CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ONCOLOGY DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 09/18-19/97

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SLIDES (PHOTOFRIN)

Photofrin: an Efficacy Supplement for Lung Cancer

Medical Officer Presentation to the Oncologic Drugs Advisory Committee

Grant Williams, M.D.

September 18, 1997

FDA Review Team

- Medical
  - Grant Williams, M.D. (primary)
  - Robert Justice, M.D.
- Statistical
  - Tony Koutsoukos, Ph.D. (primary)
  - Claire Gnecco, Ph.D.
- Scientific Investigations: Gurston Turner
- Project Manager: Paul Zimmerman, R.Ph.

Electronic Interactions with DODP during NDA Review

- Study Reports and Protocols in electronic format
- All primary data translated to useful format
- Good documentation of data including annotated CRFs
- Electronic mail communication
- Arrangements at Pre-NDA meeting

Palliation of Obstructive NSCLC Randomized Studies

Study#	Location	Accrual (Actual/planned)
P503	Europe (15 sites)	141/150
P17	US (20 sites)	70/212

Study Design

- 2 Randomized, open-label multi-center controlled trials:

Thermal ablation with Nd:YAG (YAG)

vs.

PDT with Photofrin (PDT)

Study Design: Problems

Primary Endpoints

- TTR: Not practical.
- Symptom palliation
  - No prospective analysis plan
  - Subject to bias
  - Sensitive to quality (completeness) of data

Study Design: Problems

- Response
  - Tumor measurements not done regularly.
  - Luminal response
    - It was a component of response definition
    - 50% increase may not always be meaningful
    - Analysis plan not specified (1 wk, 1 mo, etc.)
  - Data on per cent obstruction was also collected

Study Design: Different Treatment Schedules

PDT:

A course is one Photofrin injection followed by 1-2 laser Rxs. May retreat in 30 days.

YAG:

A course may have multiple laser sessions; the course ends if palliation is achieved or if investigator deems additional treatment would be futile.

Study Design: Different Offstudy criteria

- Patients should be removed from study :
  - if there is no evidence of symptom palliation or there is no objective evidence of response (i.e., stable disease) after two complete courses of PDT (up to two injections of PHOTOFRIN II and up to four laser light treatments)

    or
  - if further treatment with the ND:YAG laser is deemed futile.

Study Design: Potential for bias

- Measurements of palliation and response may vary with treatment schedule.
- Different definitions of 'course'
- Different off-study criteria may encourage more dropouts on YAG
  - Less chance for response
  - Less time to report adverse events

Study Design FDA conclusions

- Statistical comparisons between study arms are unreliable because of :
  - Retrospective determination of primary response endpoint and time windows
  - Retrospective analytical plan
  - Asymmetry of design for off-study criteria
  - P17 was a small study, stopped prematurely

Extent of Follow-up

Studies P503 and P17 combined

	PDT n=99	Nd:YAG n=99
30 days	14	24
31-61 days	25	24
62-91 days	14	18
92-182 days	31	22
183-365 days	9	10
>365 days	6	1
Median follow-up	78d	71d

Disposition of Patients
Studies P503 and P17 combined

	PDT n=102	Nd:YAG n=109
Not treated	3 (3%)	10 (9%)
Progressive Dz	35 (35%)	39 (36%)
Death	29 (29%)	29 (27%)

•Note: At least 35% of patients in each arm went off-study for a reason other than death or progression.

Luminal Response
QLT analysis of Month 1 time window

	PDT	YAG
Trial P503	61% (42/69) p = 0.002	35% (25/72)
Trial P17	42% (14/33) p = 0.04	19% (7/37)

Note: No month 1 data in 32% on PDT and in 46% on YAG

Luminal Response
FDA analysis of Day 18 and after time window

	PDT	YAG
Trial P503	64% (44/69) p = 0.09	49% (35/72)
Trial P17	52% (17/33) p = 0.01	22% (8/37)

FDA Analyses of Response

- Other FDA ad hoc analyses of response
  - Threshold change in luminal diameter (3mm, 5mm)
  - Change in % obstruction
- Conclusions from ad hoc analyses:
  - PDT numerical advantage persists, but difference is less marked.
  - Greatest differences seen in month 1 time window.

Study Design: Problems

Other endpoints
- Time to treatment failure
- Time to Local Progression ✓

- These are not suitable for statistical comparison
  - Endpoints are aggregates of fuzzy elements
  - Some elements subject to bias or missing data

Symptom improvement
QLT analysis: Month 1 improvement

	PDT	YAG
Dyspnea	30%	17%
Cough	27%	13%
Hemoptysis	30%	21%
Sputum	20%	13%
Missing Data	26-28%	41-44%

Quality of symptom data
Problems with comparing Study Arms

- No prospective analysis plan
- Missing data
  - Large amount
  - Asymmetric
- Month one cutoff favored PDT
  - Excluded 8 improvements on YAG versus 2 on PDT (Trial P503)

Skewed in time positive

Clinically Important Benefit
QLT Definition

- Defined as any of the following
  - Marked improvement in Sxs at month 1
    - 2-3 grades improvement or
    - 40% improvement in FEV1
  - Moderate improvement in Sxs at month 2
    - 1-2 grade improvement or
    - 20% improvement in FEV1
  - Durable Luminal Response (month 2)

Clinically Important Benefit
QLT and FDA Results

- Patients showing benefit, QLT analysis
  - 36 PDT patients
  - 23 YAG patients
- FDA
  - Reviewed Graphical summary of 36 PDT patients
  - Concurs with clinical benefit in 33 PDT patients (32% overall)

Safety Findings
Selected Categories of Toxicity, PDT vs YAG

	PDT(%) n = 99	YAG(%) n=99
Photosensitivity	20	0
Psychiatric	14	5
Dyspnea	32	17
Bronchitis	11	3
Hemoptysis	18	12

Safety Findings
Selected Categories of Toxicity, PDT vs YAG

	PDT(%) n = 99	YAG(%) n=99
FMH	10	6
No prior XRT	2	0
Prior XRT	24	14
AE's		
Severe	22	25
Life-threatening	19	8
Median survival	166d	157d
Deaths w/i 30d	16%	17%

PDT for Palliation of NSCLC
Summary of findings

- PDT Efficacy findings
  - 64% and 52% luminal response after day 18
  - 32% with 'clinically important benefit'
  - Efficacy findings numerically superior to those on YAG arm; statistical comparisons suspect.
- PDT Safety findings
  - More photosensitivity, dyspnea, bronchitis, psychiatric AE's
  - Nonsignificant increase in hemoptysis and FMH

Photofrin for Superficial NSCLC Single Arm Studies

Study#	Total Patients	Prospectively Accrued
P505	32	14
P506	29	0
P507	41	41

INDICATION Patients

Was Surgery and XRT contraindicated?

- Of 24 INDICATION patients
  - 17 had either multifocal disease or Previous XRT
  - 7 remaining had significant pulmonary compromise with FEV1 ranging from 0.6-1.0 L
- Safety and efficacy were similar to that in ALL patients

FDA review of data quality

- Methodology
  - Reviewed individual data (electronic, tabulations, and case records)
  - Established last biopsy date
- Findings
  - In time-to-recurrence listings, there were large gaps in time between last biopsy and date of recurrence
  - Frequencies of biopsies often inadequate
  - Many CR1 had only early biopsies

Efficacy Findings

- CR1
  - All patients 79% (79/100)
  - Indication pts 92% (22/24)
- 3-month CR1
  - All patients 47% (46/97)
  - Indication pts 62% (16/21)

QLT CR1 and FDA 3-month CR1 by baseline tumor stage

Tumor Stage	# Total	CR1	3-month CR1
T1	61	50 (82%)	31 (51%)
T2-T3	8	2 (25%)	1 (13%)
TIS	28	27 (96%)	14 (50%)

Findings in T1 patients

(refer to listing, p 13 review update)

- 31/61 (51%) documented 3-month CR1
- 19/61 (31%) documented 1-year CR1
- Individuals with negative biopsies out to 5 years.

Efficacy Findings (cont.)

- Median Disease-Specific Survival: 5.7 years
- Median Survival: 3.5 years

Superficial tumors: Safety

- Adverse Events (102 patients)
  - Severe: 6%
  - Life-threatening 5%
- More AE's reported in Study P505
  - 94% had at least one AE
  - 33% incidence of stricture
- 3 deaths from FMH; one 20 days after procedure

Superficial Tumors, conclusions

- Important questions
  - In view of the natural history of superficial tumors do the response data (CR1, 3-month CR1, etc.) represent clinical benefit for this group or for a major subgroup (T1 tumors)?
  - Were Surgery and Radiotherapy indeed contraindicated in the INDICATION patients?

PHOTOFRIN® (porfimer sodium) for Injection

PRESENTATION SLIDES
ONCOLOGIC DRUGS ADVISORY COMMITTEE

September 18, 1997

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, B. C. V5Z 4H5

PHOTOFRIN® PDT Supplement - Lung Cancer

Palliation

- Two adequate and well controlled studies demonstrated the efficacy and safety of PHOTOFRIN® PDT in the palliation of endobronchial obstruction.

Superficial Cancer

- These independent studies and literature review provided consistent evidence of efficacy and safety of PHOTOFRIN® PDT in the treatment of patients with no standard therapeutic option.

NDA 20-451 S-002
for Lung Cancer

PHOTOFRIN® (porfimer sodium)
for Injection

Intro-1

PHOTOFRIN® (porfimer sodium)
for Injection

- First approval - December 1995
  - Palliation of obstructing esophageal cancer
- Supplement for lung cancer - February 1997

Intro-2

Supplemental Indication

1. "Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer (NSCLC)"

   - Parallels first approval
   - 2 company-sponsored studies, 211 patients
   - P17 (US) discussed with FDA

Intro-3

Supplemental Indication

2. "Treatment of endobronchial carcinoma in situ or microinvasive NSCLC in patients for whom surgery and radiotherapy are not indicated"

   - 3 investigator-sponsored studies, 102 patients over 10 years (1986-1996)
   - Consistent with draft guidelines

Intro-4

PHOTOFRIN® for Lung Cancer

Introduction:	**Alexandra Mancini, MSc** Vice President, Regulatory Affairs, QLT
Palliation:	**Mohammad Azab, MD, MSc** Vice President, Clinical Research and Medical Affairs, QLT
Superficial Tumors:	**Eric Edell, MD** Associate Professor of Medicine, Mayo Medical School
Conclusions:	**Mohammad Azab, MD, MSc**

External Consultants

Thoracic Surgeon:	**Harvey Pass, MD** Professor of Surgery and Oncology Wayne State University Chief, Thoracic Surgery VA Hospital, Detroit
Radiation Oncologists:	**Seth Rosenthal, MD** Assistant Radiation Professor University of California (SF) Radiation Oncologist Radiation Oncology Centers of Northern California
	Howard Sandler, MD Associate Professor, Department of Radiation Oncology, Associate Chair for Clinical Research University of Michigan

PHOTOFRIN® PDT

Palliation of Obstructing Endobronchial NSCLC

Mohammad Azab, MD, MSc
Clinical Research
QLT PhotoTherapeutics Inc.

Intro-7

APPEARS THIS WAY
ON ORIGINAL

PHOTOFRIN® PDT

Palliation of Obstructing Endobronchial NSCLC

Mohammad Azab, MD, MSc
Clinical Research
QLT PhotoTherapeutics Inc.

Background

- 178,000 new lung cancer cases per year (1997)
- 160,000 deaths per year (1997)
- Leading cause of cancer deaths
- Approximately 20% of newly diagnosed cases present with symptoms/complications of endobronchial obstruction

Palliation of Endobronchial Obstruction

Current Therapeutic Options

Physical	Cytotoxic
Rapid Effect	Slower Effect
• Thermal ablation – Nd:YAG • Mechanical debridements/stents • Others	• Radiotherapy • Chemotherapy

Palliation-11

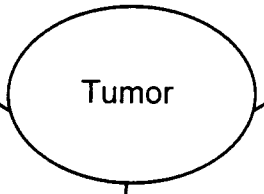
PHOTOFRIN® PDT Mechanism of Action

PHOTOFRIN®

2 mg/kg IV

Light Source

630 nm red light



Local Selective Cytotoxicity

- Direct tumor kill
- Neovasculature shutdown

Palliation-12

PHOTOFRIN® PDT
Clinical Development Program

Study	Design	No. Pts
Key Studies		
P17	Phase III	70
P503	PHO PDT vs. Nd:YAG	141
		211
Supportive Studies		
P21	Phase II dose ranging	170
P2		57
P18	Phase III	35
P23	PHO PDT + XRT	25
P504	vs. XRT	78
		365

Palliation-13

PHOTOFRIN® PDT vs Nd:YAG
Key Clinical Studies

- Open label, randomized, identical design
- Symptomatic pts with endobronchial obstruction

Study P17	20 centers	US/Canada	70 pts
Study P503	15 centers	Europe	141 pts
			211 pts

Palliation-14

Protocol's Treatment Schedule

PHOTOFRIN® PDT Single Course

Day 1	Day 3	Day 5
PHOTOFRIN® 2 mg/kg IV	**Light session (630 nm nonthermal red light) 200 J/cm**	**Debridement + optional 2nd light session**

Palliation-15

Protocol's Treatment Schedule

Nd:YAG Single Course

- Unlimited number of sessions and light energy dose
- Goal to ablate all accessible tumor
- Debridement

Palliation-16

Protocol's Efficacy Endpoints

- Objective Tumor Response : endoscopic assessment of smallest luminal diameter
  - Complete response
  - Partial response
- Symptom Palliation : prospective scales
  - Dyspnea, cough, hemoptysis, sputum

Protocol's Efficacy Endpoints

- Time to Tumor Recurrence → Time to Local Progression
- Time to Treatment Failure

➢ Assessments : Week 1, Month 1, 2, 3, 6
➢ Analyses : intention-to-treat

Results
Baseline Characteristics

	P17		P503	
	PHO n=33	Nd:YAG n=37	PHO n=69	Nd:YAG n=72
Men	73%	78%	87%	83%
Median age	64	66	68	65
Median KPS	70	70	70	70
Squamous Cell Carcinoma	73%	68%	86%	74%
Stage III or IV	82%	78%	70%	82%
Cardiovascular or respiratory disease	73%	65%	62%	57%
Prior treatment	88%	95%	33%	31%

Palliation-19

Results
Baseline Characteristics
(continued)

	P17		P503	
	PHO n=33	Nd:YAG n=37	PHO n=69	Nd:YAG n=72
Mainstem tumors	61%	46%	51%	54%
≥ 90% endobronchial obstruction	67%	57%	61%	64%
Atelectasis	79%	95%	57%	58%
Dyspnea	97%	92%	88%	88%
Cough	91%	90%	95%	89%
Hemoptysis	58%	59%	61%	56%
Sputum	82%	76%	73%	70%

Palliation-20

Course 1 - ITT Analysis

Objective Tumor Response

Week 1 (Day 1-17)
Month 1 (Day 18-45)

	P17		P503	
	PHO n=33	Nd:YAG n=37	PHO n=69	Nd:YAG n=72
CR + PR				
Week 1	45%	51%	65%	61%
Month 1	42% *	19%	61% *	36%

* $p < 0.05$

Palliation-21

Course 1 - ITT Analysis

Objective Tumor Response

	P17		P503	
	PHO n=33	Nd:YAG n=37	PHO n=69	Nd:YAG n=72
Stable disease				
Week 1	18%	14%	22%	17%
Month 1	3%	24%	12%	17%
Progression				
Week 1	3%	3%	3%	0%
Month 1	9%	11%	1%	3%
Not assessed				
Week 1	33%	32%	10%	22%
Month 1	45%	46%	26%	46%

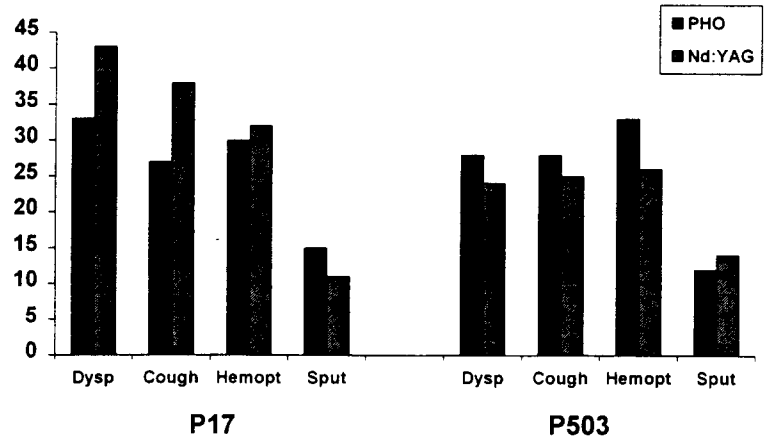
Palliation-22

Objective Tumor Response
Discussion

- Consistency of higher PHO PDT responses in 2 randomized multicenter trials in ITT analysis
- Higher PHO PDT response rate in the analysis of evaluable patients
- Same pattern of higher PDT response rate
  - Using different response criteria
  - Using best response at any time point

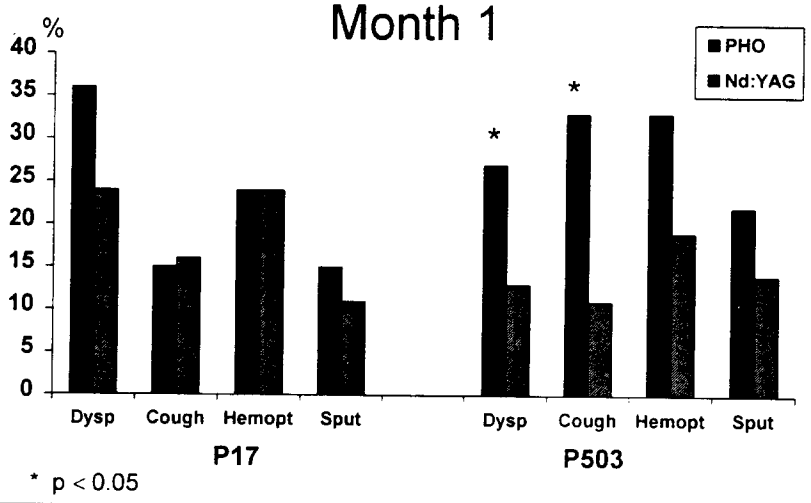
Palliation-23

Symptom Palliation (ITT)
% Patients With Improved Symptoms
Week 1



Palliation-24

Symptom Palliation (ITT)
% Patients With Improved Symptoms
Month 1



* $p < 0.05$

Palliation-25

Month 1 Palliation of Patients With Severe Symptoms (Gr ≥3)

	P17 + P503 COMBINED	
	PHO	**Nd:YAG**
	n=102	**n=109**
Dyspnea	n=30	n=39
Improvement ≥ 1 grade	**50%**	**28%**
Improvement ≥ 2 grades	**33%**	**13%**
Cough	n=14	n=11
Improvement ≥ 1 grade	**50%**	**27%**
Improvement ≥ 2 grades	**29%**	**9%**
Hemoptysis	n=6	n=11
Improvement ≥ 1 grade	**50%**	**18%**
Improvement ≥ 2 grades	**50%**	**18%**
Sputum	n=1	n=4

Palliation-26

Clinically Important Benefit

- Clinically Important Symptom Relief
  - 2 grades dyspnea, or 3 grades of cough or hemoptysis at Month ≥ 1
  - 1 grade dyspnea, or 2 grades cough or hemoptysis through Month ≥ 2
  - Elimination of all symptoms

and/or

Durable CR or PR to Month ≥ 2

- No or minimal adverse events
- No intervening therapy

Palliation-27

Clinically Important Benefit

	P17 + P503 COMBINED	
	PDT n=102	Nd:YAG n=109
Pts with clinically important benefit	**36%**	**23%**
Clinically important symptom relief	**23%**	**12%**
Durable objective tumor response	**27%**	**19%**
Median duration of benefit (days)	**63+**	**67+**
Range	**(1+ - 738)**	**(1+ - 542+)**
Number of patients still in response at last assessment	**23**	**20**

Palliation-28

Efficacy Summary

Efficacy Parameter	P17 + P503 COMBINED PHO n=102	Nd:YAG n=109
CR + PR (Week 1)	59%	58%
CR + PR (Month 1)	55% *	29%
Symptom palliation (Month 1)		
Dyspnea	30% *	17%
Cough	27% *	13%
Hemoptysis	30%	21%
Sputum	20%	13%
Pts with clinically important benefit	36%	23%
Median TLP (days)	80	67
Median TTF (days)	58 *	40
Median survival (days)	166	157

* $p \leq 0.05$

Palliation-29

Safety Results

- Combined data overview (all treated patients)
- All adverse events (AEs) presented by worst severity and irrespective of relationship to therapy
- AEs collected over the whole follow-up period

Palliation-30

Extent of Follow-Up

	P17 + P503 COMBINED	
	PHO n=99	Nd:YAG n=99
≤ 30 days	14%	24%
31 - 91 days	39%	42%
> 91 days	46%	33%
Median days of follow-up	78	66
Range (days)	5 - 753	6 - 552

Palliation-31

Safety Results Overview

	P17 + P503 COMBINED	
	PHO n=99	Nd:YAG n=99
At least 1 adverse event	73%	64%
Severe or life-threatening	41%	33%
≤ 30 days	23%	21%
All deaths (≤ 30 days)	16%	17%
Withdrawal due to AEs	3%	3%

Palliation-32

Life-Threatening Pulmonary Events

	Key Studies		XRT Studies		
	P17 + P503		P2 + P18 + P23 + P504		
	PHO	Nd:YAG	PHO+XRT	XRT	XRT+EBT
	n-99	n=99	n=82	n=78	n=28
Fatal Massive Hemoptysis	10 (10%)	6 (6%)	14 (17%)	6 (8%)	7 (25%)

Possible causes of FMH:

- **Tumor progression eroding a pulmonary vessel**
- **Treatment-induced tumor resolution**
- **Instrumentation injury**

Life-Threatening Pulmonary Events

FMH

- Incidence is consistent with literature (4-32%)
- Early FMH (≤ 30 days of treatment):
  - PHOTOFRIN® vs. Nd:YAG - 4% on each arm
- Proposed label :
  - PDT is contraindicated in patients with tumor eroding into a major blood vessel

Life-Threatening Pulmonary Events

	P17 + P503	
	PHO n=99	Nd:YAG n=99
Respiratory insufficiency	5 (5%)	1 (1%)
≤ 30 days	3	1
> 30 days	2	0

Possible causes:
- Necrotic debris
- Mucus plug

Proposed label:
- Mandatory debridement bronchoscopy
- Caution in main airway lesions

Palliation-35

Frequently Occurring Adverse Events (≥ 10 %)

	P17 + P503 COMBINED	
	PHO n=99	Nd:YAG n=99
Photosensitivity reaction	20%*	0%
Psychiatric	14%*	5%
Dyspnea	32%*	17%
Hemoptysis	18%	12%
Cough	17%	13%
Pneumonia	12%	10%
Bronchitis	11%*	3%
Fever	15%	10%
Pain	6%	12%

* $p \leq 0.05$

Palliation-36

Photosensitivity

- Mild to moderate sunburn in 19/20 patients
- Transient, self-limiting
- Prevented by patient education
- Instructions provided in the label

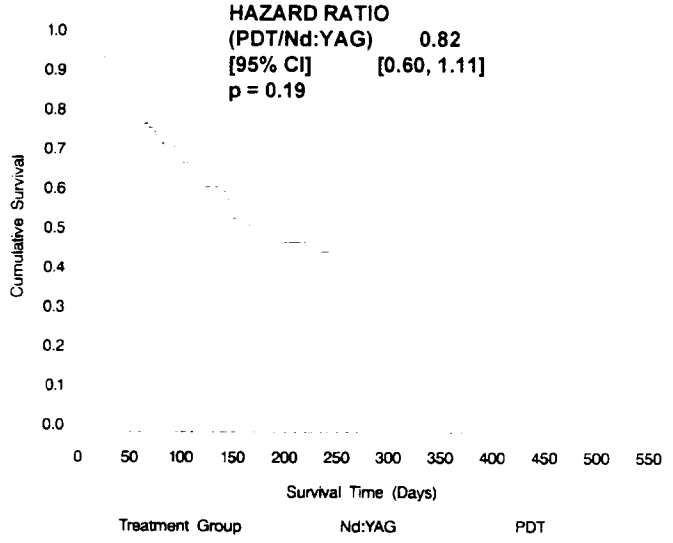
Palliation-37

Dyspnea - Temporal Relationship to Treatment Procedure

	PHO	Nd:YAG
Total Patients	**32%**	**17%**
≤ 30 days	**16%**	**11%**
> 30 days	**16%**	**6%**

Palliation-38

P17 + P503 COMBINED Survival



Palliation-39

Palliation of Endobronchial Cancer PHOTOFRIN® Efficacy Summary

- Relief of endobronchial obstruction in 50%, and symptom palliation in 30%
- Better objective response than Nd:YAG
- PHOTOFRIN® PDT was equal or better than Nd:YAG in symptom palliation
- Approximately one-third of patients achieved clinically important benefit

Palliation-40

PHOTOFRIN® Safety Summary

- Incidence of pts with any AEs, deaths ≤ 30 days, severe or life-threatening AEs, overall survival and withdrawal similar between PHO PDT and Nd:YAG
- PHOTOFRIN® local effects consistent with its pharmacological action (transient inflammatory reaction/acute tumor resolution)
- The safety profile of PHO PDT is acceptable for the proposed indication

Treatment of Superficial Endobronchial Tumors

Eric Edell, MD
Associate Professor of Medicine,
Division of Pulmonary and Critical Care
Mayo Medical School

Background

- Overall survival results unsatisfactory
  - 14% 5-yearsurvival
- Treatment of early stage cancer offers the best opportunity for long-term survival
- NCI-sponsored multicenter screening study:
  - Memorial Sloan-Kettering
  - Johns Hopkins
  - Mayo Clinic

superficial-1

Background

- Mayo Lung Project 1970's identified 54 pts with radiographically occult cancer
- Hematoporphyrin derivative (HpD) first used for localization
- Risk of developing second cancer
  - 1-5% per year
- Need for tissue-sparing therapy
- Nonsurgical pts with early cancer (HpD-PDT)
  - First treated Tokyo and Mayo 1980

superficial-2

PDT for Early Lung Cancer

- Tokyo Medical College - since 1980
  - 297 cancers (251 pts)
  - 116 early cancers (95 pts)
    - CR 77 pts (81%)
    - recurrence 12 (16%)
- PHOTOFRIN® PDT approved in Japan in 1994

superficial-3

PDT for Early Lung Cancer

- Mayo Clinic - since 1980
  - 58 nonsurgical pts - early cancer
    - CR after first PDT - 49 pts (84%)
    - Recurrence after single treatment - 19 pts (39%)
      - median Time to Tumor Recurrence (TTR) of 4.1 years
      - recurrence after second treatment - 11 pts (22%)
    - Median survival of 3.5 years

superficial-4

PDT for Early Lung Cancer in Surgical Candidates

- Mayo currently treating both nonsurgical and surgical patients with early superficial cancer

• Surgical candidates	21 pts
– CR after first PDT	15 pts (71%)
– Recurrence after first PDT	4 pts (19%)

  - follow-up 24-116 mos (median 72)

superficial-5

Indication

Treatment of endobronchial carcinoma in situ or microinvasive NSCLC in patients for whom surgery and radiotherapy are not indicated.

superficial-6

Studies Analyzed by QLT

- 3 open label, single arm studies
  - P505 - Dr. Karl Haüssinger, Germany : 32 pts
  - P506 - Dr. Stephen Lam, Canada, and
    Dr. Thomas Sutedja, The Netherlands : 29 pts
  - P507 - Dr. Michel Leroy, France : 41 pts

Patient Population

- 102 patients treated over 10 years
- Tis, T1, T2 N0 M0
- Radiologically occult
- Patients considered inoperable by referring and treating physicians
- Some may have been eligible for radiotherapy

Selection of INDICATION Subset

- Eligibility for radiotherapy or surgery based on independent expert evaluations
- Expert consultants:
  - 2 radiation oncologists: Dr. Rosenthal, Dr. Sandler
  - 1 thoracic surgeon: Dr. Pass
- Final subset of 24 patients

superficial-9

Why Neither Surgery Nor Radiotherapy Were Indicated (n=24)

	Surgery		Radiotherapy	
Poor pulmonary function	12	(50%)	7	(29%)[a]
Prior high dose radiation	0	(0%)	9	(38%)
Multifocal, multilobar disease	5	(21%)	8	(33%)[a]
Proximal airway	5	(21%)	0	(0%)
Prior Stage III disease	2	(8%)	0	(0%)
Poor medical condition	0	(0%)	1	(4%)

[a] 1 patient had both

superficial-10

Baseline Characteristics

	INDICATION n=24	ALL n=102
Men	92%	90%
Median Age	61	64
Prior Therapy	75%	56%
Median FEV_1	1.0 L	1.7 L
Multiple tumors	42%	22%

superficial-11

Baseline Tumor Characteristics

	INDICATION n=24	ALL n=102
Squamous	83%	85%
T_{is}	42%	23%
T_1	58%	62%
T_2/T_3	0%	8%
Radiologically occult	79%	88%

superficial-12

Prior Lung Cancer

	INDICATION n=24	ALL n=102
Prior Lung Cancer	17 (71%)	56 (55%)
Prior stage:		
Tis	5	6
T 1	4	18
T 1 N1	1	2
T 2 N0	3	14
T 2 N1-2	1	7
T 3	0	1
T 3 N1-2	2	3

Efficacy Endpoints

- Histologic Complete Tumor Response
- Time to Tumor Recurrence
- Survival
- Disease-Specific Survival

Histologically Confirmed CR Percentage of Patients

	INDICATION n=24	ALL n=100
Total CR	22 (92%)	79 (79%)
[95% CI]	[81,100]	[71,87]
After 1 course	92%	75%

superficial-14

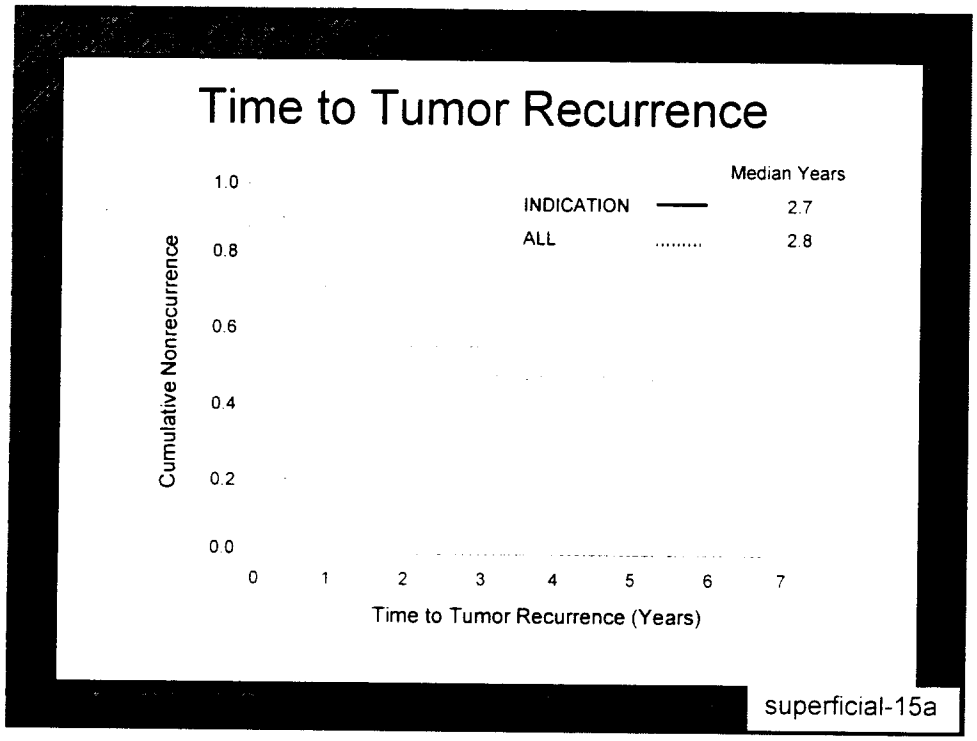
Time to Tumor Recurrence (TTR) After First CR

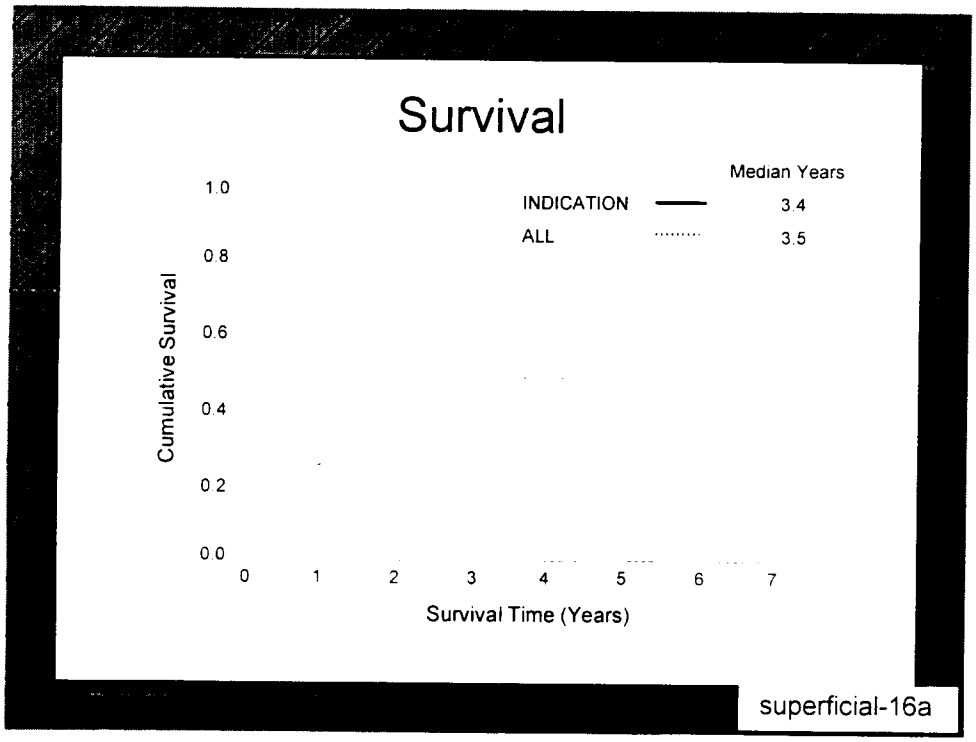
	INDICATION n=22	ALL n=79
Recurrences	10 (46%)	35 (44%)
Median TTR (years)	2.7	2.8
[95% CI]	[1.0, —[a]]	[1.5, —[a]]
Range (years)	(0.1 - 10.1[b])	(0.1[b] - 10.1[b])

[a] cannot be estimated

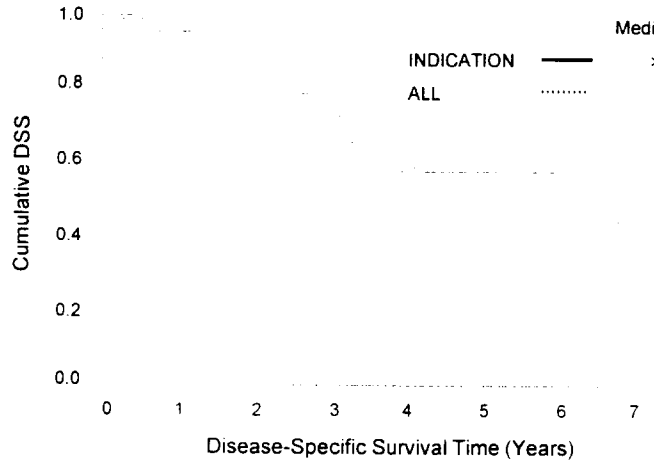
[b] censored - patients still in response

superficial-15





Disease-Specific Survival



[a] Cannot be accurately estimated

superficial-17a

Tumor Response

	All n=100	FDA Approach n=97
CR	79 (79%)	46 (47%)
Median TTR (yrs)	2.8	>3.0
[CI]	[1.5, —[a]]	[2.7, —[a]]

[a] could not be estimated

Survival by T Stage

Stage	n	Survival	[CI]	4-yr Survival
Tis	23	> 3.5 yrs	[3.3, —[a]]	55%
T1	63	3.0 yrs	[2.3, 5.7]	44%

[a] could not be estimated

Disease-Specific Survival by T Stage

Stage	n	DS Survival	[CI]	4-yr DS Survival
Tis	23	> 3.5 yrs	[3.5, —[a]]	63%
T1	63	5.7 yrs	[3.0, —[a]]	56%

[a] could not be estimated

Safety Results Overview

	ALL Treated n=102
At least 1 adverse event	50%
Severe or life-threatening	11%
≤ 30 days	6%
Deaths (within 30 days)	1%
Withdrawal due to AEs	0%

superficial-18

Severe/Life-Threatening Events ≤ 30 Days

- Photosensitivity (2%)
- Dyspnea with/without cough (4%)
  - 2 received light overdose
  - 1 treated concurrently in both mainstem bronchi
  - 1 treated in sole remaining airway

superficial-19

Safety
Most Frequent Adverse Events (≥ 5%)

n=102

Photosensitivity reactions	23%	
Respiratory		
Exudate	23%	22 mild, 1 severe
Obstruction	21%	All mild
Edema	18%	All mild
Stricture	10%	All mild
Ulceration	9%	All mild
Cough	8%	Mixed
Dyspnea	6%	Mixed
Bronchitis	5%	4 mild, 1 moderate

superficial-20

Efficacy Summary

	n	CR	Recurrence	Median Survival
P505, P506, P507				
All	100	79%	44%	3.5 yrs
Indication	24	92%	46%	3.4 yrs
FDA method	97	47%	29%	3.5 yrs
Japan	251	81%	16%	–
Mayo Clinic	58	84%	~~38%~~ 22%	3.5 yrs

superficial-21

Conclusion

PHOTOFRIN® PDT is a safe and effective therapy for the treatment of carcinoma in situ or microinvasive NSCLC in patients for whom surgery and radiotherapy are not indicated.

superficial-22

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ONCOLOGY DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 09/19/97

SLIDES (PAXENE)

NDA 20-826: Paxene® for advanced AIDS-KS

Oncology Drugs Advisory Committee
September 19, 1997

Review team

	Primary Reviewer	Secondary Reviewer
Medical	Ken Kobayashi, M.D.	John Johnson, M.D.
Statistics	Anthony Koutsoukos, Ph.D.	Clare Gnecco, Ph.D.
Pharmacology	Margaret Brower, Ph.D.	Paul Andrews, Ph.D.
Biopharm	Elena Mishina, Ph.D.	Atiquur Rahman, Ph.D.
Chemistry	Yung-Ao Hsieh, Ph.D.	Rebecca Wood, Ph.D.
DSI	Gurston Turner, Ph.D.	
Project management	Dianne Spillman	Dottie Pease

Proposed indication

"PAXENE® is indicated after failure of first line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related Kaposi's sarcoma"

OBJECTIVE TUMOR RESPONSE

+

CLINICAL BENEFIT

Regulatory history

- 6/22/94 IND submitted
- 9/93-1/95 study 139-174 (Saville et al.)
- 2/95-12/95 study 139-281 (Gill et al.)
- 7/95 study proposal for 100 pt RCCT
- 9/95 study IX-110-081 protocol submitted
- 12/4/96 applicant-FDA meeting
- 1/96-9/97 study IX-110-081 active
- 8/15/96 pre-NDA teleconference
- 3/31/97 NDA submitted
- 8/19/97 applicant-FDA meeting
- 9/15/97 special considerations meeting

Studies submitted for review

Protocol	Site	N	Design	Primary endpoint	Secondary endpoints	Prior chemo	Treatment schedule
IX-100-081 (Paxene®)	multi	89	open-label, single arm	RR	TTR TTP QOL	89	100 mg/m² 3h q 14d
139-174 (Taxol®)*	NCI	29	open-label, single arm	RR		19	135 mg/m² 3h q 21d
139-281 (Taxol®)*	USC MGH	59	open-label, single arm	RR	TTR DOR survival	27 13	100 mg/m² 3h q 14d
unknown (Taxol®)*	Brown	4	open-label, single arm	RR	RR	4	30 mg/m² q 7d x4

 *literature reports only

Study objectives

- To determine response rate and median time to tumor progression for patients with advanced refractory AIDS-KS treated with a 3h infusion of Paxene® at a dose of 100 mg/m^2 q14 d;
- To determine the toxicity profile of this dose and schedule;
- To evaluate clinical benefit in this patient population.

Eligibility

- Advanced AIDS-KS;
- Failure of at least 1 prior systemic chemorx regimen to maintain significant benefit;
- Systemic rx indicated for:
  - ✓ ≥ 25 mucocutaneous lesions
  - ✓ (symptomatic) visceral involvement
  - ✓ symptomatic lymphedema

Eligibility (cont'd)

- ≥ 5 measurable (raised) cutaneous lesions;
- KPS ≥60%;
- ≥ 2 weeks since last systemic chemorx

Response criteria

- **Complete response: "Absence of any detectable residual disease, incl. tumor-associated edema, persisting for at least 4 weeks."**
- **Biopsy required for persistent pigmented macular lesions**

Response criteria (cont'd)

- **Partial Response: No *new* lesions, visceral disease, or new/ worsening tumor-associated edema or effusions; AND**

Response criteria (cont'd)

- ✓ **≥ 50% decrease in lesion counts for >= 4 weeks; OR**
- ✓ **≥ 50% decrease in the total area of the five marker lesions; OR**
- ✓ **complete flattening of ≥ 50% of all previously raised lesions.**

Response criteria: progression

- New or progressing visceral disease; or
- new or increasing tumor associated edema lasting ≥ 1 week which interferes with normal activity; or

Response criteria: progression (cont'd)

- a ≥ ***25%*** increase in the total lesion count; or
- a ≥ 25% increase in the total area of the marker lesions; or
- a change in the character of ≥ 25% of all previously "flat" lesions to "raised".

Response criteria: problems

- Does not address situation in which progression according to increase in tumor area occurs prior to PR based on total lesion count or raised lesion count
- Method of calculating progression based on lesion flattening subject to individual interpretation

FDA response analysis: methods

- **Followed protocol specifications with the following comments:**
  - ✓ **Response was not limited to first 10 cycles;**
  - ✓ **All initial demonstrations of PR required confirmation at 4 weeks;**
  - ✓ **Progression on any subscale defined the overall response as progression on that date.**

Patient characteristics: IX-110-081

	N (%)
Median KPS (range)	80 (60-100)
T_1	74 (83)
I_1	75 (84)
S_1	72 (81)
≥ 25 mucocutaneous lesions	72 (81)
Sx visceral disease	23 (26)
Visceral disease (enrolled after 7/96 amendment)	5 (6)
Sx lymphedema	45 (50)

Patient characteristics (cont'd)

	N (%)
No. of prior chemo median (range)	1 (1-5)
≥ 2 prior chemo	10 (11)
any prior Doxil®	27 (30)
any prior DaunoXome®	40 (45)
last rx stopped for toxicity	15 (17)
last rx stopped for PD	69 (77)
PD best response to last rx	30 (34)

Objective response in cutaneous disease: IX-110-081 primary analysis

	N	(%)
PR (FDA draft)	31	(35)
PR (FDA revised)	37	(42)
SD	16	(18)
PD	22	(25)
NE	14	(16)
total	89	(100)

Time to event parameters: IX-110-081 cutaneous disease primary analysis

	Median (95% c.i.)
time to response, days median (range)	34 (13-231)
time to progression, days	163 (105-221)

Extent of prior therapy in patients receiving Doxil®

	N (%)
0	13 (48)
1	12 (44)
2	2 (7)
Total	27 (100)

Response to Paxene® in patients following first-line Doxil® therapy

	N (%)
PR	3 (23)
SD	6 (46)
PD	2 (15)
NE	2 (15)
total	13 (100)

Response to Paxene® in patients following 2nd line or greater Doxil® therapy

	N (%)
PR	6 (43)
SD	3 (21)
PD	2 (14)
NE	3 (21)
total	14 (100)

Discrepancies arising during review: IX-110-081 cutaneous disease (original)

Issue	N	Subgroup totals
Claimed CR not confirmed at 28d	1	
Claimed CCR changed to PR	1	2
Progressed before claimed response	8	
Claimed PR only documented at <28d	7	
PR not documented w/decline ≥ 50%	1	
PR incompletely evaluated	1	17
SD upgraded to PR	3	
SD changed to either PD (1) or NE (1)	2	5
Total	24	24

Discrepancies arising during review: IX-110-081 cutaneous disease (revised)

Issue	N	Subgroup totals
Claimed CR not confirmed at 28d	1	
Claimed CCR changed to PR	1	2
Progressed before claimed response	5	
Claimed PR only documented at <28d	1	
PR not documented w/decline ≥ 50%	1	7
SD changed to either PD (12) or NE (1)	13	
SD upgraded to PR	3	16
PD upgraded to SD	2	
NE upgraded to SD	1	3
Total	28	28

Objective response in other reported experience with Taxol®

	Gill et al. N (%)*	Saville et al. N (%)*
complete response	1 (2)	2 (7)
partial response	32 (57)	18 (62)
overall response (prevs rx only)	21/40 (52)	14/19 (74)
progression	9 (16)	1 (3)
total	56	29

* all patients

Progression criteria: flattened lesions

a change in the character of ≥ 25% of all previously "flat" lesions to "raised"

Example: patient 651

cycle	day	no. flat 1a	no. flat 1b	no. raised	Δ raised
1	1	8	8	38	0
.	.	.	.	.	.
3	33	17	17	29	9
4	48	30	41	5	-24
5	61	26	41	12	+7
6	75	25	41	6	-6
7	96	26	41	5	-1
.	.	.	.	.	.
10	139	24	41	7	+2
.	.	.	.	.	.
14	229	13	43	14	+7

Differing interpretations of progression criteria

	Method of determining baseline for progression	Reference value	New lesions needed for PD
1a	Obs. no. flat lesions at nadir of raised lesions	30	7
1b	Calculated no. flat lesions at nadir of raised lesions	41	10
2	Obs no. flat lesions in cycle immed prior to nadir of raised lesions	17	4
3	No. of raised lesions that flattened by nadir of raised lesion count	33	8
4	Nadir raised lesion count	5	1

Baselines for progression: 651

cycle	day	no. flat 1a	no. flat 1b	no. raised	Δ raised from start
1	1	8	8	38	0
.	.	.	.	.	.
3	33	*17*	17	29	9
4	48	*30*	41	5	*-33*
5	61	26	41	12	-26
6	75	25	41	6	-32
7	96	26	41	5	-33
.	.	.	.	.	.
10	139	24	41	7	-31
.	.	.	.	.	.
14	229	13	43	14	-24

Progression criteria: outcomes

Method	New lesions needed for progression	Day of progression	Overall response
1a	7	day 61	PD
1b	10	>day 229	*PR*
2	4	day 61	PD
3	8	day 229	PR
4	1	day 61	*PD*

Objective response rate in cutaneous disease: IX-110-081

	N (%)
Draft FDA (method 4)	31/89 (35)
Revised FDA (method 1b)	37/89 (42)
"Relaxed" FDA	40/89 (45)
Eligible patients only (FDA)	36/79 (46)

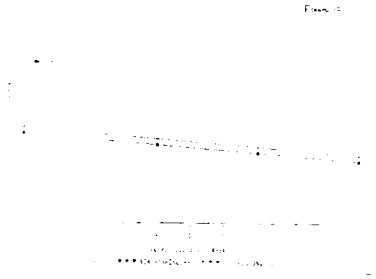
Elements of clinical benefit

- Foot KS
- Facial KS
- Edema
- Lung KS
- KPS
- KS-related pain

FDA review of photographs

	improved N (%)	not improved N (%)	total N
Facial lesions	6 (25)	18 (75)	24
Foot lesions	1 (9)	10 (91)	11
Lower extremity lymphedema	6 (12)	42 (88)	48

QoL: Mobility by response status

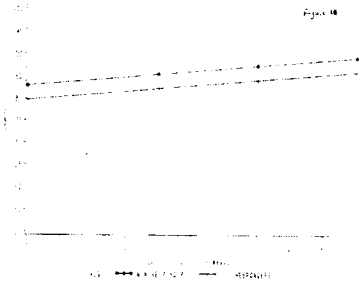


Visceral disease: lung

	N (%)
Pts enrolled with visceral disease	28/89 (31
Pts with visceral marker lesion(s) identified	7/89 (8)
Pts with evaluable visceral disease*	5/89 (6)
Response in pts with evaluable disease	3/5 (60)

*all lung lesions

QoL: KPS by response status



ODAC, 9/19/97 37

Safety analysis

- Deaths
- Infections
- Hematologic toxicities and cytokine use
- Non-hematologic toxicities

ODAC, 9/19/97 38

Deaths

	N
Total reported	22/89
Deaths ≥ 30 days	11
Possibly related to Paxene®	7

ODAC, 9/19/97 39

Breakdown of deaths possibly related to Paxene®

	N (%
cytopenia/infection*	5/22 (14
septic shock/respiratory arrest	1/22 (4
pulmonary hypertension with congestive heart failure (applicant attribution)	1/22 (4
total	7/22 (32

*includes 1 death partially attributed to hypocalcemia and 1 death partially attributed to possible TB

Infections

	Recurrent	de novo	ongoing	other	total N (%)
MAI	2	3			5 (6)
Tuberculosis		1	1	1	3 (3)
Candida	21	8			29 (32)
Pneumocystis carinii	7	1			8 (9)
Cryptococcal meningitis	1	1			2 (2)
Viral	11	18		1	29 (32)
Other		3			35 (39)

Hematologic toxicity

	gr 3	gr 4-5	total N (%)
Neutropenia	20	37	76 (85)
Febrile neutropenia			11 (12)
Leukopenia	17	44	76 (85)
Thrombocytopenia	5	2	27 (30)
Anemia	8	2	82 (92)

Hematopoietic support

	rx initiated while on Paxene® N (%)	total N (%)
G-CSF	34 (38)*	37 (41)
Erythropoietin	7 (8)	7 (8)
RBC transfusion	15 (17)	15 (17)

*includes 3 pts continuing prior rx w/G-CSF

Non-hematologic toxicities

	gr 3	gr 4	total N (%)
Liver	12	2	78 (88)
Isolated elev bilirubin*	6	2	9 (10)
Alopecia			49 (55)
Diarrhea	2	0	20 (22)
Arthralgia/myalgia/arthritis	26	2	29 (32)
Renal	3	3	9 (10)
Neuro	2	0	34 (38)
Malignancy/lymphadenopathy			3 (3)

*prob due to protease inhibitors

Conclusion

- **The submitted phase II study in 89 patients provides evidence of objective tumor response after failure of first line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related Kaposi's sarcoma with an overall response rate of 42%**

Conclusion

Proof of clinical benefit is less clear and is an important point for Advisory Committee deliberation

Domain	FDA assessment	N (%)
Facial KS	• improvement in facial lesions	6/24 (25)
Foot KS	• improvement in foot lesions	1/11 (9)
Edema	• decrease by visual assessment	6/48(12)
Lung KS	• decrease in lung lesions	3/5 (60)

Conclusion

- **The Phase II study was not adequate and well controlled to evaluate the secondary endpoints:**
  - ✓ time to progression
  - ✓ duration of response
  - ✓ survival

INTRODUCTION
AT
O D A C

September 19, 1997

Samuel Broder, M.D.

Kaposi's sarcoma (KS) is an angioproliferative tumor characterized histogically by endothelial and spindle cell proliferation, angiogenesis, inflammatory cell infiltration, and edema. In 1994, a new human herpes virus, HHV-8 or KSHV, was discovered and found to be closely associated with this tumor and may play a role in its pathogenesis.

This tumor is one of the hallmarks of AIDS. **Slide 1 [Face KS Patient]** The inter-relationship between immunodeficiency diseases and cancer

generally, and between AIDS and Kaposi's sarcoma specifically, has been a very high priority of the National Cancer Institute and its viral cancer programs.

Thus, clinical research done at NCI suggested that KS is sensitive to paclitaxel, a natural product originally derived from the pacific yew. This line of work is an extension of about 30 years of research on paclitaxel by NCI.

Slide 2 [Mechanisms of Action of Paclitaxel]

Paclitaxel, of course, has effects on tubulin and the state of tubulin

polymerization. But perhaps even more interesting are newly described mechanisms of actions for this agent. Paclitaxel inhibits angiogenesis and induces apoptosis by Bcl-2 phosphorylation triggered by Raf-1 activation. It is possible that these new mechanisms may be induced by lower plasma concentrations of paclitaxel than the effects on the microtubule system.

AIDS-related Kaposi's sarcoma frequently can be an aggressive disease, often with extensive cutaneous lesions, but also involvement of the oral cavity

and visceral organs. AIDS-related KS can be complicated by lymphedema

Slide 3 [Patient with Lymphedema]

of the extremities, the face, or the genitalia. GI lesions may cause bleeding, pain and obstruction, and pulmonary lesions may be associated with respiratory insufficiency or death. Even in the absence of symptomatic visceral disease or edema, KS may have a serious impact on Quality of Life by causing disfigurements and social isolation or by serving as a visual reminder of an AIDS diagnosis. When KS lesions can be covered or obscured by clothing, a patient's recognition that

lesions are growing or progressing is still a serious medical challenge.

Slide 4 [Therapeutic Options]

Although milder forms of AIDS-KS with slow progression and without life threatening visceral involvement can be treated with local or intralesional therapies, the more serious, advanced forms, if left untreated, do not spontaneously resolve, as a general rule, and require cytotoxic chemotherapy.

As is true in virtually all oncology, the status of prior chemotherapy is an important consideration. Efficacy

results with patients naive to chemotherapy should generally not be pooled with results in second or third-line therapy.

Since the early 1990s, the ABV regimen, which consists of doxorubicin, bleomycin and vincristine, has been considered the standard of care. In evaluating individual patients or in making comparisons between clinical trials, it is important to know whether the patients have been previously treated with doxorubicin. Moreover, in the past two years, liposomal anthracyclines have been introduced,

but for a variety of reasons, it is important not to lump these two therapies together indiscriminately. **Slide 5 [DaunoXome]** DaunoXome, i.e., liposomal daunorubicin, was approved as first-line treatment based on a prospective randomized comparison versus ABV. Although response rates were similar (23% for DaunoXome and 30% for ABV), significantly less alopecia and neuropathy were observed with DaunoXome. **Slide 6 [Doxil]** Doxil, i.e., liposomal doxorubicin, was approved as second-line treatment of advanced

AIDS-Kaposi's sarcoma based on a 27% response rate in 34 evaluable patients.

By contrast the response rates reported for paclitaxel for second-line treatment of KS have been higher, as discussed at the ODAC immediately preceding this meeting. or safety purposes it is probably wise to use all available patients - but paclitaxel is not an exception to the rule that for efficacy purposes it is important not to pool first and second-line patient data.

Also, because of the non-linearity of paclitaxel pharmacokinetics, caution is

in order when one extrapolates from one dosing level or apparent dose-intensity to another. We will touch upon these points in our presentation.

Slide 7 [Paxene in AIDS-KS] We believe our study of Paxene makes an important contribution to the knowledge base for paclitaxel in second-line AIDS-KS therapy. Our study included advanced patients who frequently had failed second-line or third-line treatments. Specifically, many of the patients were Doxil failures. Another ma or point is that the study presented today is the first

prospective multicenter study of paclitaxel in advanced KS and, as such, may give a more realistic estimate of community based results. We will also provide important information on pharmacokinetics as well as information on co-administration with protease inhibitors. We believe that much of this information is unavailable in any other form. or prescribers, it is important to have as much empirical data as possible on both the positive features and limitations of paclitaxel.

inally, we wish to thank the DA and this committee for permitting some of

the patients who participated in this study to speak here today, at the conclusion of our scientific presentation.

All clinical progress depends on the willingness and courage of patients to enter studies on the safety and efficacy of new drugs.

Thank you.

BRODER # 2
Cycle 2

Paclitaxel
Mechanisms of Actions

- Microtubule Stabilization
- Anti-Angiogenesis
- Apoptosis (Bcl-2 Phosphorylation)
  Raf-1 Activation

ODAC-9/19/97

We present data today on the PKs of paclitaxel in AIDS-KS patients in the study just described by Dr. Gill. It must be recognized that these studies were very difficult to conduct given the demands on the patient's time and we are very grateful to the patients who participated in this pharmacokinetic study.

S1 Eleven (11) patients from one site volunteered for the pharmacokinetic sampling. These patients were taking 4 to 20 concomitant medications, which included one or more RTIs, imidazole antifungals, and the protease inhibitor indinavir. The protease inhibitors are of particular interest because paclitaxel and protease inhibitors are metabolized by CYP4503A and almost all of the marketed protease inhibitors carry a warning in their product label of potential interactions with concomitant medications that also utilize this metabolic pathway.

Serial plasma sampling, which involved about 20 samples per patient, occurred over 51 hours during and after the 3-hr infusion of paxene on one of the cycles.

Nine patients were studied on one cycle and 2 patients were studied twice on 2 consecutive cycles.

S2 The next slide shows the mean plasma concentration time curve for paclitaxel in the 9 patients who were studied on one cycle.

S3 Mean pharmacokinetic parameters are shown in this slide. I wish to point out that peak plasma concentration (Cmax) was

about 1100 ng/mL or about 1.3 uM and body clearance averaged 27 L/hr/m2.

S4 A comparison of the some of the pharmacokinetic parameters obtained at 100 mg/m2 was made using a weighted analysis to values obtained from other Paxene studies in 37 patients with solid tumors when a higher dose (175 mg/m2) was adminstered. As noted on the left-hand side of the slide, a 75% increase in the administered dose (that is from 100 to 175 mg/m2), was accompanied by a much greater increase in peak paclitaxel plasma levels and in areas under the plasma concentration time curves to the last detectable concentration and to infinity. The dashed line would be the expected increase in these parameters if the drug obeyed linear kinetics. These data demonstrate the nonlinearity of the pharmacokinetics of paclitaxel over the range of 100 to 175 mg/m2.

S5 We also evaluated the pharmacokinetics of paxene in those patients taking indinavir and those who did not. As noted on this slide there were no differences in the average values for Cmax, CL, Vd or t1/2 between these 2 groups. In another 2 patients, paclitaxel kinetics were obtained on 2 consecutive cycles, one in the absence of indinavir and the second after 2 weeks of indinavir therapy. As shown here, the plasma levels of paclitaxel were similar with and without indinavir confirming that indinavir does not alter the disposition of paclitaxel.

Imidazole antifungal agents are known to inhibit CYP 450 enzymes and it was of interest to assess whether those patients taking imidazole antifungals, primarily fluconazole, had greater exposure to paclitaxel. On this slide, it is clear

S6

that there was no indication that patients taking antifungals had higher Cmax or reduced clearance values compared to those not taking these drugs.

S 7 In conclusion these studies define for the first time 1) the pharmacokinetics of paclitaxel in AIDS-KS patients taking multiple HIV therapies, 2) the nonlinear pharmacokinetics of paclitaxel over the range from 100 to 175 mg/m2 and 3) there was no appreciable interaction between paclitaxel and indinavir or imidazole antifungal agents.

1. This Paxene study was conducted in patients with advanced AIDS-related KS. It was a prospective phase II trial in patients who had failed prior cytotoxic chemotherapy. The trial was conducted at 9 centers in the US with accrual and data collection between in Jan 96 and April 97.

2. Patients were eligible for this trial if they had advanced disease defined by the presence of one or more of the following criterias, had failed prior systemic chemotherapy, and had KPS of 60 or above. Concommitant use of anti-retroviral therapy including Protease inhibitors was allowed.

3 Primary study end points included best response and time to progression. Secondary end points included change in symptom distress scale and KPS over time. Paxene Pharmacokinetics were also done in a subset of the cases and the data will be presented by Dr. Ken Duchin.

4. The response criteria are similar to those defined by the ACTG- Oncology committee for the past several years, shown here. Complete and partial responses were required to be maintained for at least 28 days.

5. The treatment regimen consisted of Paxene given at a dose of 100 mg/M2 over 3 hrs every two weeks. One dose reduction to 75 mg/M2 was allowed; in the event of more severe toxicity, treatment was withheld until recovery, as outlined in the protocol. Use of G-CSF was allowed for neutropenia.

6. 89 patients were enrolled at 9 sites through April 97

7. Patient demographics are outlined here. The mean age of the study population was 38 yrs. The median baseline CD4 count was 40, and majority of the patients had KPS between 70 and 80.

8. Antiretroviral therapy was taken by 71% at the time of study entry, including use of protease inhibitors in 33 cases. A third of the patients were receiving therapy for CMV infection and 30% of the patients were receiving G-CSF.

9. Tumor assessment at baseline showed mucocutaneous disease in all but 2 patients, facial disease in 42 and oral KS in 40. Tumor associated edema was present in nearly half the cases, and visceral disease in a third of the cases. Pulmonary disease was the most common visceral site of involvment.

10. TIS staging system is based on three prognostic factors which include tumor burden, immunological status, and systemic symptoms as outlined here.

11. Based on the TIS system, 90% of the patients in this study had 2 or more poor risk factors.

12. All patients had received prior cytotoxic chemotherapy. Just over a third of the patients received two or more prior regimens. Among these, 41 patients had received liposomal daunorubicin, and 27 had received liposomal doxorubicin.

13. A median of 8 cycles of Paxene was administered with a range of 1 to 27. 34 patients remain on therapy after 10 cycles. The median dose intensity was 44 mg/M2/week.

12. Response rates were assessed by intent to treat analysis. Complete and partial responses were observed in 46%, with a 95% confidence interval of 41 to 62 percent. These data represent the independent review by Dr. Kaplan who was not an investigator in this trial.

The following slides are representative examples of responding patients.

13. This patient with advanced cutaneous disease and extensive edema causing severe pain and requiring crutches showed marked improvement after 19 cycles.

14. Another patient with facial lesions and edema showed marked improvement of the tumor and local edema.

15. The response rates were 47% in patients who had received only one prior chemotherapy regimen, and 44% for those who received two or more regimens. The response rates in those who had received prior liposomal duanobucin or doxorubicin were 51 and 33% respectively.

16. The impact of protease inhibitor use was also examined. 29 patients did not receive any protease inhibitor during the trial. The response rates in this group were similar to the overall group. These data suggest that the protease inhibitor use does not appear to have a significant impact on the response rates.

17. The median time to response was 49 days. The duration of response was calculated from the initiation of treatment, and the median has not yet been reached and is in excess of 306 days.

18. Time to treatment failure for the whole study population occurred after a median of 234 days.

ODAC PRESENTATION
September 19, 1997

Slide: Thank you. Good morning ladies and gentleman, members of ODAC and guests. My name is Gregory Harriman and I am with Baker Norton Pharmaceuticals. Before beginning my presentation, I would like to have Dr. Duchin from Baker Norton get up and give a brief presentation of the pharmacokinetic studies.

Ken Duchin

First, I would like to summarize study results relating to quality of life and patient benefit. Then, I will review the safety results, including the safety of PAXENE in patients on protease inhibitors. Finally, I will provide some conclusions regarding the efficacy of PAXENE in the treatment of patients with advanced AIDS-KS who have failed prior cytotoxic chemotherapy. In many cases, these patients have failed more than one cytotoxic chemotherapy regimen, including Doxil. Such patients are an important group of patients for whom the identification of effective treatment can be challenging.

Slide: Quality of life was assessed by a prospectively-obtained, patient-administered Symptom Distress Scale, as well as by Karnofsky Performance Status and photographs. The Symptom Distress Scale contains 15 questions relating to overall well-being (for example outlook, concentration and fatigue), and disease-related symptoms (for example appearance, pain, mobility and breathing).

Each question uses a 5-point Likert-type format in which a score of 1 is the best possible score, meaning no distress, and a score of 5 is the worst possible score, meaning severe distress. The Symptom Distress Scale was to be administered at baseline and every 3rd cycle. Internal consistency and test-retest reliability estimates have indicated the scale is reliable, and the scale has been previously validated.

Karnofsky Performance Status was to be assessed at baseline and each cycle. Photographs of marker lesions and other involved areas were to be obtained at baseline and every 6 weeks.

Slide: Shown here is the median total score from all 15 questions for patients at baseline, and cycles 4, 7 and 10. There was a highly statistically significant improvement in the median score at cycles 4, 7 and 10. Very few patients were lost between baseline and cycle 4, indicating that the improvement seen at cycle 4, at least, is unlikely due to bias.

Assessment of tumor responses can be difficult and open to a certain amount of interpretation. Thus, it is possible for a patient to not be scored as having a tumor response, despite having clear evidence of clinical benefit.

Slide: Patient 695. Shown here is a patient previously treated with Doxil. He had extensive involvement of his foot with tumor and a large ulcer. The patient was informed that he might need to have his foot amputated. Following treatment with PAXENE, the patient had a dramatic improvement in the tumor and ulcer on his foot. This

HARRIMAN # 4
Cycle 8

Patient 695

Pre-Study

Cycle 16

patient was not scored as having a tumor response, although he clearly benefited from his treatment. This patient, and others, are with us today, and they hope to have an opportunity to tell you about their experience with PAXENE.

Slide: Patient 674 This patient had extensive lesions of his gums as well as a very severe lesion on his chest. While there were some differences of opinion as to whether he was a responder, he clearly has had improvement in his disease.

Slide: Shown here are median scores in patients with facial lesions for questions relating to the patients appearance at baseline and cycles 4, 7 and 10. There was a statistically significant improvement in this score at cycles 4, 7 and 10. Again, few patients were lost between baseline and cycle 4, indicating that the improvement at cycle 4, at least, is unlikely due to bias.

Slide: Patient 676. As can be seen, this patient had severe, disfiguring lesions and edema on his face. I should mention that the patient agreed to have these pictures shown. With treatment, he had a marked improvement in lesions and edema.

Slide: This slide shows improvement in symptoms, such as pain and mobility, related to lymphedema. Again, there was a statistically significant improvement in these symptoms at cycle 4. While improvement continued at cycles 7 and 10, it was no longer statistically significant.

Slide: Patient 627. This patient had marked lymphedema in his right leg which responded well to treatment, with maintained improvement to cycle 13 at shown here.

Slide: Patient 857. This patient had severely crusted lesions with significant lymphedema in his left lower extremity. The lymphedema showed definite improvement with treatment at cycle 3.

Slide: This slide shows improvement in symptoms related to pulmonary disease, which include breathing and cough. A statistically significant improvement in the median score was seen at cycles 4 and 7. Although a similar magnitude of improvement was seen at cycle 10, this was not statistically significant.

Slide: Patient 648. This patient had severe pulmonary involvement and had previously been treated with both DaunoXome and Doxil. Of note, he was on oxygen prior to treatment, but was able to discontinue this following treatment with PAXENE.

Slide: Patient 692. This patient also had pulmonary involvement. At cycle 13 of treatment, pulmonary lesions were significantly improved, as demonstrated by a decrease in the pulmonary lesion seen of this cut of the CT scan.

Slide: Forty-six percent of patients had improvement in their Karnofsky Performance Status during treatment. The improvement seen was statistically significant. The majority of remaining patients had no change in their Karnofsky status and only a few patients had worsening.

Thus, improvement in quality of life was seen in patients treated with PAXENE, as judged by improvement in symptoms, by Karnofsky Performance Status and by photographic improvement.

Safety

Slide: With regard to safety, frequent hematologic and non-hematologic adverse events which occurred in the 89 patients are summarized here. The major toxicities were hematologic, including neutropenia and anemia. Other frequently occurring adverse events included asthenia, alopecia, nausea and/or vomiting, arthralgias/myalgias, peripheral neuropathy and rash.

Slide: Adverse events were analyzed by whether or not patients were on protease inhibitors as shown in this slide. There was little difference in the incidence of adverse events between the two groups of patients and none of the differences were statistically significant.

Slide: There were a total of 70 opportunistic infections in 30 patients, which represents 34% of patients. Of these opportunistic infections, 17 which involved mycobacteria, pneumocystis, cryptococcus and CMV would be considered serious.

Slide: There were 11 deaths which occurred while patients were on study. Of these 11 deaths, the investigator felt 4 were related to PAXENE. Three of these patients died of sepsis with associated neutropenia and one patient died of congestive heart failure due to pulmonary hypertension.

Slide: We also have substantial safety data with PAXENE, using different doses and schedules, in patients who have other forms of

cancer. Shown here are adverse events, included in the NDA, on not only AIDS-KS patients, but an additional 226 patients who received PAXENE at either 140 mg/m2 over 96 hours or 175 mg/m2 over 3 hours. Again, the major toxicities are hematologic.

Slide: However, alopecia, arthralgia/myalgia and peripheral neuropathy were also fairly common, although severe grades of these toxicities were not common. Hypersensitity reactions were also relatively uncommon. We currently have safety data on a total of over 500 patients.

In summary, while AIDS-KS patients are potentially at increased risk because of their underlying disease and multiple concomitant, no unusual or unexpected toxicities were observed in AIDS-KS patients treated with PAXENE.

Slide: Now, I would like to summarize all the data which has been presented by responding to the questions which were addressed by FDA to ODAC. First - Is the Paxene® study size of 89 patients adequate for approval of a drug for the use "after failure of first line or subsequent systemic chemotherapy for the treatment of AIDS-related Kaposi's sarcoma"?

Slide: To answer this question, this study must be put into perspective with respect to studies which led to the approval of other drugs for a similar indication. As discussed, the study reported here was a prospective, multicenter study enrolling 89 patients, with two geographically distinct sites (Los Angeles and Boston) enrolling 25 or more patients each. It should again be kept in mind that all 89

patients had failed prior cytotoxic chemotherapy and many had failed two or more cytotoxic chemotherapies. Thus, these patients, by-and-large, represent a very refractory population.

In looking at the study sizes for other drugs currently approved for second-line treatment of AIDS-KS, there were 2 studies upon which Taxol was approved for this indication. One study, which looked at a dose and schedule of 135 mg/m2 every 3 weeks, enrolled 29 patients. However, only 19 of these patients had received prior systemic therapy, of which only 7 evaluable patients had received cytotoxic chemotherapy. Moreover, only 4 of these had received an anthracycline. The second Taxol study used a dose and schedule of 100 mg/m2 every 2 weeks. In this study, 56 patients were enrolled, however only 40 of these patients had received prior systemic chemotherapy.

The approval of Doxil for second-line therapy in AIDS-KS was based on 77 patients who had received prior combination chemotherapy. However, only 34 of these patients were felt by the FDA to be evaluable.

Thus, the PAXENE study containing 89 patients, and representing a refractory population of patients, is larger than any other study used to support approval of a drug for second-line or subsequent treatment of advanced AIDS-KS.

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

Slide: As previously discussed, the overall tumor response rate with PAXENE was 46%. Patients had advanced AIDS-KS, as demonstrated by the large number of patients with disfiguring lesions, tumor related edema and visceral disease. In addition, the vast majority of these patients were poor risk by TIS staging. Moreover, as mentioned, these patients were a very refractory population with respect to prior cytotoxic chemotherapy. Thus, the 46% tumor response rate should be viewed as highly significant. The fact that patients had substantial response rates, even after failing Doxil, which Xuntil August 4th of this year the only approved drug for second-line treatment of advanced AIDS-KS, and the significant response rates in patients who have failed 2 or more prior cytotoxic regimens, should be viewed as evidence of substantial activity. Time to progression and duration of response with PAXENE were also substantial given this patient population.

Slide: Moreover, patients demonstrated improvement in quality of life, based upon significant improvement in total Symptom Distress Scale scores, as well as improvement in symptoms related to facial lesions, lymphedema and pulmonary disease. This is the first time that a prospective QOL assessment containing such a Symptom Distress Scale has been used in AIDS-KS patients. Significant improvements were also seen in Karnofsky Performance Status and evidence of improvement was documented by photographs.

In sum, the combination of high tumor response rates, as well as improvements in quality of life measurements provide substantial evidence in support of patient benefit.

Slide: "Is the Paxene® safety acceptable in view of the efficacy results andd results available with alternative therapy?

Slide: Efficacy results were just discussed. With regard to safety, this slide shows the most important or the most common adverse events with PAXENE in comparison to adverse events reported in AIDS-KS patients with Taxol and Doxil. The point here is that PAXENE exhibited no higher incidences for any of the toxicities seen with Taxol, and in some cases, the rate may be a lower.

Slide: As discussed earlier, in this study a substantial amount of safety experience was gained with the coadministration of protease inhibitors and PAXENE. No significant differences were seen in the rates of major or common adverse events. Furthermore, pharmacokinetic studies were performed to assess the effects of protease inhibitors on the pharmacokinetics of paclitaxel.

Thus, while PAXENE has some significant toxicities, as expected with this cytotoxic drug, its safety is no worse and in certain adverse events may be better than that of Taxol, which is currently approved for second-line treatment of AIDS-KS.

Slide: Is the Paxene® NDA approvable for the indication of use "after failure of first line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related chemotherapy"?

Slide: PAXENE demonstrates a high tumor response rate in patients, all of whom have failed at least one or more cytotoxic chemotherapies. Moreover, the tumor response rate is similar to that of Taxol when usedd at the same dose and schedule of 100 mg/m2 every 2 weeks and is higher than that of Doxil. Importantly, PAXENE demonstrates substantial tumor response rates even in patients who have failed Doxil. In contrast, only one patient, who previously received Doxil was treated with Taxol in registration-seeking studies.

Slide: Conclusion 1 In conclusion, PAXENE induces tumor responses, as defined by ACTG criteria, in 46% of patients with advanced, AIDS-related KS who had failed first line or subsequent systemic chemotherapy. PAXENE improves quality of life, as assessed by a Symptom Distress Scale and Karnofsky Performance Status. PAXENE is safe in the treatment of AIDS-related KS.

Slide: Conclusion 2 PAXENE induces tumor responses in 33% of patients who failed prior Doxil therapy and 41% in patients who received at least two prior cytotoxic chemotherapies. PAXENE is safe and effective in patients on concomitant protease inhibitors.

Slide: The proposed indication is: "PAXENE is indicated after failure of first-line or subsequent chemotherapy, including liposomal doxorubicin, in patients with advanced AIDS-related Kaposi's sarcoma, and for relief of disease-related symptoms. Coadministration with protease inhibitors does not diminish the efficacy or alter the side effect profile of PAXENE."

I would now like to provide an opportunity for some of the patients who have been treated with PAXENE to come up and share their experiennces with you. Thank you very much.

Thank you. That concludes our presentation and we will be happy to answer any questions.

Therapeutic Options

- Dependent on Extent of Disease, Rate of Disease Progression, KS Associated Symptoms
- Local Therapy
  - Surgical, Cryotherapy
  - Radiotherapy, Laser
  - Intralesional Chemotherapy, Biologicals
- Systemic Therapy
  - Interferon
  - Chemotherapy

Liposomal Daunorubicin - DaunoXome®

- First Line Cytotoxic Treatment for Advanced AIDS-Related KS (from Product Label)

	DaunoXome (n = 116)	ABV (n = 111)
Respone Rate	23%	30%
Median Response Duration	3.6 Months	3.7 Months
Median Survival	11.2 Months	9.6 Months
Neutropenia Grade IV	15%	5%
Alopecia	8%	36%
Neuropathy	13%	41%

Liposomal Doxorubicin - Doxil®

- Treatment of AIDS-related KS (After Failure or Intolerance of Combination Chemotherapy (from Product Label)

Number of Evaluable Patients	34
Response Rate	27%
Median Response Duration	2.4 Months

Paxene® in AIDS-KS

- Second and Third-Line Treatment
- Doxil Failures
- Prospective – Multicenter
- Pharmacokinetics
- Co-Administration with Protease Inhibitors

PAXENE® (Paclitaxel) in Advanced AIDS-Related Kaposi's Sarcoma

IX-110-081

Study Design

- Failed First Line or Subsequent Chemotherapy
- Open-Label, Phase II, Prospective
- 9 US Sites
- Enrollment Jan 96 with Follow-Up Through Apr 97

Eligibility Criteria

- Advanced AIDS-KS
  - ≥ 25 Mucocutaneous Lesions
  - Visceral Involvement
  - Symptomatic Lymphedema
- Failed First Line or Subsequent Systemic Chemotherapy
- Karnofsky Performance Status ≥ 60
- Concomitant Anti-Retroviral Therapy Allowed – Including Protease Inhibitors

Endpoints

- Primary
  - Best Tumor Response First 10 Cycles
  - Time to Progression
- Secondary
  - Symptom Distress Scale
  - Karnofsky Performance Status
- Pharmacokinetics

ACTG Response Criteria

Complete

Absence of Any Detectable Disease

Biopsy Required for Confirmation

Partial Response

No New Lesions, No New Visceral Sites or
Tumor-Associated Edema AND

≥ 50% Decrease in: Total Number of Lesions OR
Surface Area of 5 Marker Lesions OR
Measurable Visceral Disease OR

Complete Flattening of at Least 50% All Previously Raised

Dosing Schedule

- PAXENE® 100 mg/m^2 3-Hour I.V. Every Two Weeks
- Premedication
  - Dexamethasone
  - Cimetidine or Ranitidine
  - Diphenhydramine
- One Dose Reduction to 75 mg/m^2 per Protocol
- Concomitant G-CSF Allowed

Enrollment
(N = 89)

Investigator	Institution	N (%)
Gill	USC	39 (44)
Groopman/Scadden	Harvard	25 (28)
Saville	UCSD	8 (9)
Friedman-Kien	NYU	6 (7)
Others	Univ Oregon	11(12)
	NY Med Coll	
	St Vincent's Hosp (NY)	

Patient Characteristics (N = 89)

	N (%)
Race/Ethnicity	
White	49 (55)
Hispanic	27 (30)
Other	13 (15)
Age	38 ± 7
CD4 (mm^3)	
Median	40
Range	0 -1139
Karnofsky Performance Status	
≥ 90	25 (29)
70 - 80	53 (61)
60	9 (10)

Concomitant Therapy at Study Entry (N = 89)

	N (%)
Anti-Retroviral Therapy	63 (71)
Reverse Transcriptase Inhibitors	52
Protease Inhibitors	33
Antiviral Therapy (CMV Retinitis)	
Ganciclovir/Cidofovir/Foscarnet	30 (34)
G-CSF (Filgrastim)	27 (30)

Disease Sites (N = 89)

Site	N (%)
Mucocutaneous Lesions	87 (98)
Facial	42
Oral	40
Tumor-Associated Edema	45 (51)
Visceral	37 (42)
Pulmonary	20
Gastrointestinal	12
Liver, Adrenal, Peritoneal	5

TIS Staging

	Good Risk	Poor Risk
T	Skin, Lymph Nodes Minimal Oral KS	Edema, GI-KS, Visceral KS Extensive Oral KS
I	CD4 $\geq$ 200	CD4 $<$ 200
S	No Prior OI No B-Symptoms KPS $\geq$ 70	Prior OI Prior B-Symptoms KPS $<$ 70

TIS Staging
Patient Characteristics

Category	Poor Risk N (%)
Tumor Burden	74 (83)
Immune Status	75 (84)
Systemic Illness	72 (81)
1 or More Poor Risk	86 (97)
2 or More Poor Risk	80 (90)
3 or More Poor Risk	55 (62)

Prior Cytotoxic Chemotherapy (N = 89)

Number of Previous Treatments	N	%
1	57	64
≥ 2	32	36
	89	100
Previous Chemotherapy		
Liposomal Daunorubicin (Daunoxome®)	41	46
Liposomal Doxorubicin (Doxil®)	27	30
Other Anthracycline	28	31

PAXENE® Therapy

Number of Cycles	
Median	8
Ongoing Beyond 10 Cycles	34
Dose Intensity (mg/m^2/week)	
Median	44

Tumor Response (N = 89)

	ITT Analysis N (%)
Overall Response	41 (46)
(95% CI)	(41 - 62)
Complete Response	2 (2)
Partial Response	39 (44)
Stable Disease	29 (33)
Progression	5 (6)
Not Evaluable	14 (16)

GILL # 16
Cycle 7

Patient 659

Pre-Study

Cycle 19

Response by Previous Cytotoxic Chemotherapy (N = 89)

Previous Regimens	Tumor Response N	%	95% CI
1	28/57	47	(36 - 62)
≥ 2	13/32	41	(23 - 59)
Daunoxome	21/41	51	(36 - 67)
Doxil	9/27	33	(15 - 52)
Other Anthracycline	14/28	50	(14 - 53)

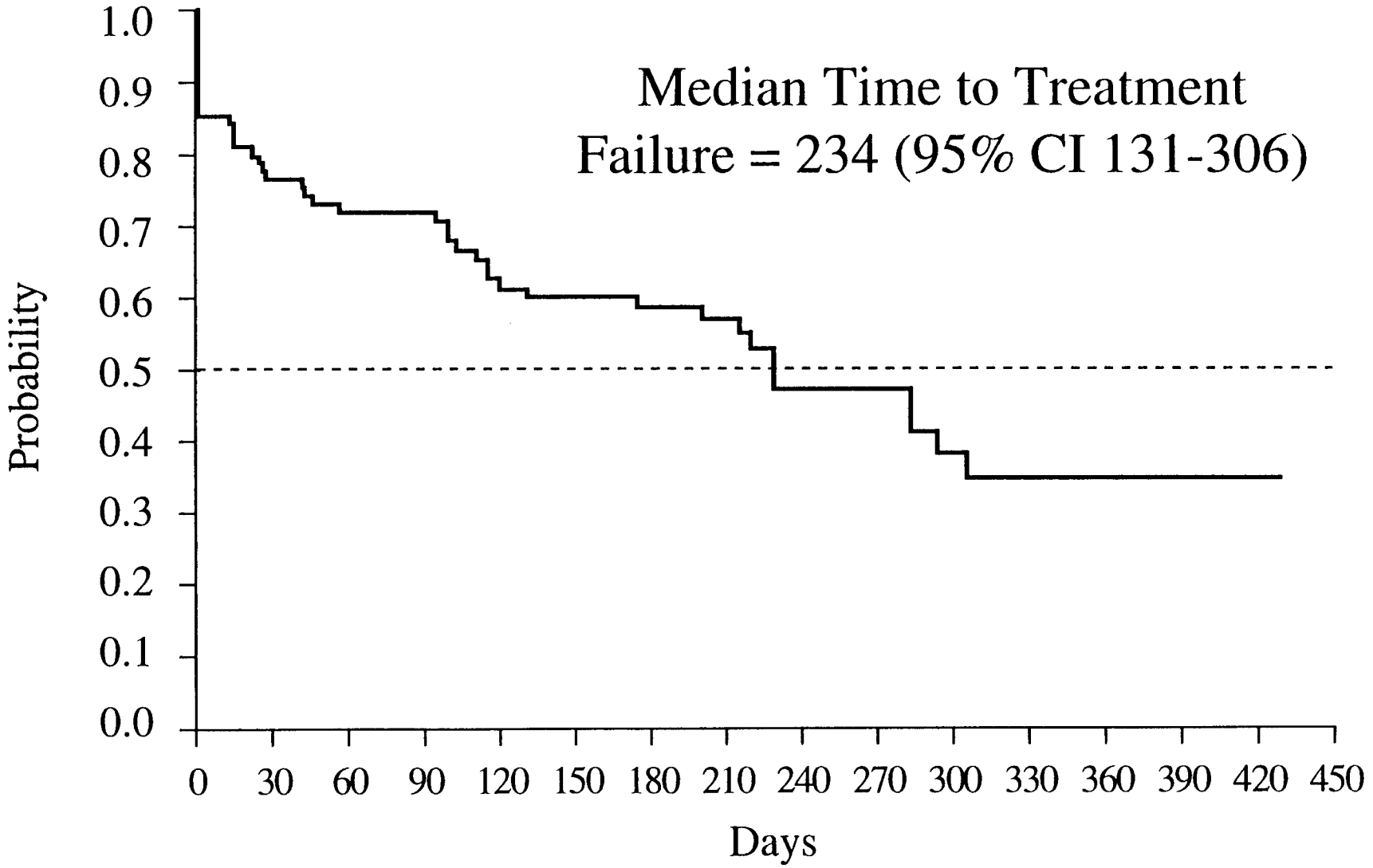
Tumor Response: All Patients Compared to No Protease Inhibitors

	Tumor Response N (%)	95% CI
All Patients	41/89 (46)	(36-57)
No Use of Protease	12/29 (41)	(27-60)

Longitudinal Response Parameters

	Median (Days)	95% CI (Days)
Time to Response (N = 41)	49	(33-61)
Duration of Response (N = 41)	Not Reached	306 - Not Reached

Time to Treatment Failure



Paxene® Pharmacokinetics

- 11 Patients

  Reverse Transcriptase Inhibitors
  (D4T, ZDV, 3TC, DDI)

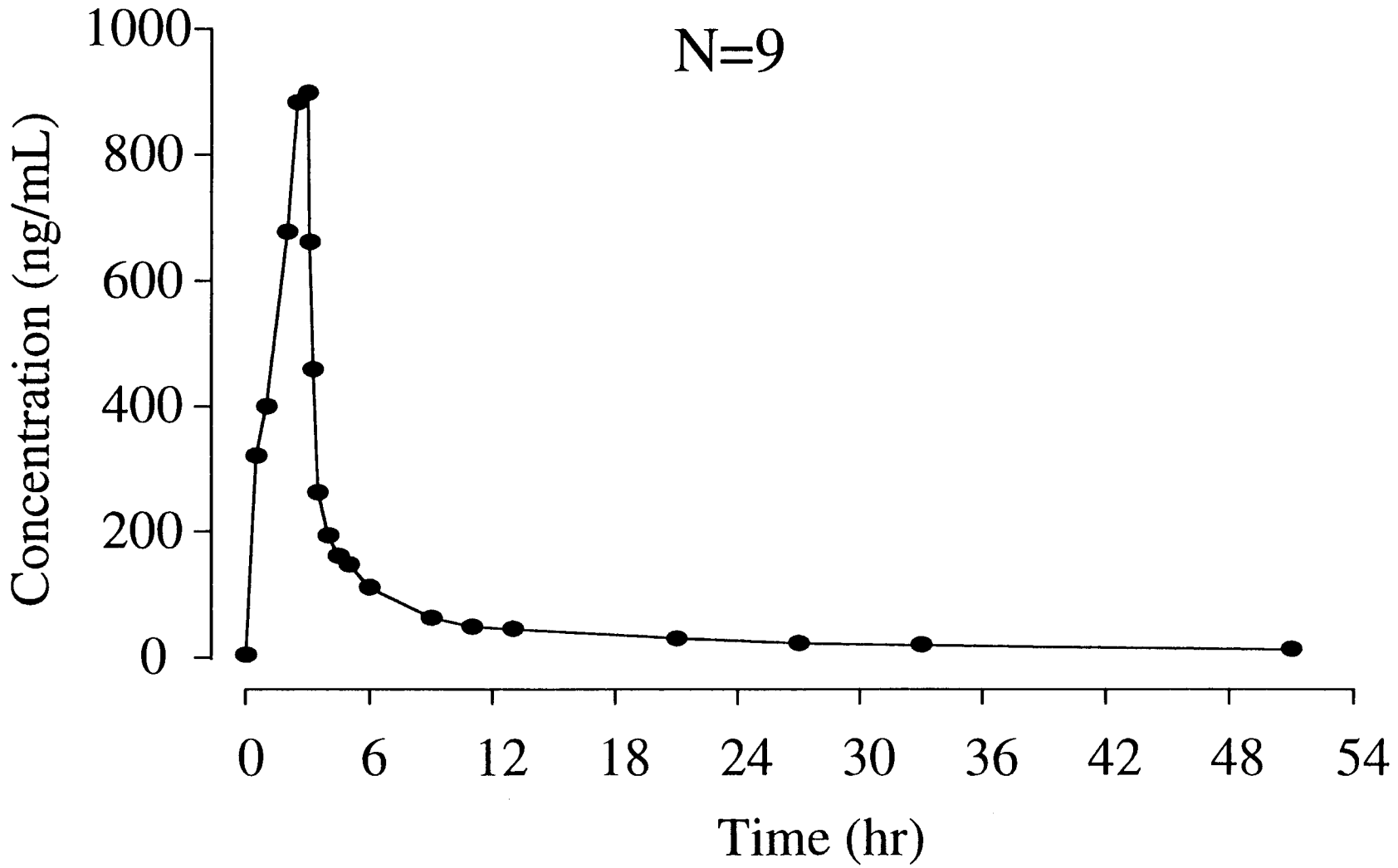
  Imidazole Antifungal Agents

  Indinavir

- 9 Patients Studied Once, 2 Patients Studied Twice
- Plasma Sampling (> 250 Samples) for 48 hr Post Infusion

DUCHIN # 2
Cycle 4

Mean Plasma Paclitaxel Concentrations During and After Paxene (100 mg/m^2 x 3 hr) in AIDS-KS

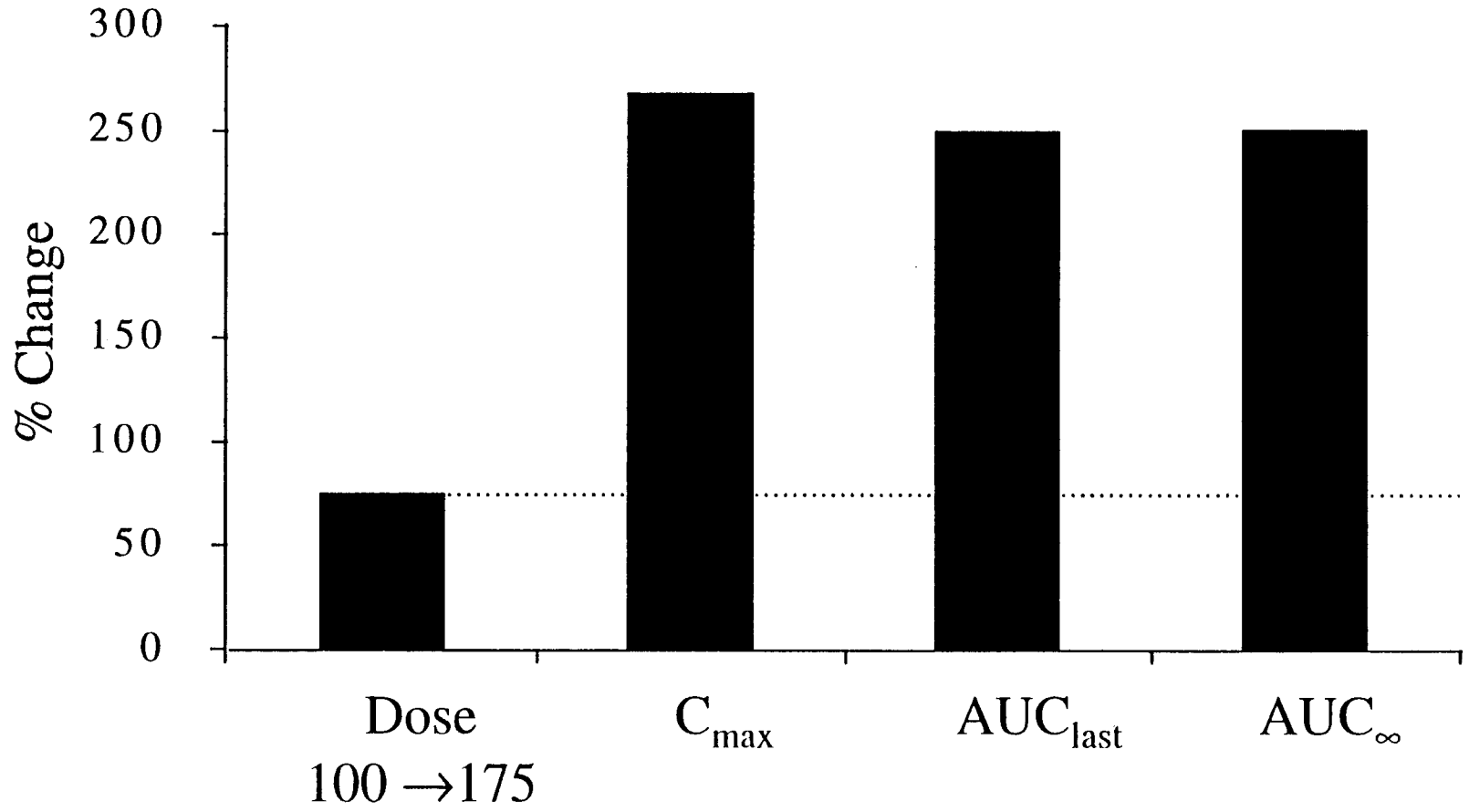


PK Parameters of Paxene® in AIDS-KS

	Cmax (ng/mL)	CL ($L/hr/m^2$)	V_{dss} (L/m^2)	$t^1/_2$ (hr)
Mean	1118	27	402	25
SD	300	7	151	6
CV	27	25	38	25

Paclitaxel PKs

Comparison of 100 mg/m^2 (n = 9) vs. 175 mg/m^2 (n = 37) Over 3 Hours



DUCHIN # 5
Cycle 4

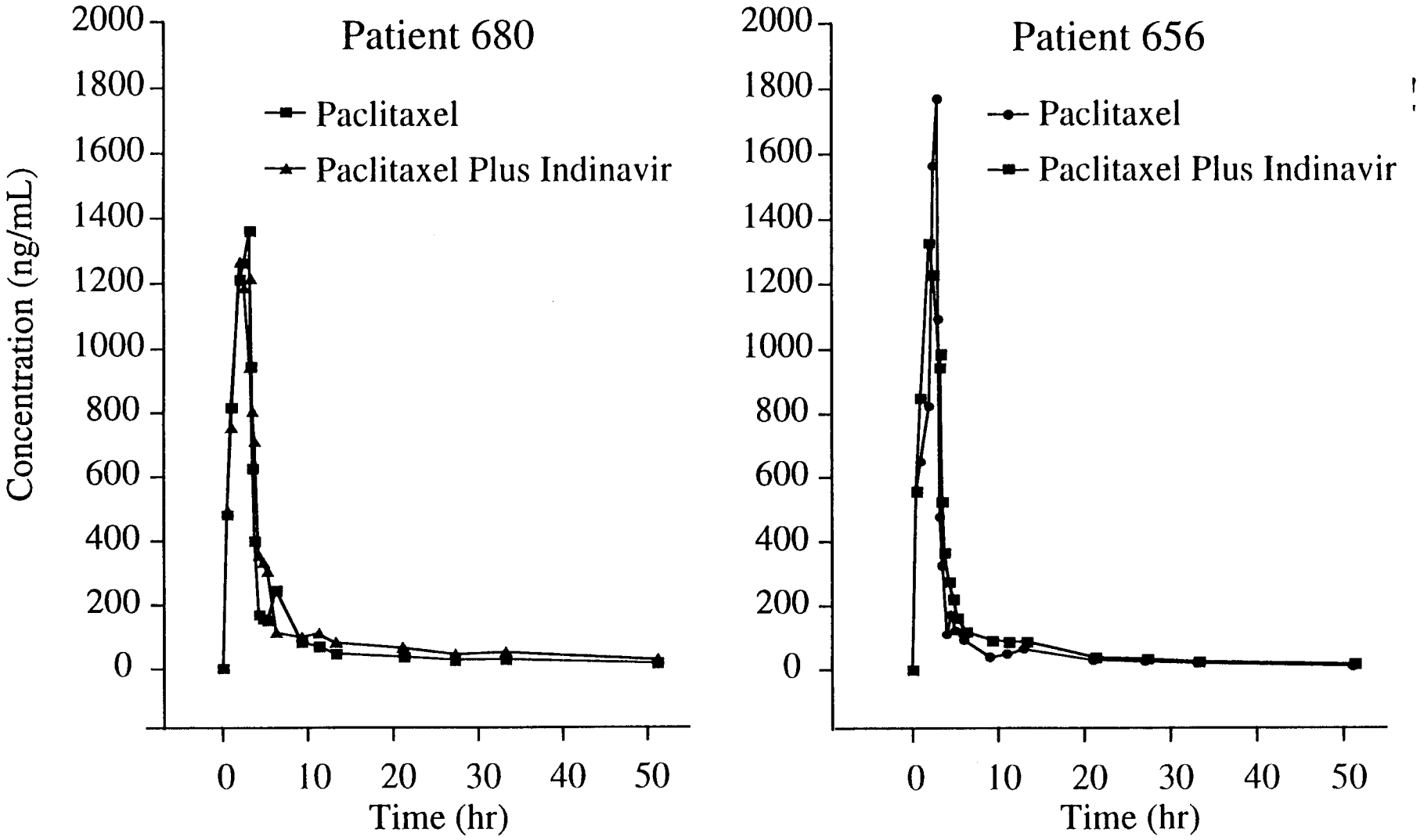
Effect of Indinavir on Paclitaxel Pharmacokinetics

Mean (SD)

	No Indinavir (N = 5)	Indinavir (N = 4)
Cmax (ng/mL)	1073 (301)	1175 (334)
CL ($L/hr/m^2$)	27 (8)	28 (5)
V_{dss} (L/m^2)	421 (168)	368 (144)
$t^1/_2$ (hr)	26 (6)	23 (8)

DUCHIN # 6
Cycle 4

Effect of Indinavir on Paclitaxel Plasma Levels



Effect of Imidazole Antifungal Agents (Fluconazole, Clotrimazole) on Paclitaxel Pharmacokinetics

Mean (SD)

	No Antifungals (N = 5)	Antifungals (N = 4)
Cmax (ng/mL)	1159 (335)	1068 (290)
CL ($L/hr/m^2$)	25 (6)	30 (7)
V_{dss} (L/m^2)	334 (158)	460 (139)
$t^1/_2$ (hr)	23 (6)	27 (7)

Paxene® Pharmacokinetics Conclusions

- Paxene Pharmacokinetics Documented in Patients with AIDS-KS in Presence of Multiple HIV Therapies
- Paclitaxel Displays Nonlinear Pharmacokinetics Between 100 and 175 mg/m^2 x 3 hr
- No Appreciable Interaction with Indinavir and Imidazole Antifungals

AIDS-Related Kaposi's Sarcoma

Quality of Life/Patient Benefit

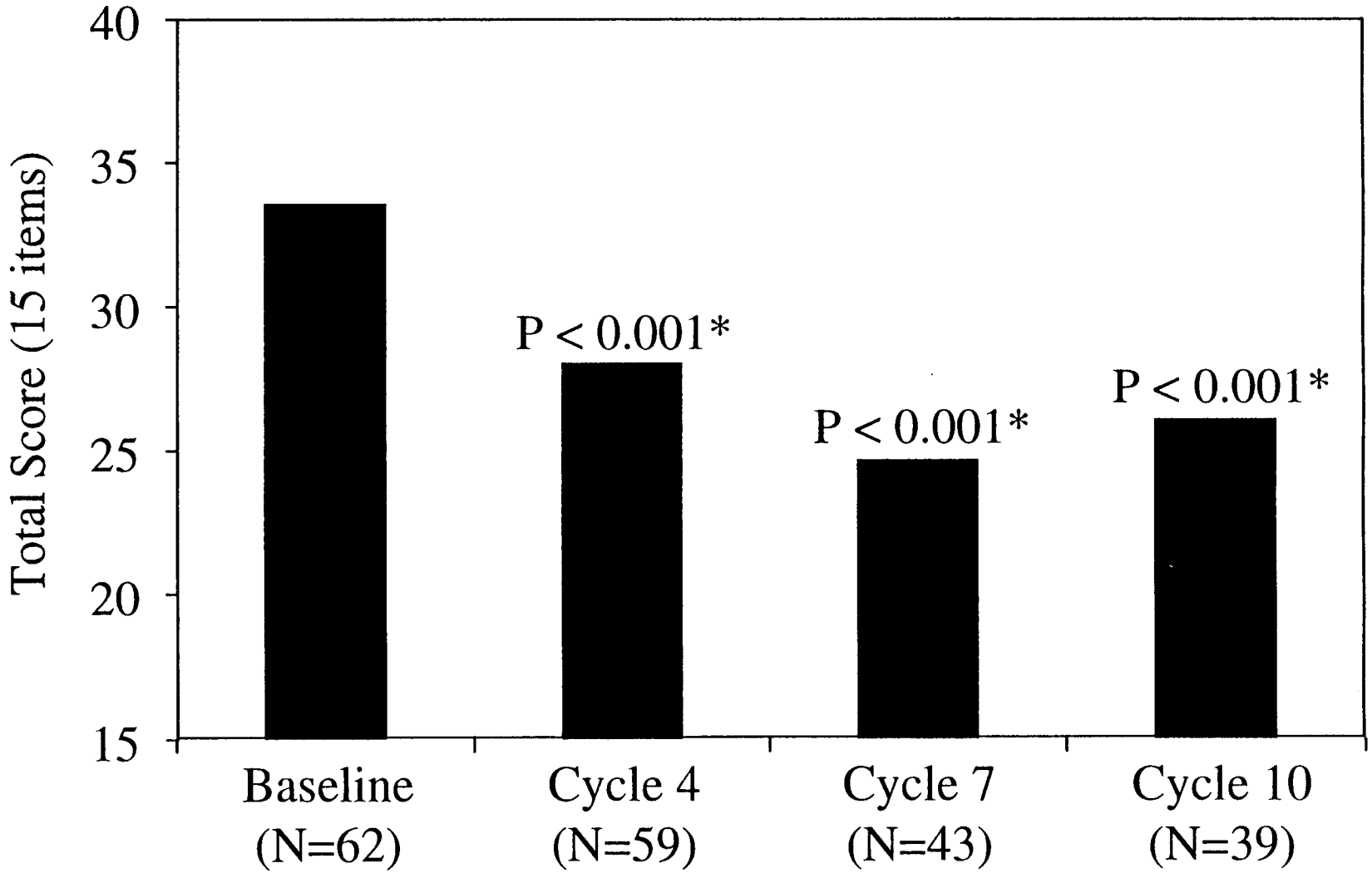
Safety

Summary/Conclusions

Quality of Life

- Prospective Symptom Distress Scale
  - Self Administered
  - 15 Questions
  - General and Disease-Related Symptoms
  - 5-Point Likert-Type Format
  - Validated
- Karnofsky Performance Status
- Photographs

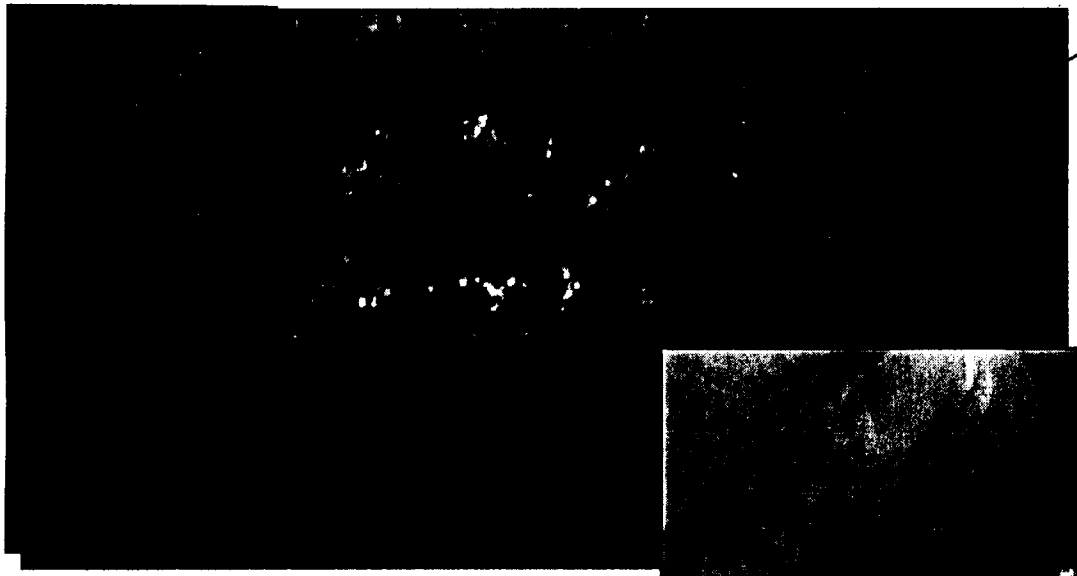
Median Symptom Improvement in Patients by Total Score



* Sign test result (two-tailed) for median change from baseline

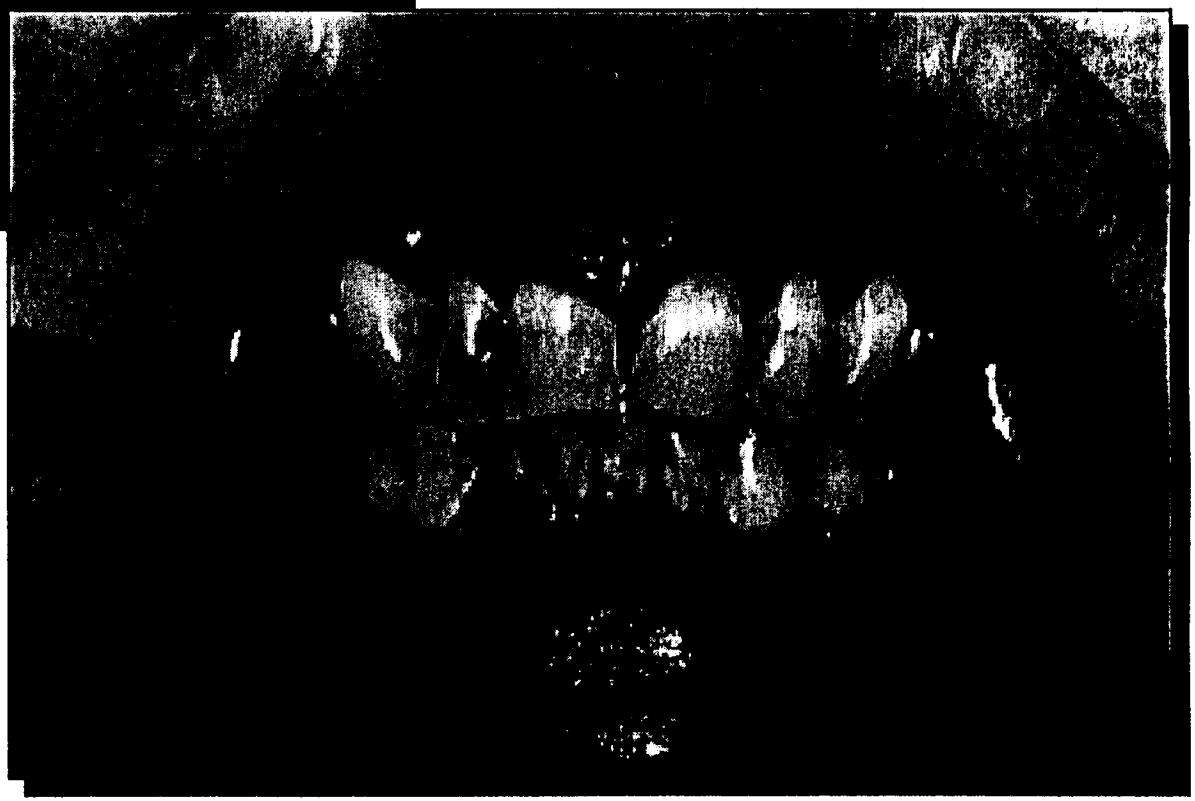
HARRIMAN # 5
Cycle 8

Patient 674



Pre-Study

After-Treatment

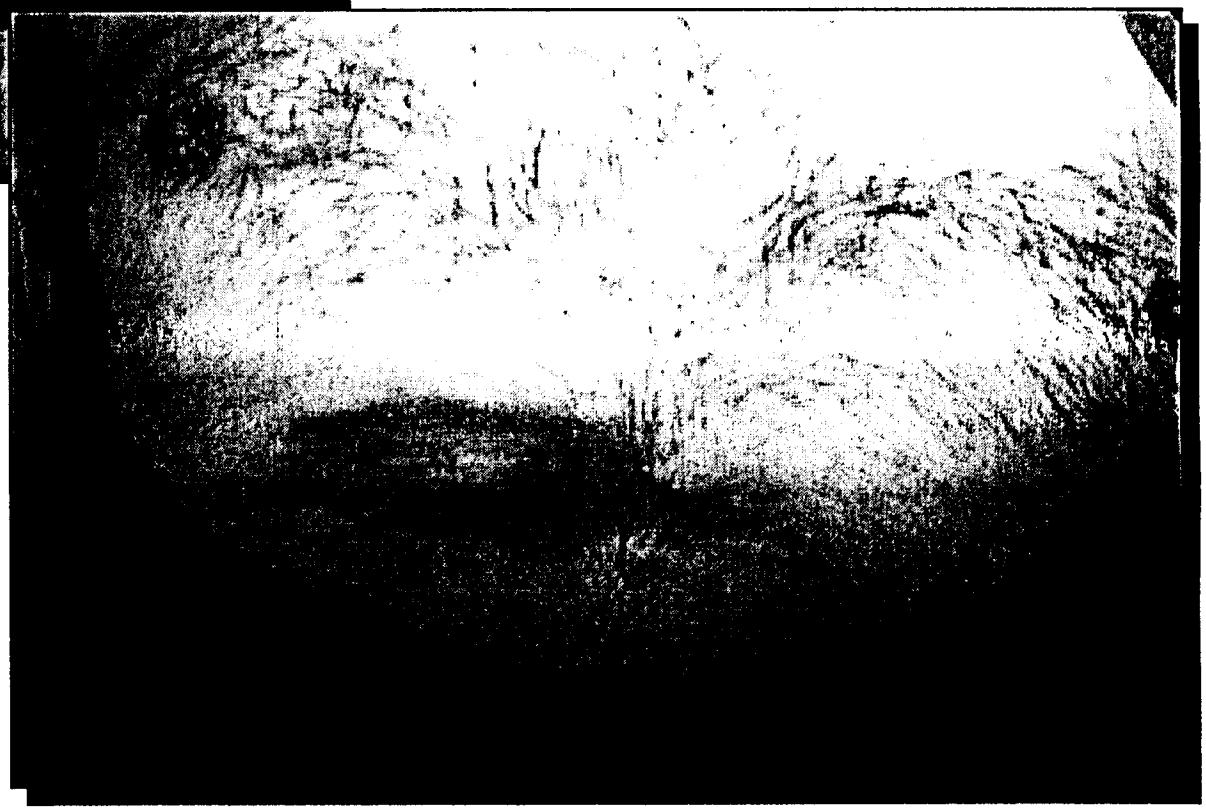


HARRIMAN # 6
Cycle 8

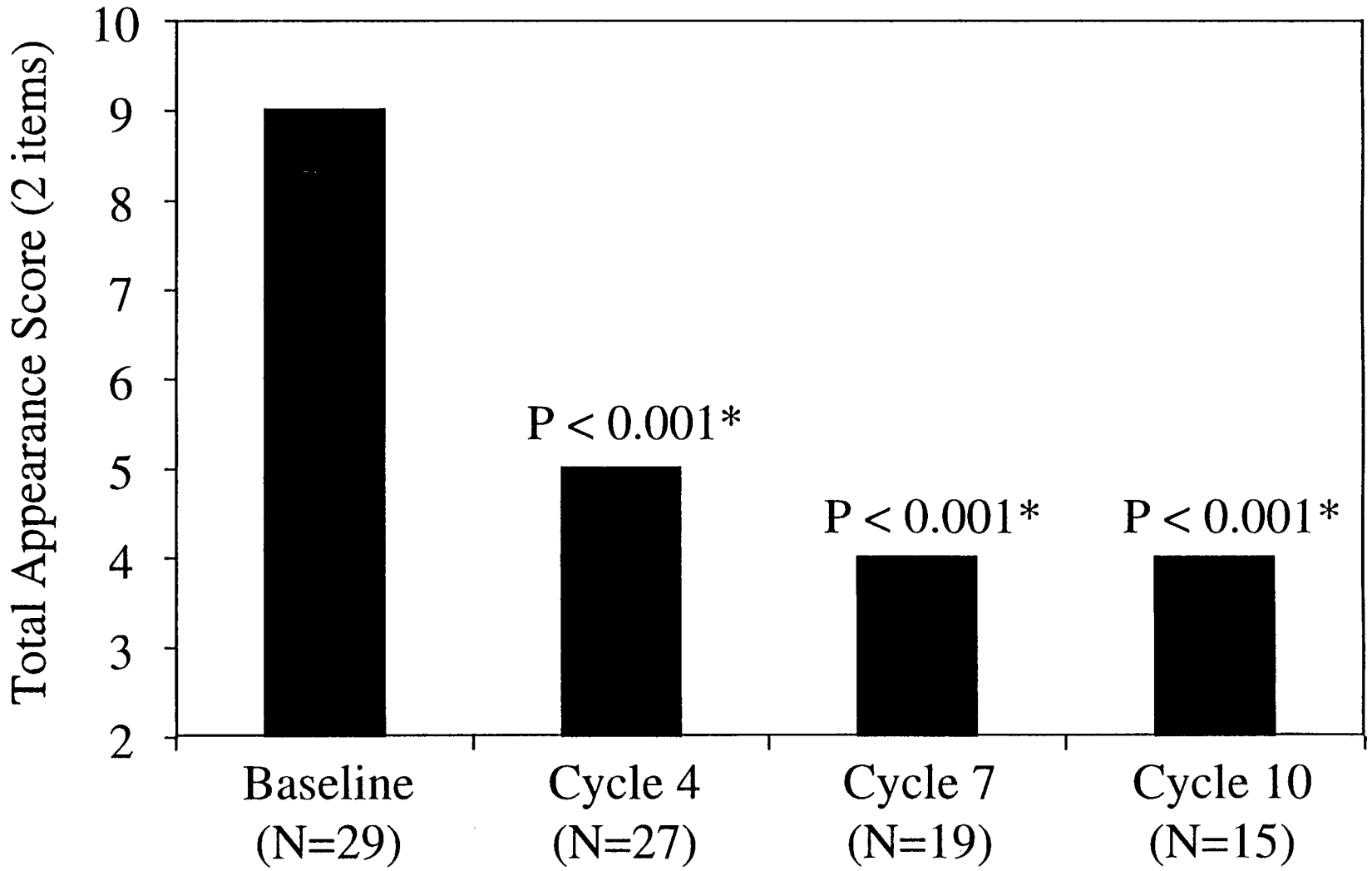
Patient 674

Pre-Study

After-Treatment



Median Symptom Improvement in Appearance of Patients with Facial Involvement



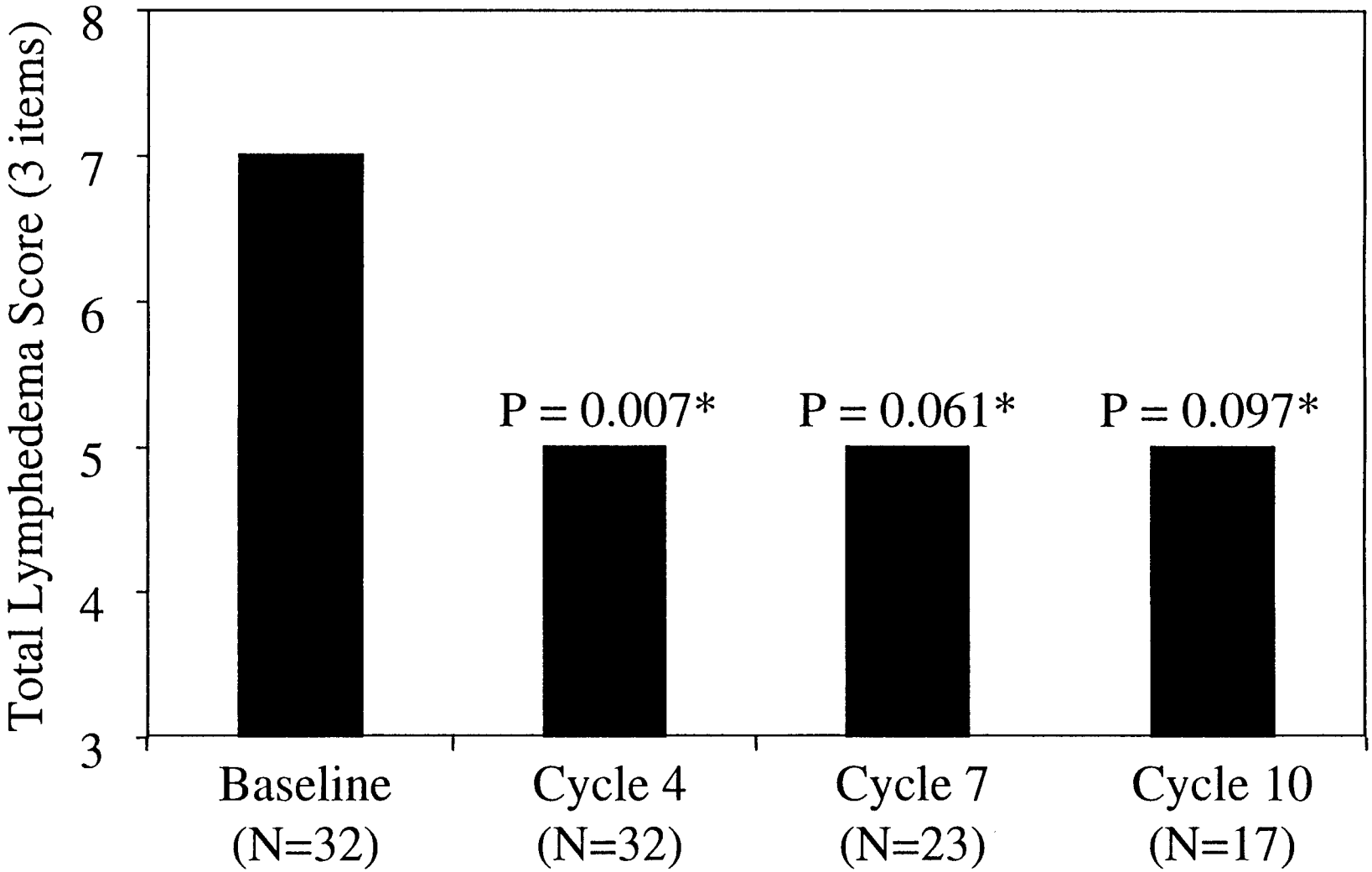
* Sign test result (two-tailed) for median change from baseline

Patient 676

Pre-Study

Cycle 16

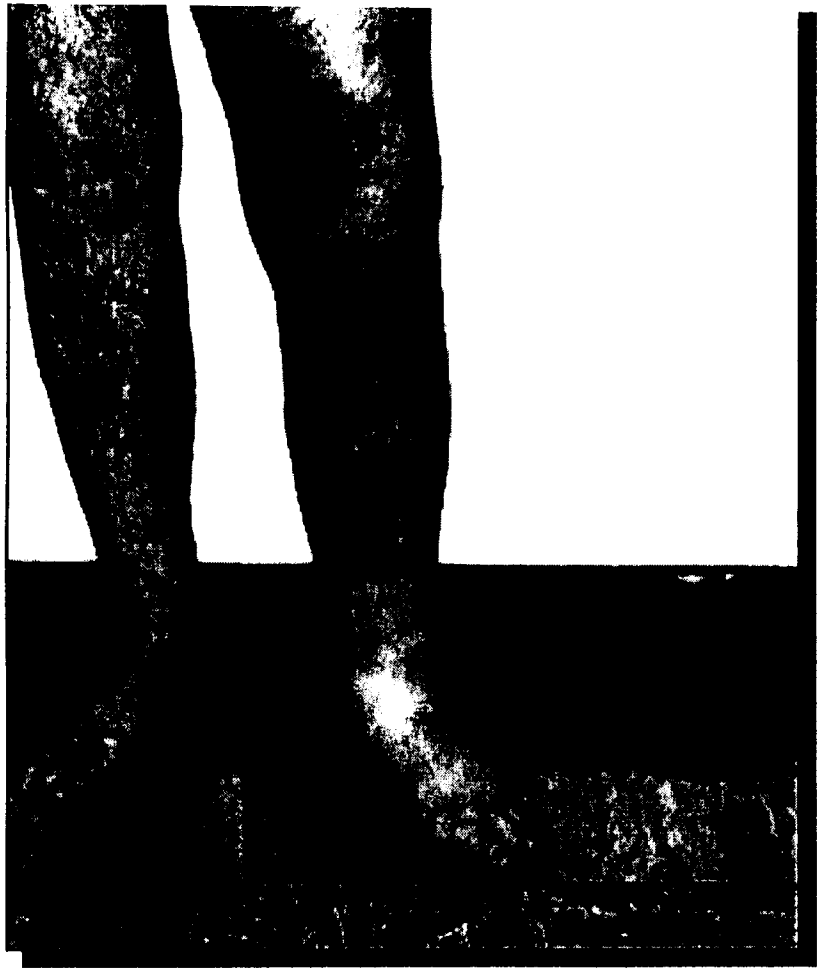
Median Symptom Improvement in Patients with Lymphedema



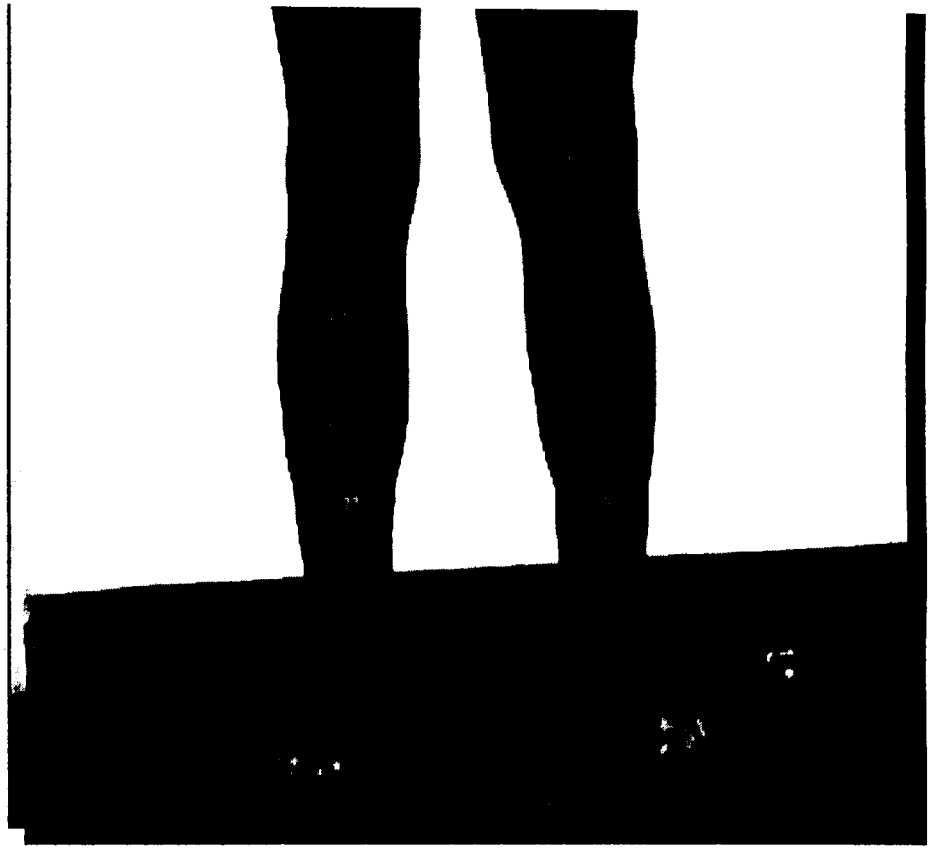
* Sign test result (two-tailed) for median change from baseline

Patient 627

Pre-Study



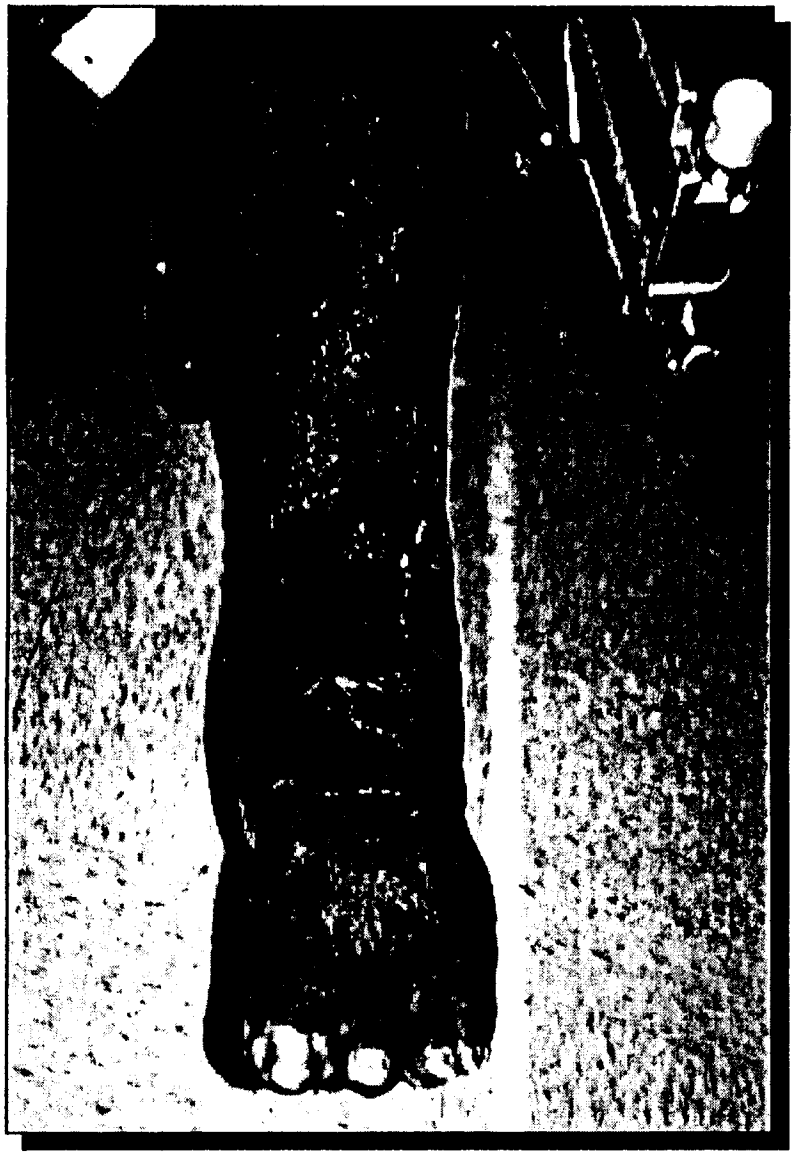
Cycle 13



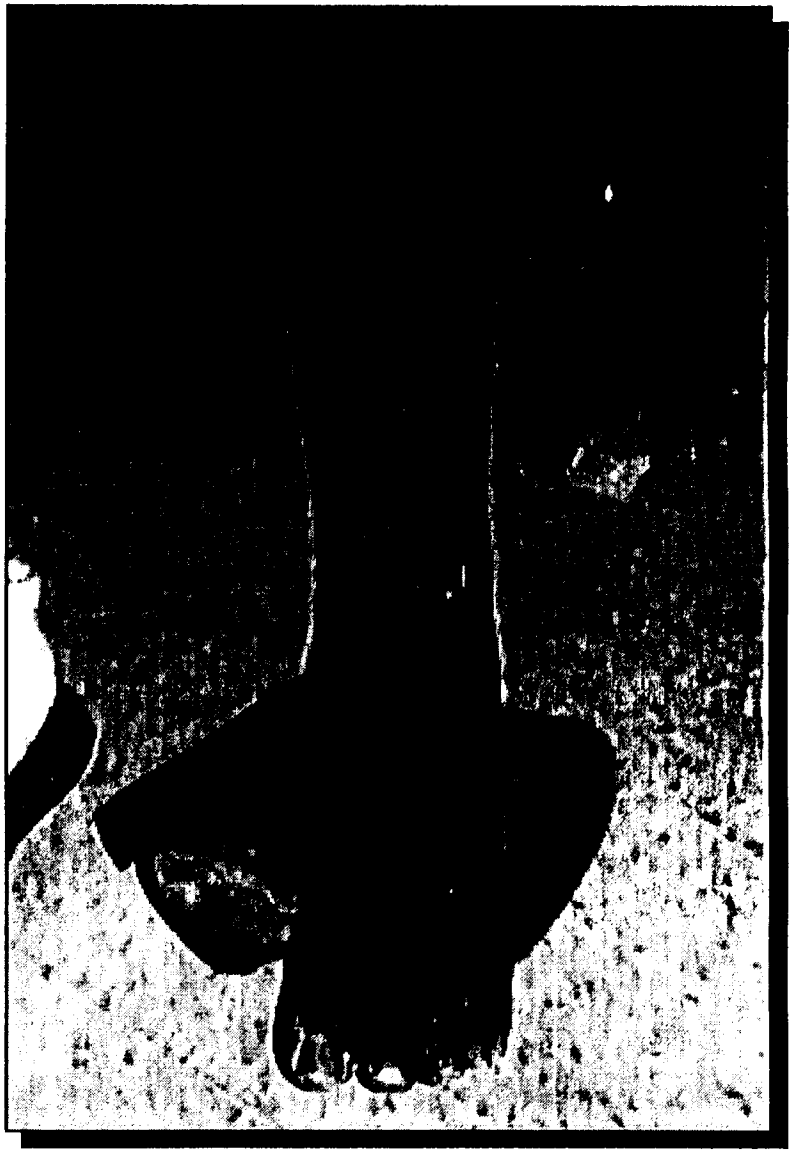
HARRIMAN # 11
Cycle 8

Patient 857

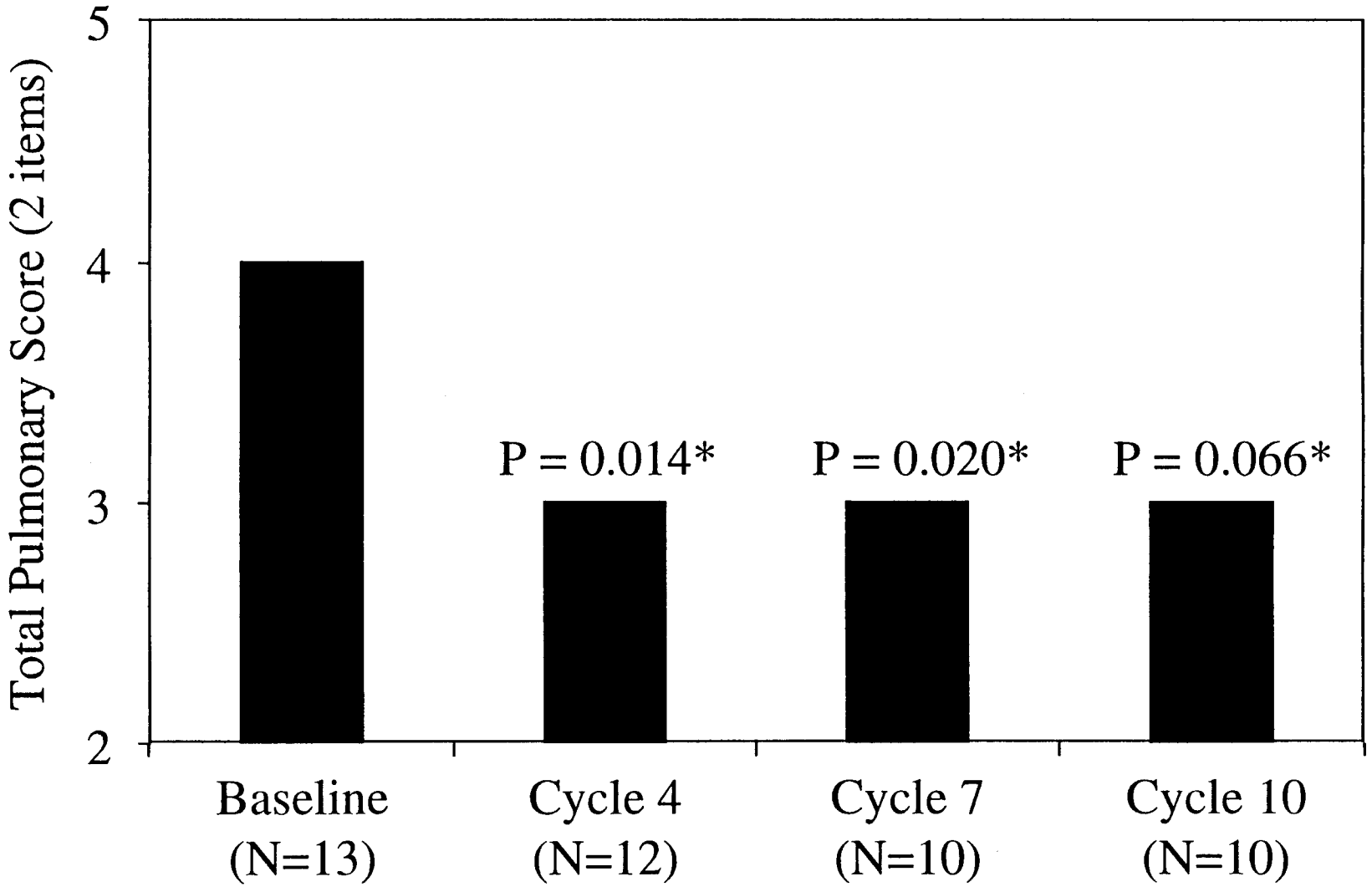
Pre-Study



Cycle 3



Median Symptom Improvement in Patients with Pulmonary Involvement

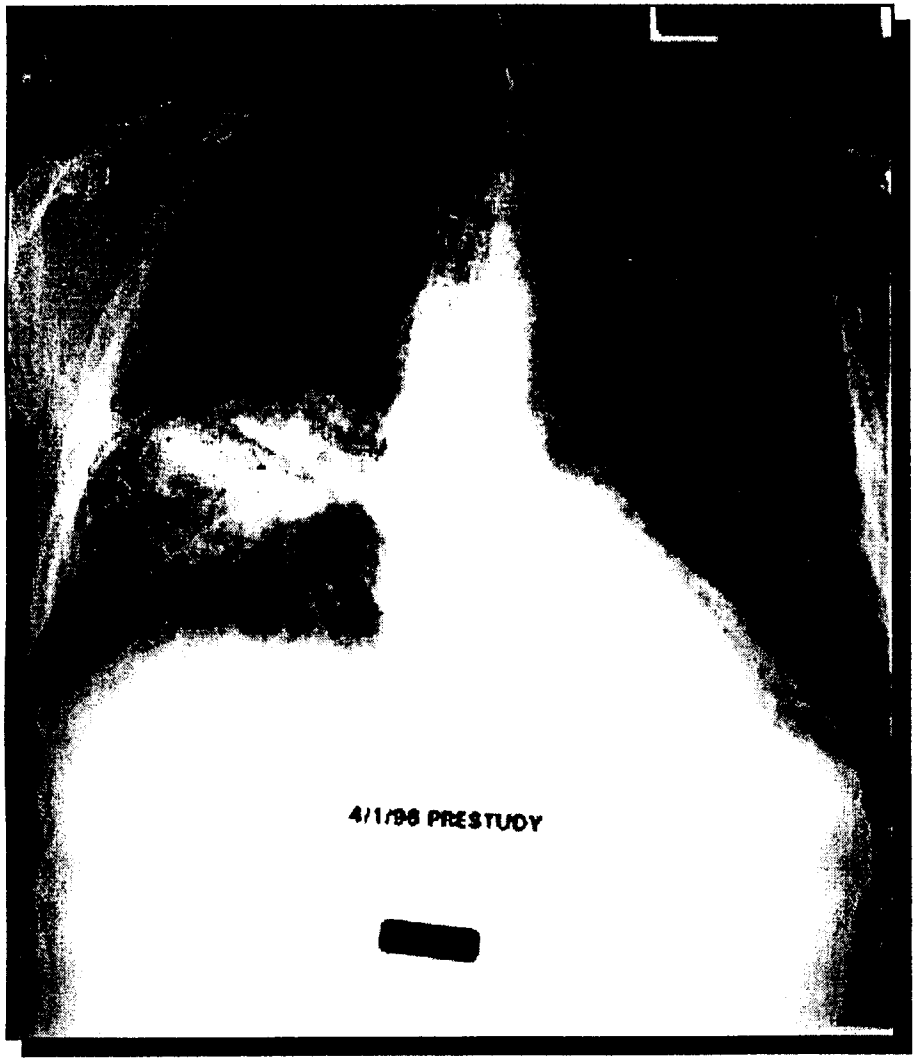


* Sign test result (two-tailed) for median change from baseline

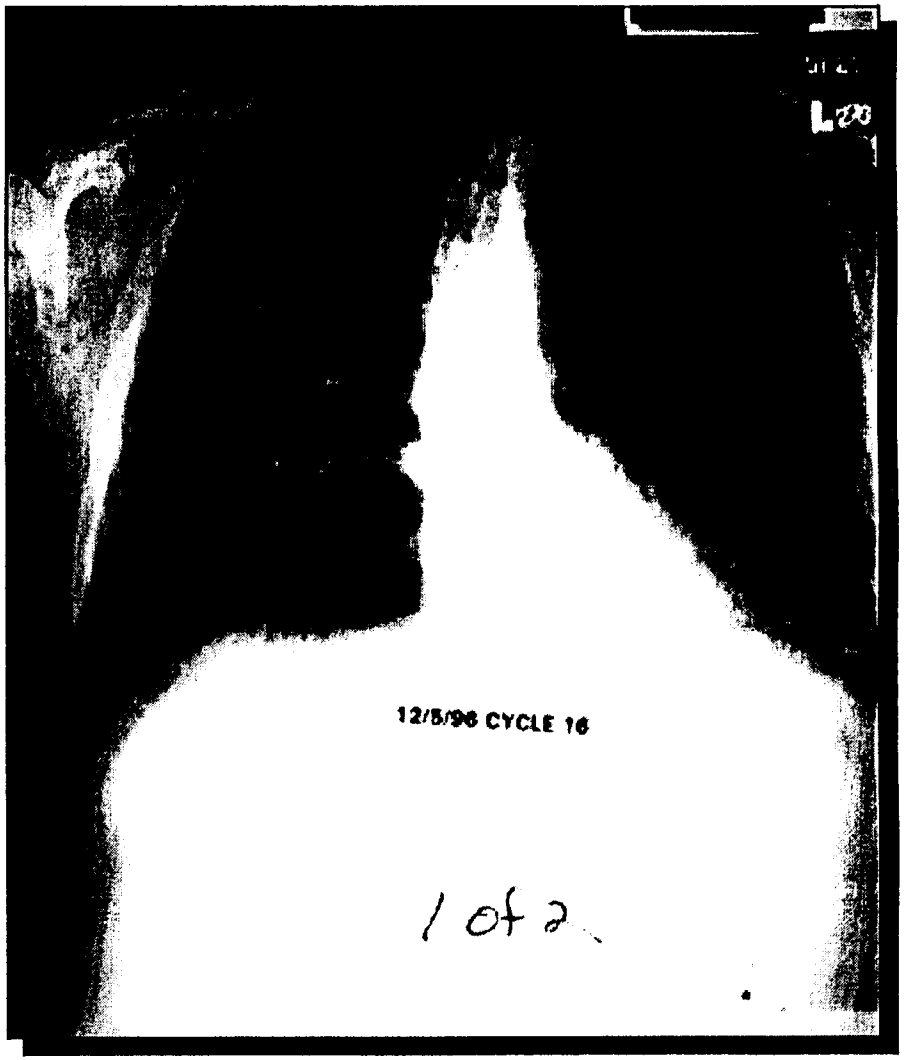
HARRIMAN # 13
Cycle 8

Patient 648

Pre-Study

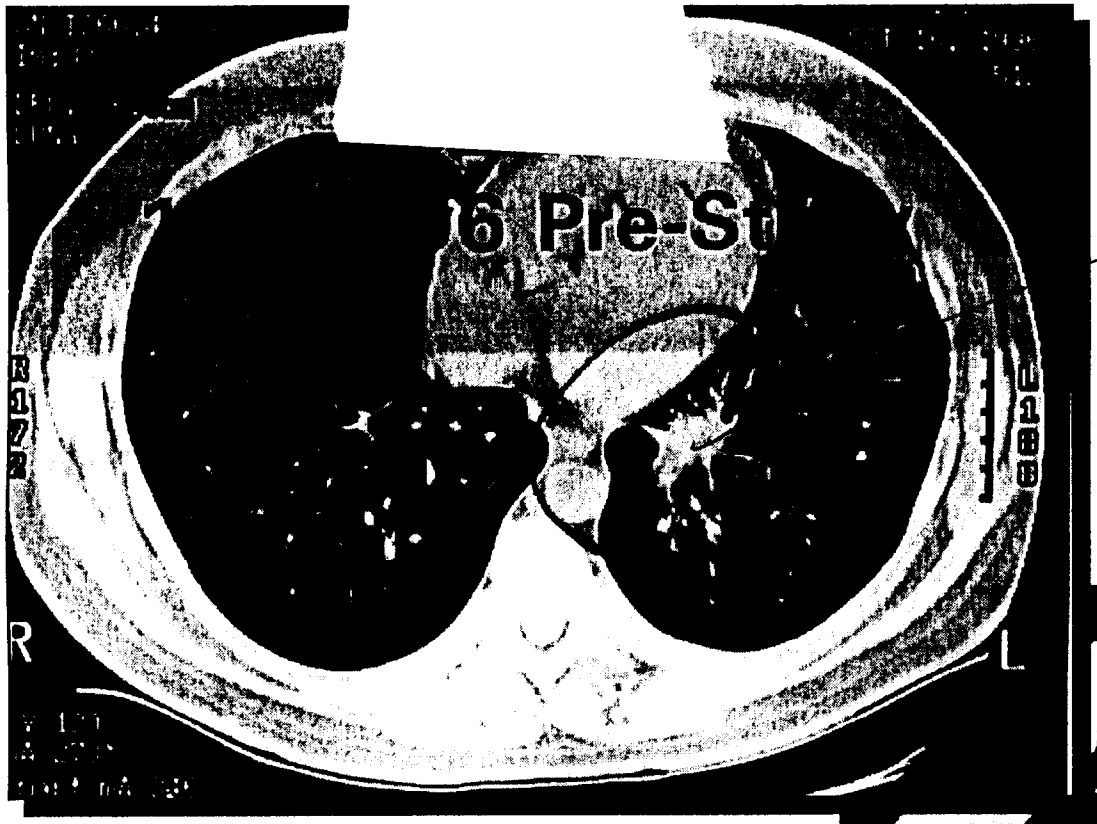


Cycle 16



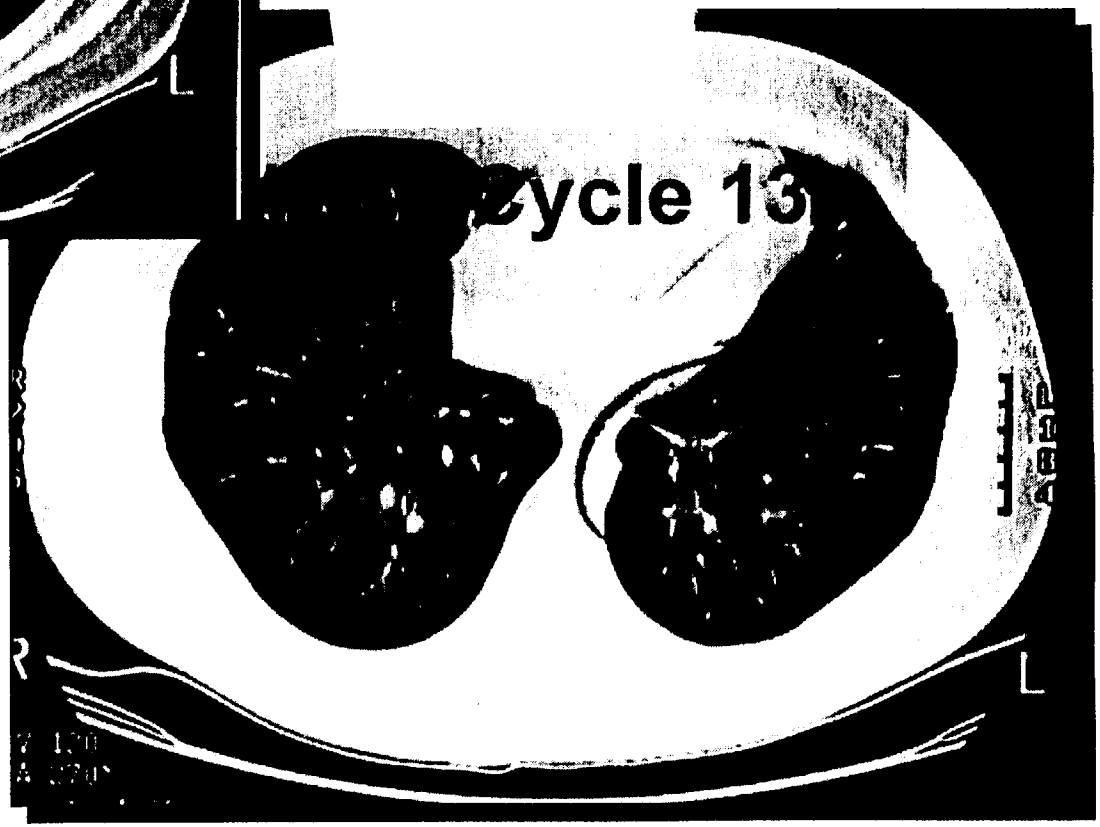
HARRIMAN # 14
Cycle 8

Patient 692



Pre-Study

Cycle 13



Karnofsky Performance Status Changes from Baseline

	N (%)
• Improved	35 (46)
• Unchanged	32 (42)
• Worsened	9 (12)

p = 0.02 Maxwell-Stuart Test
Compared with Baseline

Frequent Treatment Adverse Events

	All N (%)	Severe (≥ Grade 3) N (%)
• Hematological		
– Neutropenia	74 (83)	54 (61)
– Anemia	52 (58)	9 (10)
• Asthenia	53 (60)	3 (3)
• Alopecia	50 (56)	9 (10)
• Nausea and/or Vomiting	44 (49)	7 (8)
• Arthralgias/Myalgia	27 (30)	1 (1)
• Neuropathy	36 (41)	4 (5)
• Rash	32 (36)	1 (1)

Major Toxicities By Protease Inhibitor Use

	No PI (N=27)	PI (N=62)
Neutropenia		
– All Grades	20 (74)	48 (80)
– Severe	14 (52)	33 (55)
Febrile Neutropenia	1 (4)	4 (7)
Anemia	13 (48)	38 (63)
Hypersensitivity	2 (7)	7 (11)
Alopecia	9 (33)	28 (47)
Fever	12 (44)	25 (42)
Opportunistic Infections	10 (37)	20 (33)
Arthralgia / Myalgia	7 (26)	14 (23)
Neuropathy	6 (22)	24 (40)

Incidence of Opportunistic Infections (N = 89)

	N
Mycobacterial (TB, MAI)	3
PCP	4
Cryptococcal Meningitis	2
CMV Retinitis	8
Oral Thrush	23
Candida Esophagitis/Laryngitis	5
HSV, VZV	17
Condyloma/Molluscum	3
Oral Hairy Leukoplakia	4
Isospora Belli	1

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Paxene® Deaths on Study

	Related	Non-Related	Total
Progressive KS	0	3	3
Non-KS HIV Complications	0	2	2
Sepsis/Infection	3	1	4
Cardiopulmonary	1	1	2
Total	4	7	11

Paxene: Hematological Toxicity

major toxicity hematologic

Adverse Event	% Incidence 100 mg/m² Over 3 Hours Q2W n = 89	140 mg/m² Over 96 Hours Q3W n = 58	175 mg/m² Over 3 Hours Q3W n = 168
• Bone Marrow			
– Neutropenia			
< 2,000/mm³	83	62	84
< 500/mm³	36	22	35
– Thrombocytopenia			
< 100,000/mm³	17	25	20
< 50,000/mm³	7	2	3
– Anemia			
< 11 g/dL	58	89	79
< 8 g/dL	7	39	18

Paxene: Major Non-Hematological Toxicity

Adverse Event	% Incidence 100 mg/m^2 Over 3 Hours Q2W n = 89	140 mg/m^2 Over 96 Hours Q3W n = 58	175 mg/m^2 Over 3 Hours Q3W n = 168
• Alopecia	56	35	67
• Hypersensitivity			
– All	10	2	8
– Severe	0	0	0
• Arthralgia/Myalgia			
– Any Symptoms	30	26/29	43/32
– Severe Symptoms	2	2/0	7/7
• Peripheral Neuropathy			
– Any Symptoms	41	17	51
– Severe Symptoms	5	0	5

Paxene®

Question #1

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

Comparison of Studies Sizes

	Paxene® 100 mg/m² q2w	Taxol® 135 mg/m² q3w	Taxol® 100 mg/m² q2w	Doxil® 20 mg/m² q3w
Total Number of Patients	89	29	56	77
Failed Prior Chemotherapy	89	19	40	77
Evaluable and Failed Prior Chemotherapy	75	18	40	34

Paxene®

Question #2

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

Paxene® Study

- Overall Response 46%
- Response in Doxil® Treated Patients 33%
- Response in Patients Treated with ≥ 2 Prior Cytotoxic Chemotherapies 41%
- Median Duration of Response Not Reached
- Median Time to Treatment Failure 234 Days

Paxene® Study

- QOL/Clinical Benefit
  - Significant Improvement in Symptoms Related to Facial Lesions, Lymphedema and Pulmonary Disease
  - Significant Improvement in Karnofsky Performance Status
  - Photographic Evidence of Improvement

Paxene®

Question #3

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

Comparison of Safety (%)

Adverse Events	Paxene® 100 mg/m²	Taxol® 135 mg/m²	Taxol® 100 mg/m²	Doxil® 20 mg/m²
Neutropenia < 2000/m³	83	100	95	49*
< 500/m³	36	76	35	13
Febrile Neutropenia	9	55	9	NA†
Anemia < 11 gm/dL	58	86	73	7
< 8 gm/dL	10	34	25	NA†
Hypersensitivity or Infusion Reactions	10	14	9	7
Alopecia	56	100	86	9
Nausea/Vomiting	49	69	70	18/8
Arthralgia/Myalgia				
Any	30	93	48	< 1
Severe	2	14	16	< 1
Peripheral Neuropathy	41	79	46	< 1
Opportunistic Infections	34	76	54	50

* < 1000/m³ † Not Available

Paxene® Study

Safety

- Experience in Patients on Protease Inhibitors
- Pharmacokinetic Studies in Patients on Protease Inhibitors

Paxene®

Question #4

- Is the Paxene® NDA Approvable for the Indication of Use "After Failure of First Line or Subsequent Systemic Chemotherapy for the Treatment of Advanced AIDS-Related Kaposi's Sarcoma"?

Comparison of Efficacy

Tumor Response Rate	Paxene®	Taxol® 135mg/m²	Taxol® 100 mg/m²	Doxil®
All	46%	74%	53%	27%[A]
Doxil Failure Patients	33%	Not Studied	Unk[B]	NA[C]

[A] 34 Evaluable Patients, Investigator Assessment

[B] Only One Patient Studied

[C] Not Applicable

Conclusion

- PAXENE® Induces Tumor Responses, as Defined by ACTG Criteria, in 46% of Patients With Advanced, AIDS-Related KS Who Had Failed First-Line or Subsequent Systemic Chemotherapy
- PAXENE® Improves Quality of Life, as Assessed by a Symptom Distress Scale and Karnofsky Performance Status
- PAXENE® Is Safe in the Treatment of AIDS-Related KS

Conclusion

- PAXENE® Induces Tumor Response in 33% Patients Receiving Prior Doxil® Therapy and 41% in Patients Who Received at Least Two Prior Cytotoxic Chemotherapies
- PAXENE® Is Safe and Effective in Patients on Concomitant Protease Inhibitors

Proposed Indication - PAXENE®

- PAXENE® is indicated after failure of first-line or subsequent chemotherapy, including liposomal doxorubicin, in patients with advanced AIDS related Kaposi's sarcoma, and for relief of disease-related symptoms. Coadministration with protease inhibitors does not diminish the efficacy or alter the side effect profile of PAXENE®.

Discontinuations

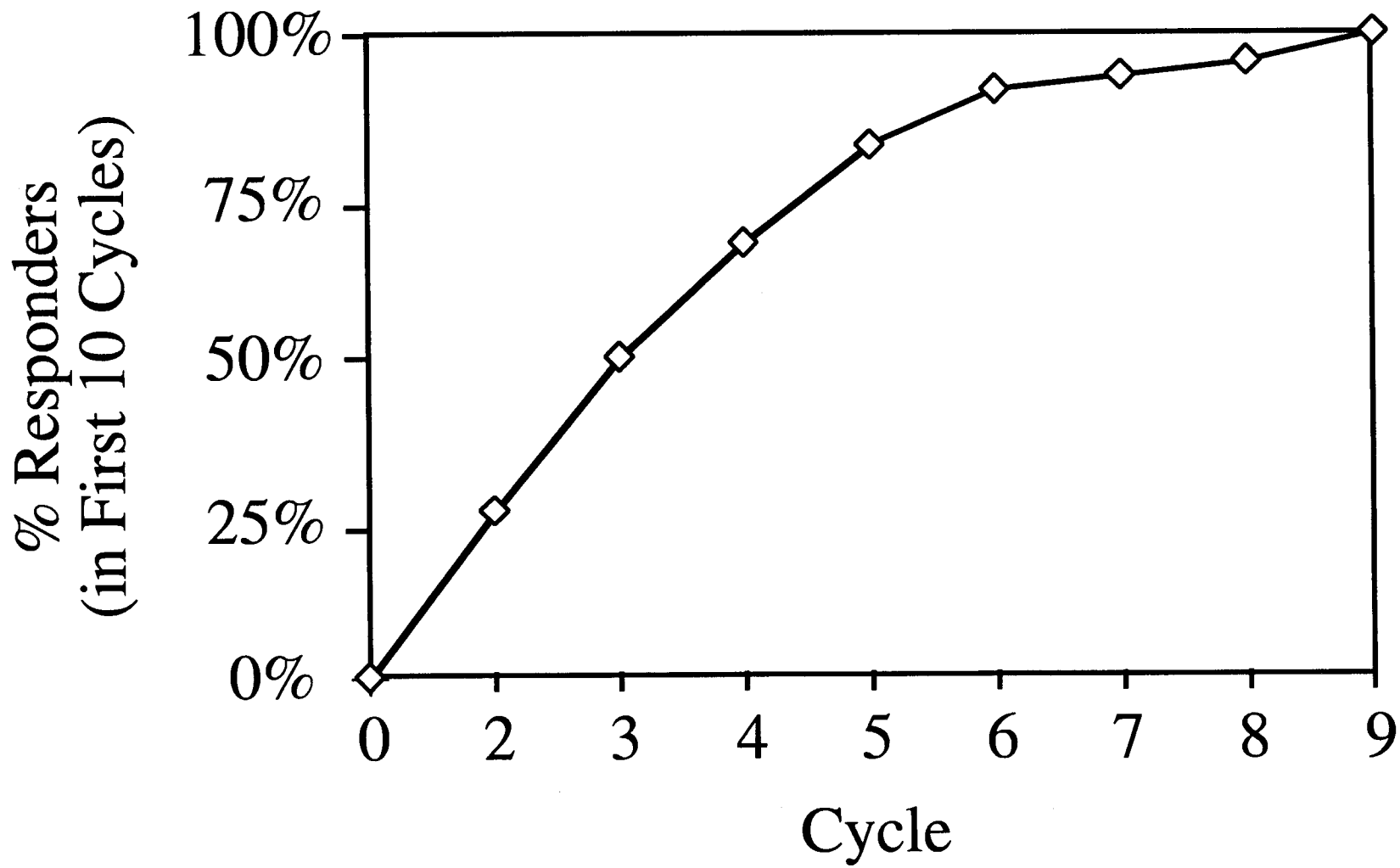
	N (%)
Treatment Discontinued (≥ 2 Cycles)	**15 (17)**
Death	2 (2)
Toxicity	2 (2)
Disease Progression	1 (1)
Refused Further Treatment	2 (2)
Other	8 (9)
Treatment Discontinued (< 2 Cycles)	**12 (14)**
Death	3 (3)
Lost to Follow-up	1 (1)
Refused Further Treatment	1 (1)
Other	7 (8)

Dosing Modifications

Dose Modifications

- A One Time Dose Reduction to 75 mg/m^2 Was Allowed for PAXENE® Related Toxicities
- Patients Could Be Brought Back to 100 mg/m^2 if Toxicity Subsided

Cumulative Number of Responses by Cycle



Best Response by Use of Protease Inhibitors (PI)

PI Use Prior to Response	Tumor Response N
Yes	18
No	23

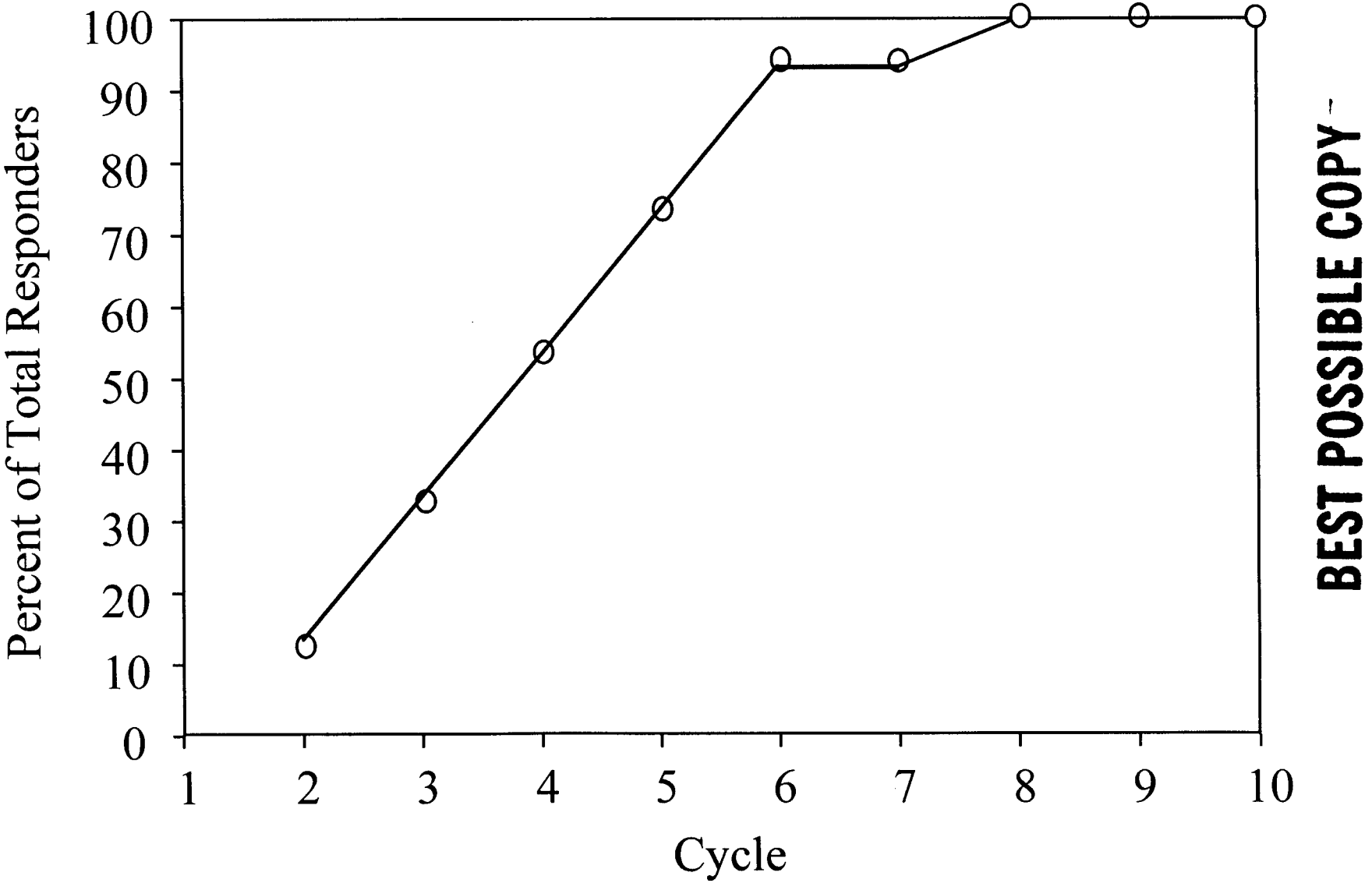
Paxene® Response in Patients Treated with Protease Inhibitors

	Tumor Response		
		%	95% CI
Received Protease Inhibitors	12/21	57	23-60
No Protease Inhibitors	12/29	41	33-70

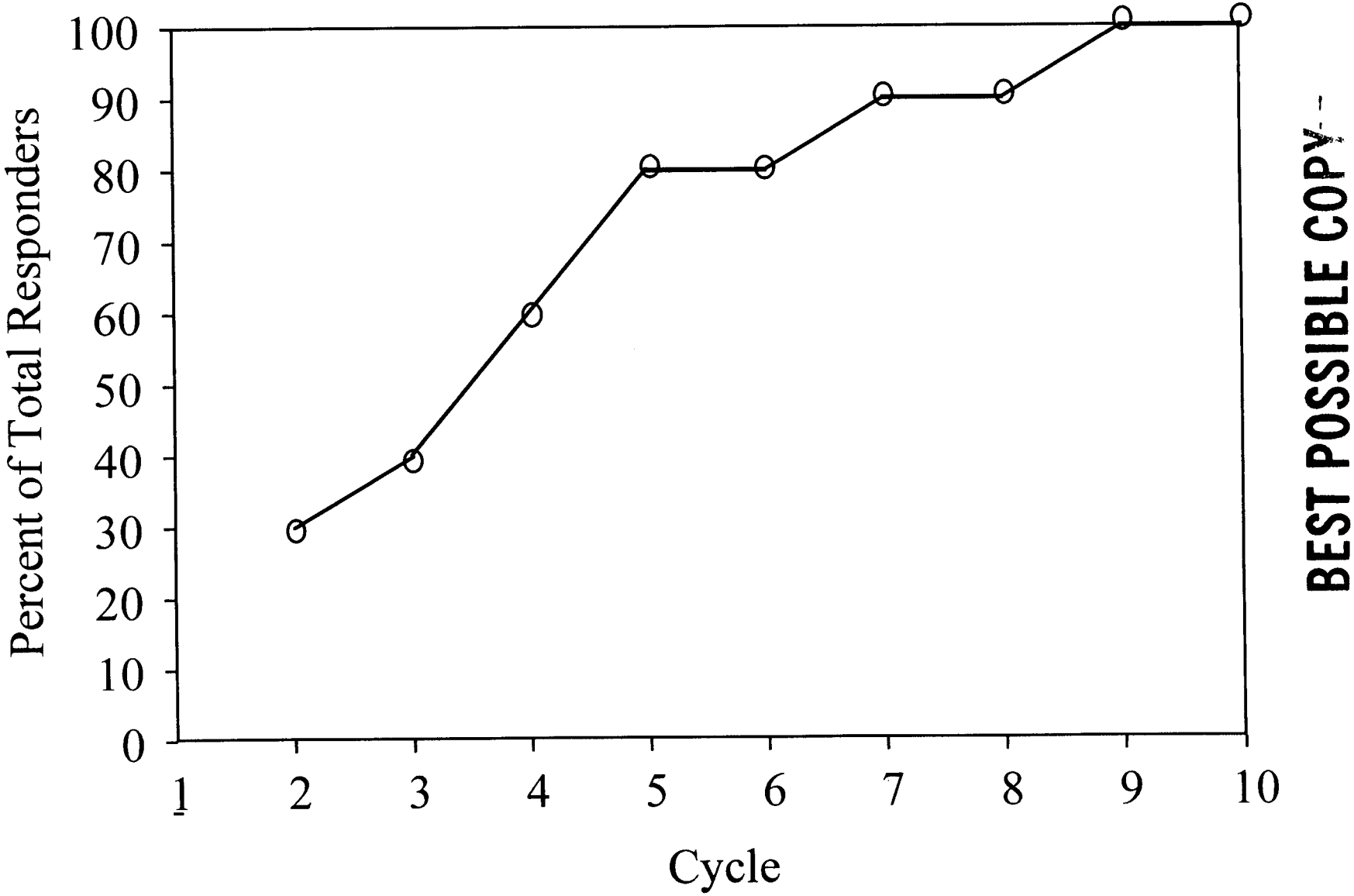
Tumor Response by Protease Inhibitor (PI) Use Subsets of Patients

Group	X/N (%)
1. No use of PI in First 10 Cycles	15/29 (51.7%)
2. Used during Study at Least 8 Cycles	10/21 (47.6%)
3. Used < 8 Cycles	21/39 (53.8%)
4. Tumor Response before use of PI	14/39 (35.9%)
5. Tumor Response after start of PI	7/39 (17.9%)
6. Total Response after start of PI (Sum 2 and 5)	17/60 (28.3%)
7. Total Response before use of PI (Sum 1 and 4)	29/68 (42.6%)

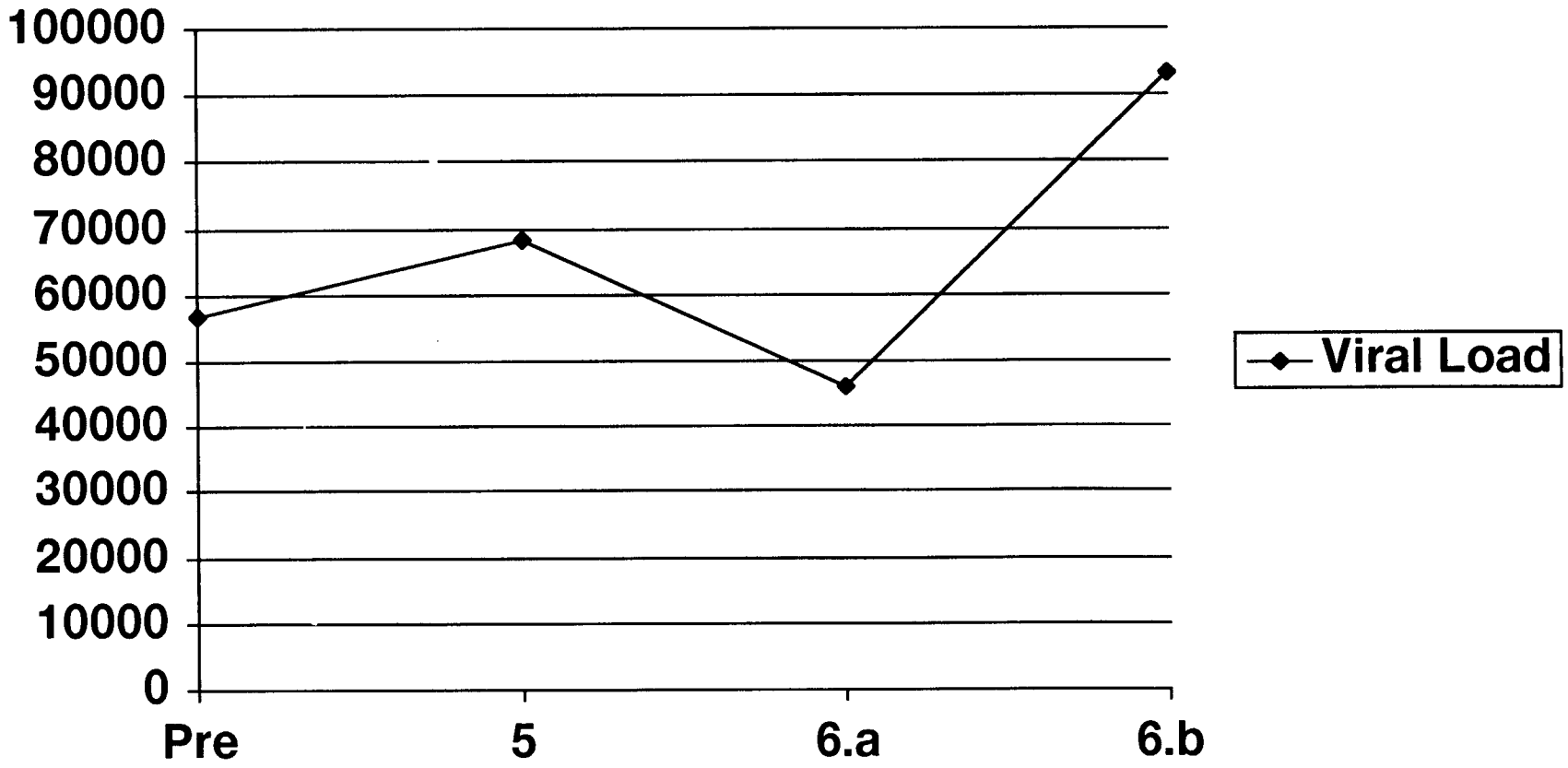
Cycle of First Response for Patients Not Using Protease Inhibitor



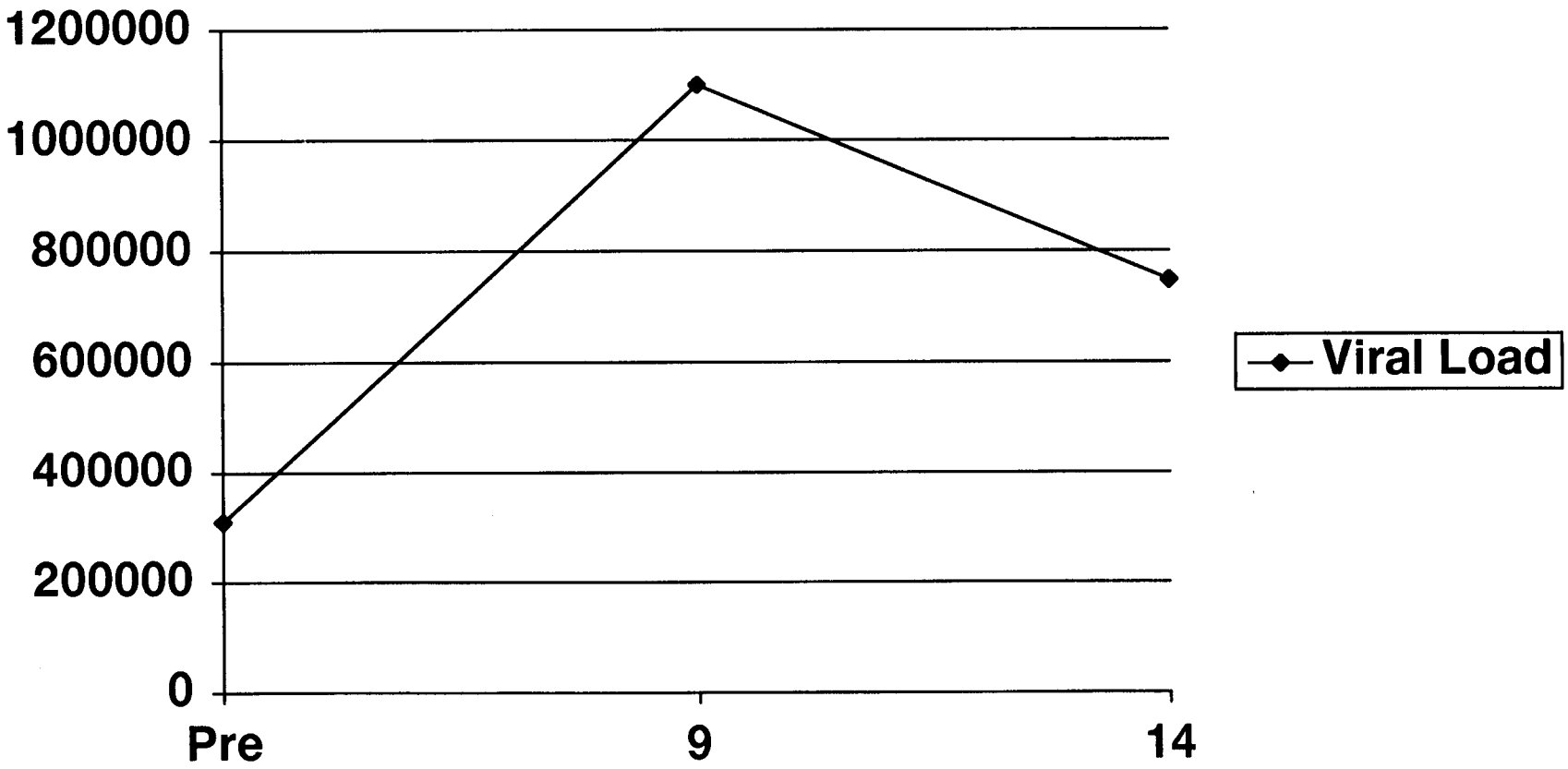
Cycle of First Response for Patients Using Protease Inhibitor



Patient # 856



Patient # 681



Patient # 683