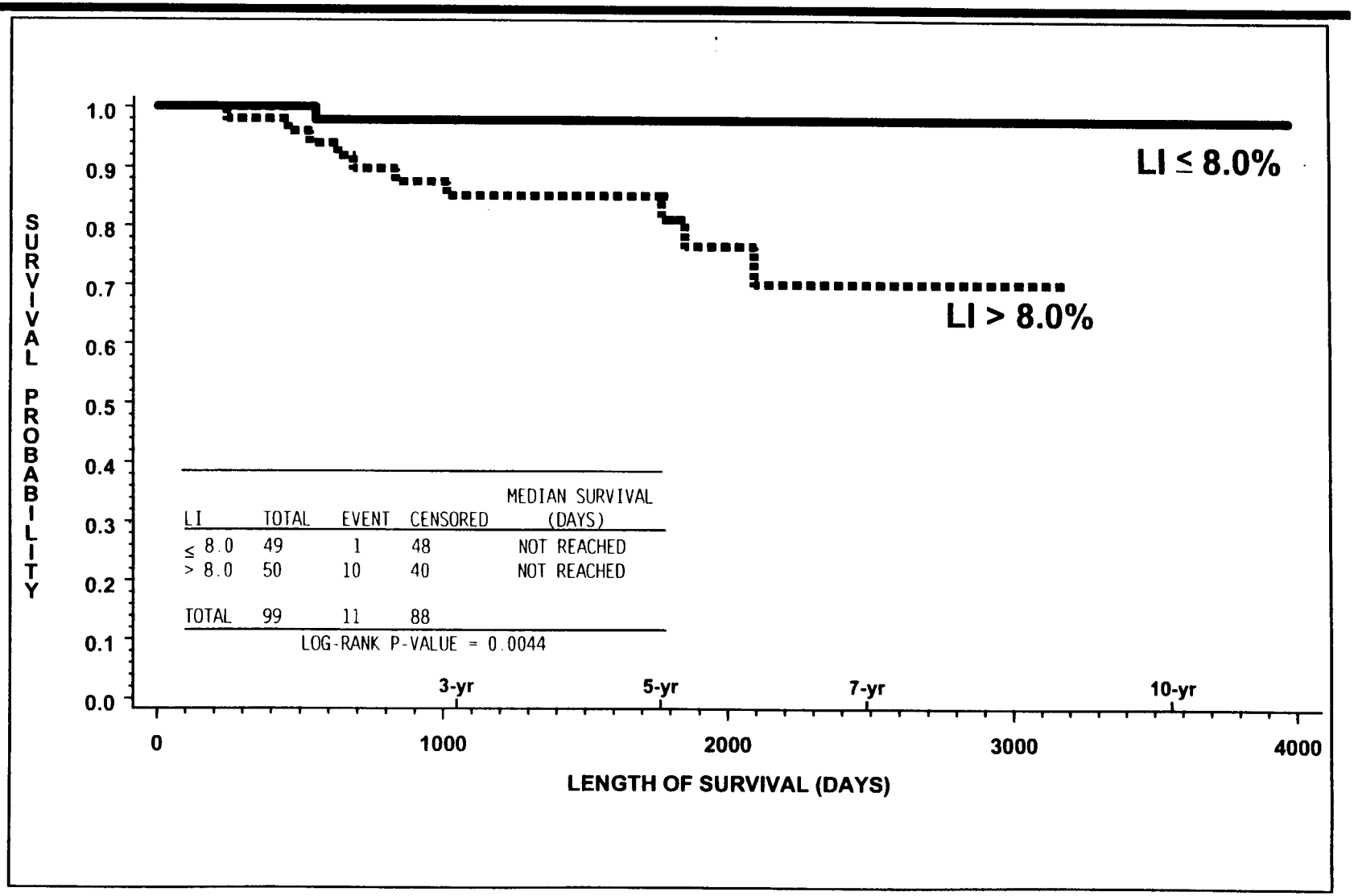
Stage II Kaplan-Meier - Survival



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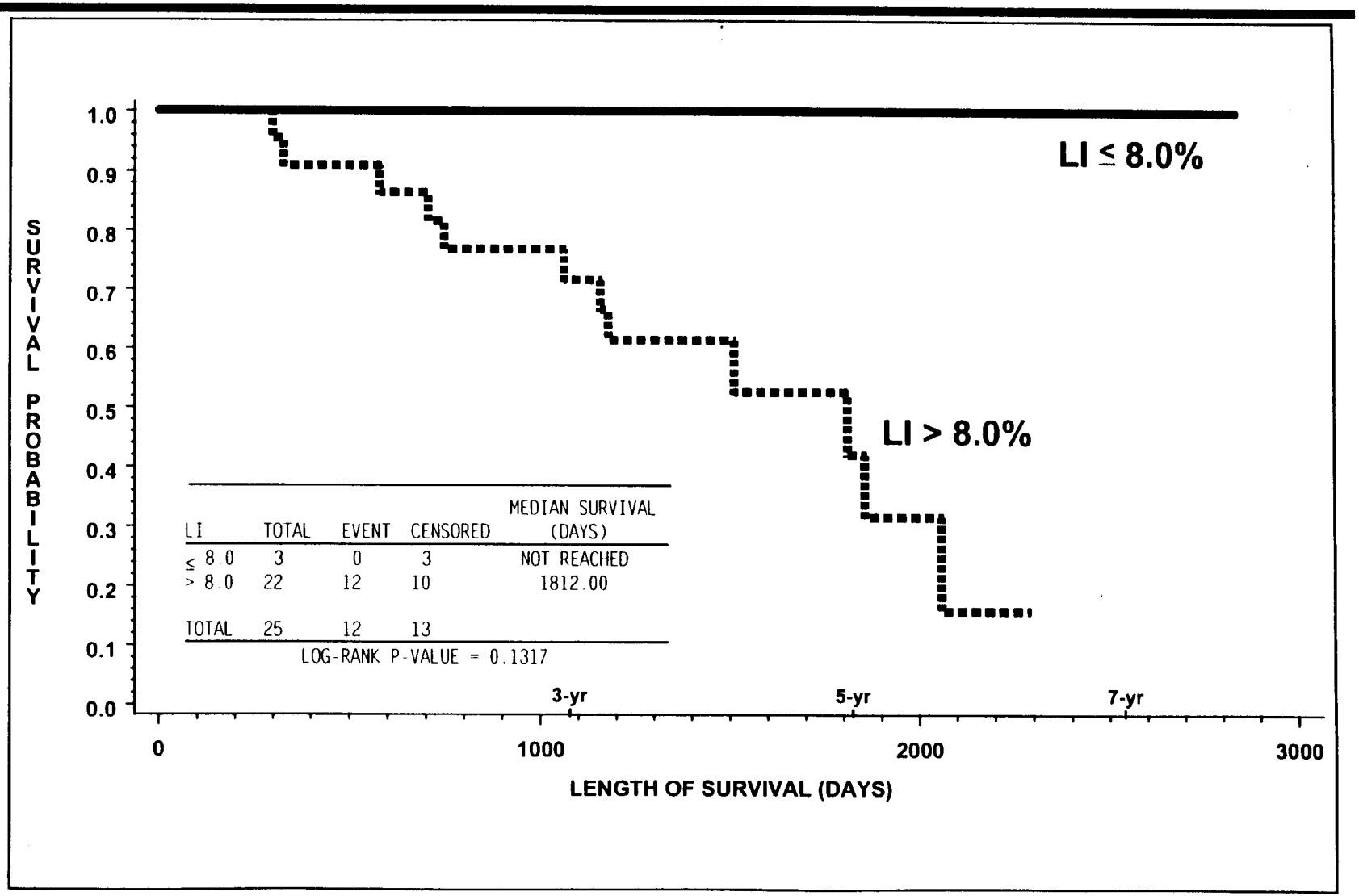
Stage III Kaplan-Meier - Survival



LI	TOTAL	EVENT	CENSORED	MEDIAN SURVIVAL (DAYS)
≤ 8.0	3	0	3	NOT REACHED
> 8.0	22	12	10	1812.00
TOTAL	25	12	13	

LOG-RANK P-VALUE = 0.1317

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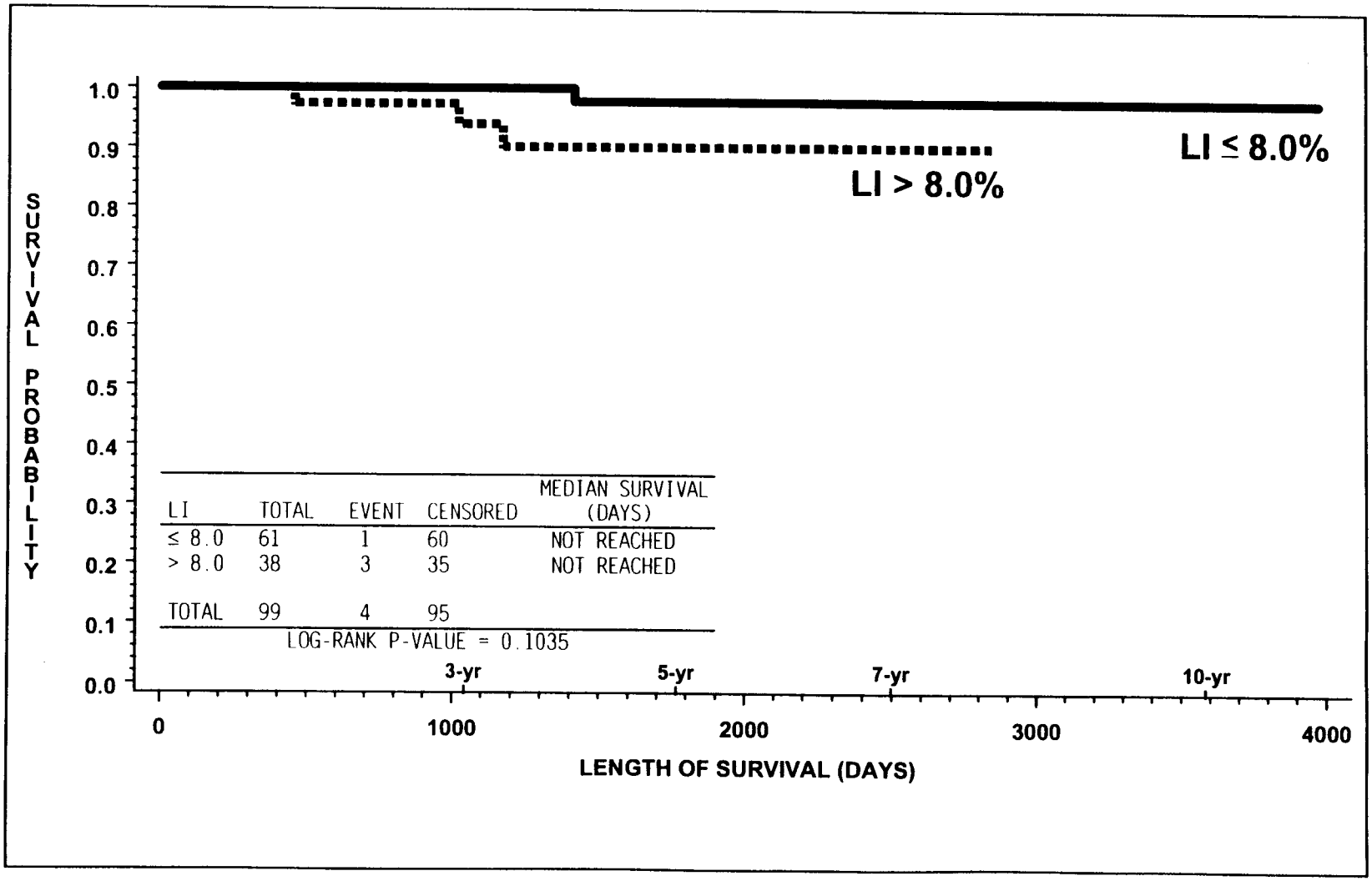
Node Negative Kaplan-Meier - Survival



LI	TOTAL	EVENT	CENSORED	MEDIAN SURVIVAL (DAYS)
≤ 8.0	61	1	60	NOT REACHED
> 8.0	38	3	35	NOT REACHED
TOTAL	99	4	95	

LOG-RANK P-VALUE = 0.1035

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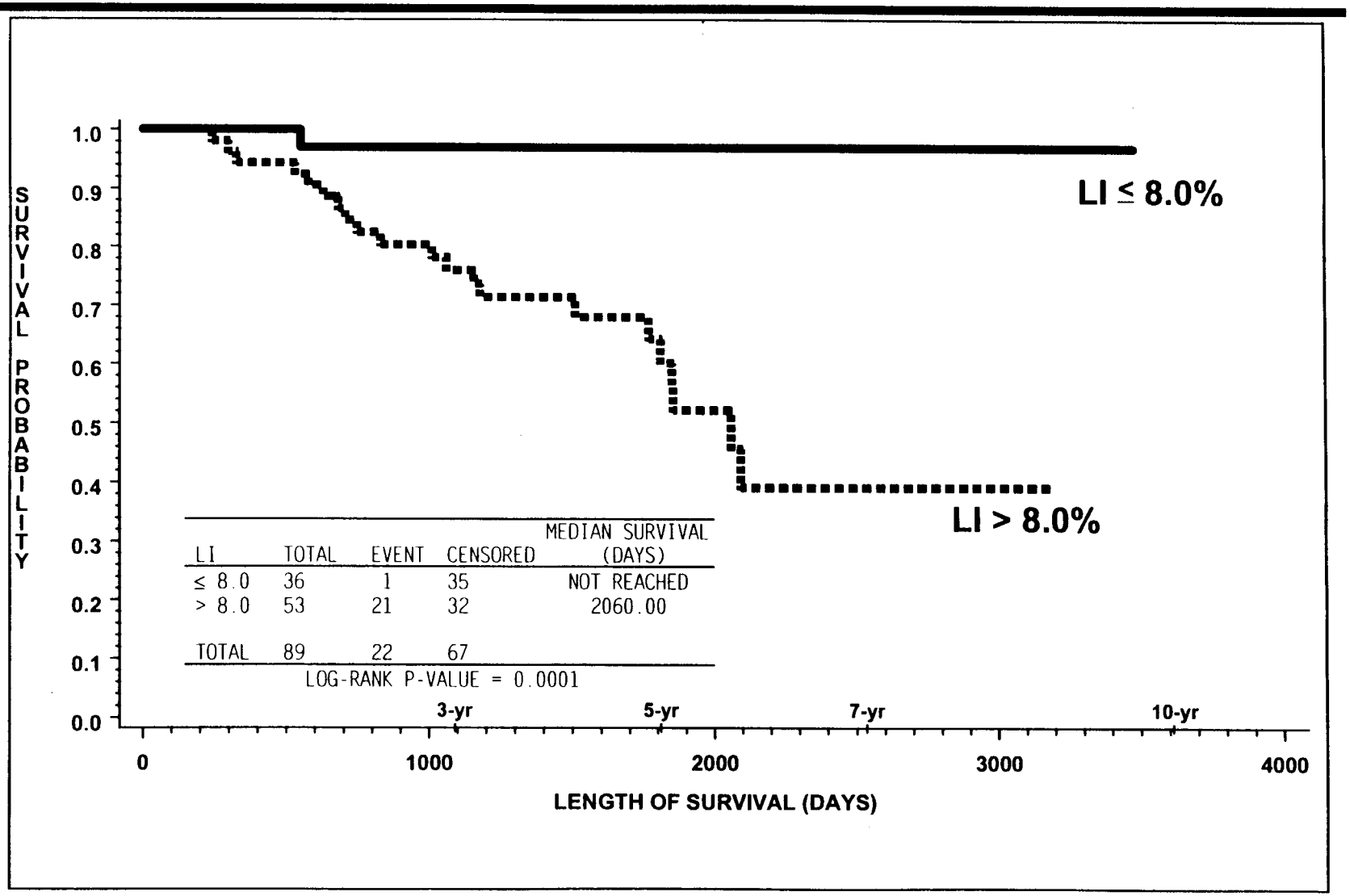
Silvestrini Cox Analysis (1997)
National Tumor Institute, Milan

- 3,800 Node Negative Patients 1972-1991.
- Labeling Index is consistently a strong predictor of survival, recurrence and distant metastases.

Population	Model	Risk Ratio	P-value
Survival	Log(LI)	1.6	0.0050
	ER positive	0.6	0.0600
	Size > 2 cm	1.3	0.3000
Recurrence	Log(LI)	1.6	0.0005
	ER positive	0.8	0.4000
	Size > 2 cm	1.5	0.0300
Metastases	Log(LI)	1.4	0.0050
	ER positive	0.8	0.2000
	Size > 2 cm	1.8	0.0100

Node Positive Kaplan-Meier - Survival



LI	TOTAL	EVENT	CENSORED	MEDIAN SURVIVAL (DAYS)
≤ 8.0	36	1	35	NOT REACHED
> 8.0	53	21	32	2060.00
TOTAL	89	22	67	

LOG-RANK P-VALUE = 0.0001

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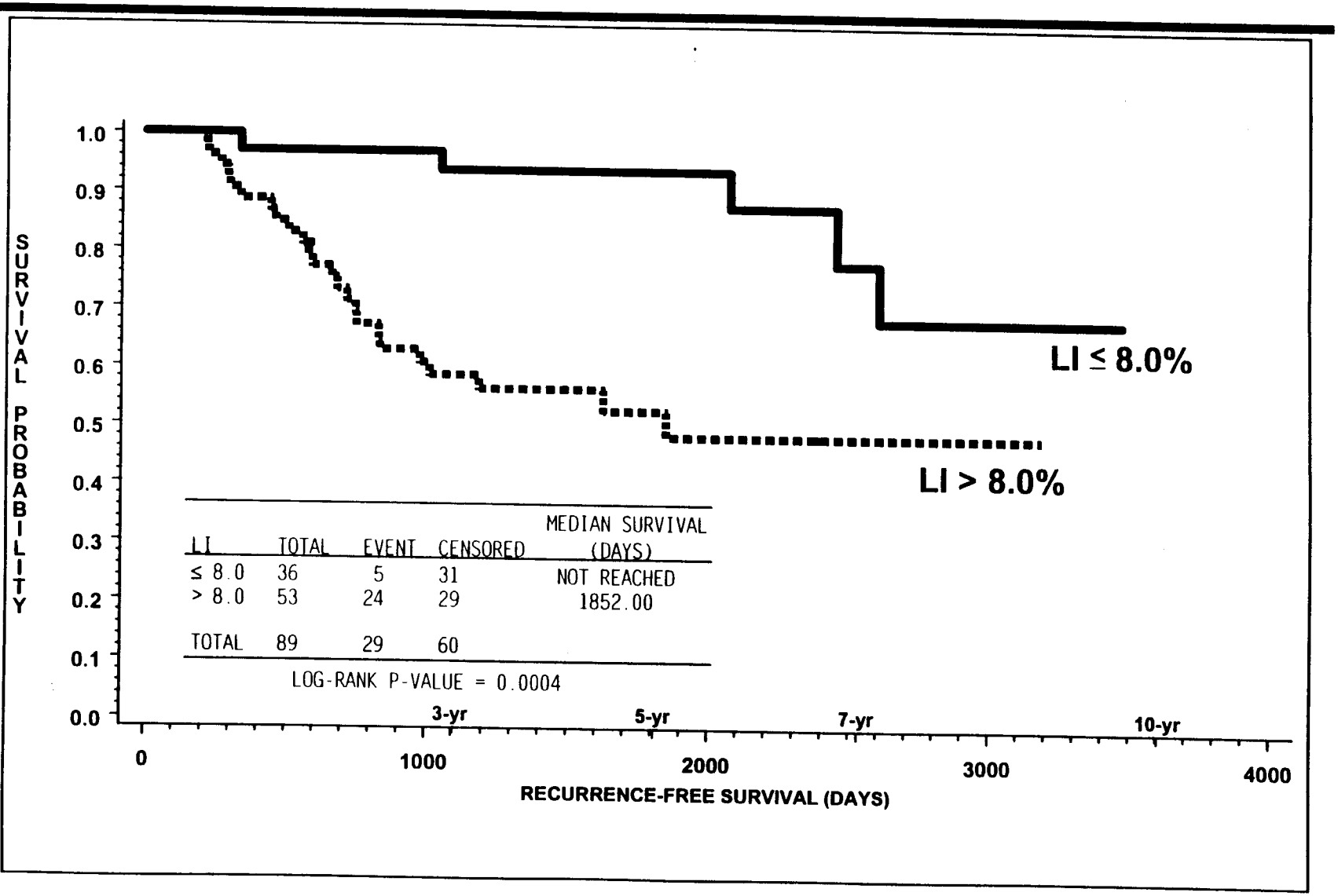
Node Positive Kaplan-Meier - RFS



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Cox Proportional Hazards

Prognostic Factors Investigated

- Study Location
- Labeling Index
- Lymph Node Status
- Menopausal Status
- Tumor Stage
- Histopathology
- Age
- Estrogen Receptor Status
- Progesterone Receptor Status
- Interactions of these factors with Labeling Index

Cox Proportional Hazards - Survival

Survival Analysis Final Model

Model Terms	Risk Ratio	P-Value
Labeling Index	1.080	0.0002
Node Status	6.029	0.0010

-2 Log (Likelihood) = 222.218

APPEARS THIS WAY
ON ORIGINAL

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Cox Proportional Hazards - Survival

Survival Analysis Final Model (LI Dichotomous)

Model Terms	Risk Ratio	P-Value
Labeling Index (> 8%)	12.412	0.0007
Node Status	4.941	0.0034

-2 Log (Likelihood) = 212.557

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ON ORIGINAL

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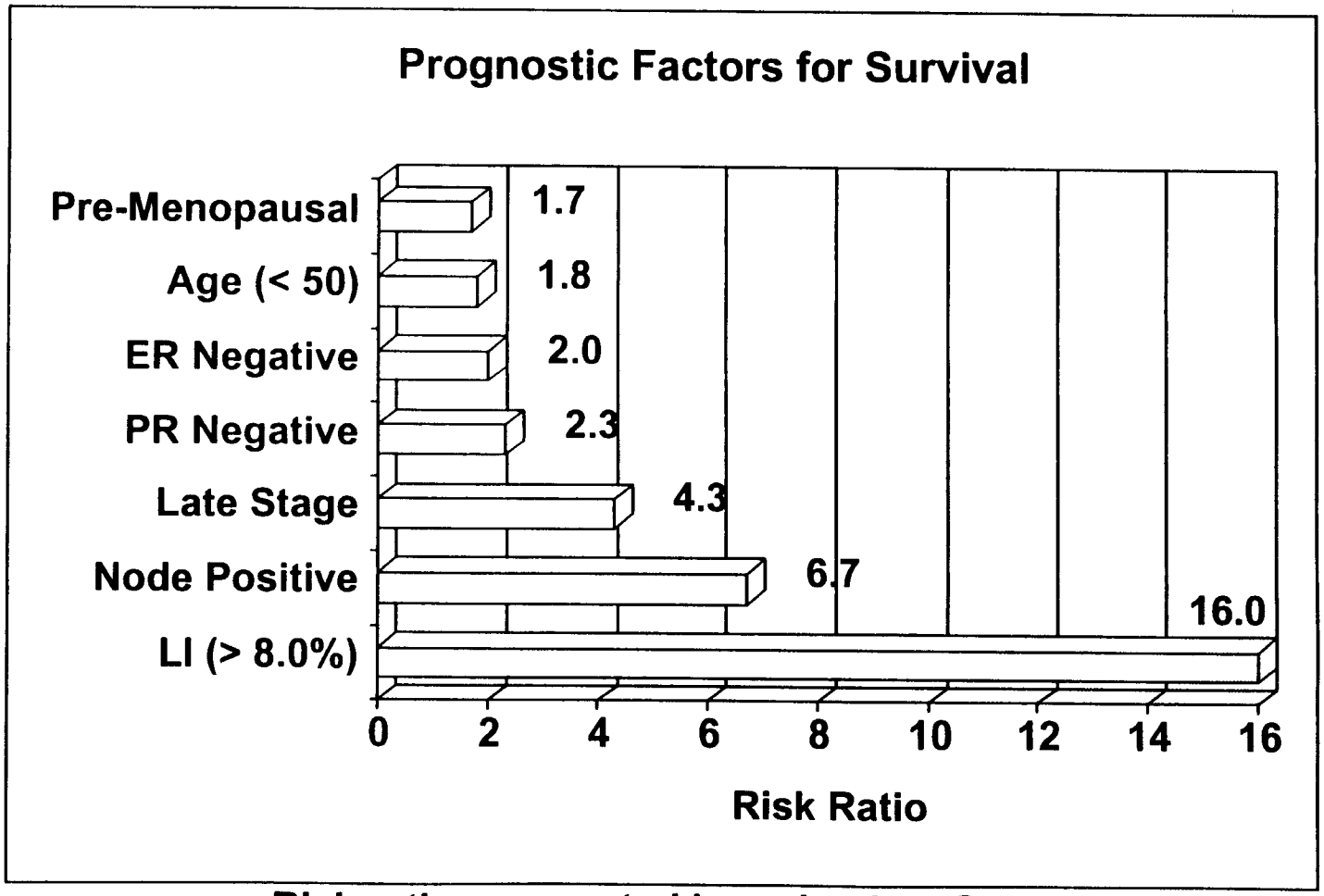
NEOMARK®-BU Labeling Index Compared to Other Known Prognostic Factors - Survival



Risk ratios generated by univariate Cox models.

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Cox Proportional Hazards - RFS

RFS Analysis Final Model

Model Terms	Risk Ratio	P-Value
Labeling Index	1.042	0.0335
Menopausal Status	2.375	0.0103
Tumor Stage	2.941	0.0001

-2 Log (Likelihood) = 355.136

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Cox Proportional Hazards - RFS

RFS Analysis Final Model (LI Dichotomous)

Model Terms	Risk Ratio	P-Value
Labeling Index (> 8%)	2.207	0.0361
Menopausal Status	2.267	0.0159
Tumor Stage	2.729	0.0003

-2 Log (Likelihood) = 354.621

APPEARS THIS WAY
ON ORIGINAL

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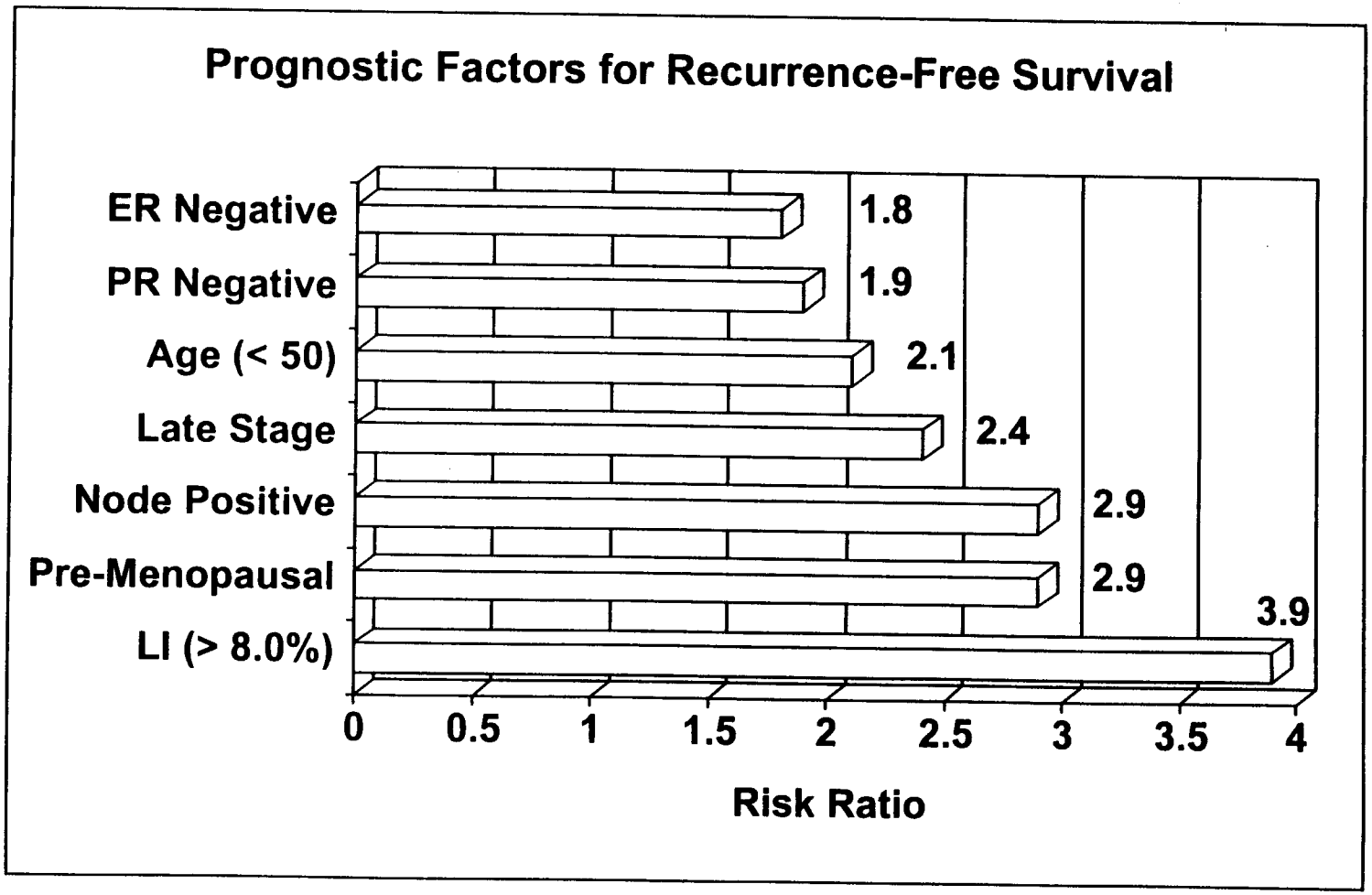
NEOMARK®-BU Labeling Index Compared to Other Known Prognostic Factors - RFS



Risk ratios generated by univariate Cox models.

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Conclusions

- Administration of NEOMARK® is safe.
- NEOMARK® determines the tumor Labeling Index.
- Labeling index is useful information.
  - Helpful planning information for patient.
  - Helpful for physicians:
    - Predicts survival and recurrence probability.
    - Predicts over and above other indicators.
    - Particularly valuable in specific instances:
      - small tumor, no or few nodes, high LI.
      - positive nodes, low LI.
      - borderline results from other indicators.
    - May represent a useful way to stage a tumor.