CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: **ONCOLOGIC DRUGS ADVISORY COMMITTEE**

DATE OF MEETING: **06/24/97**

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: **ONCOLOGIC DRUGS ADVISORY COMMITTEE**

DATE OF MEETING: **06/24/97**

SLIDES

LIAZAL™ (liarozole fumarate) Tablets

Oncologic Drug Advisory Committee

June 24, 1997

Presentation Agenda

Janssen Research Foundation

- Introduction
  - Janice Bush, MD
  - Vice President Regulatory Affairs
- LIAZAL™ Efficacy and Safety
  - Alton Kremer, MD, PhD
  - Group Director Clinical Development

Memorial Sloan Kettering Cancer Center

- Value of Post-Therapy PSA Decline in Hormone-Resistant Prostate Cancer
  - Howard Scher, MD

Invited Consultants

- Robin Murray, MD
  Peter MacCallum Cancer Institute (Melbourne, Australia)
- Daniel Petrylak, MD
  Columbia Presbyterian Medical Center
- Anastasios Tsiatis, PhD
  Harvard School of Public Health
  Visiting at North Carolina State University
- Scott Zeger, PhD
  Johns Hopkins University

Hormone Resistant Prostate Cancer (HRPC)

- Few therapeutic options
- Survival is short
- Second most common cause of cancer death in men
- Significant need for novel, active agents

LIAZAL™ (liarozole fumarate)

LIAZAL™ is indicated for the treatment of advanced prostate cancer in patients who relapsed after first-line hormonal therapy.

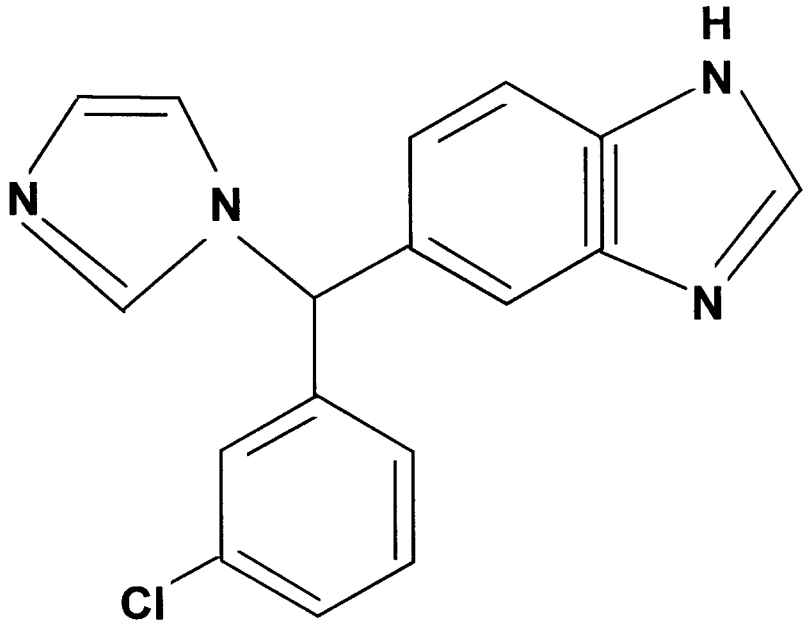
APPEARS THIS WAY
ON ORIGINAL

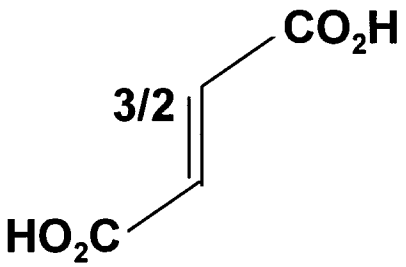
LIAZAL™ (liarozole fumarate)

- Liarozole produced longer survival in one comparator trial
- PSA response is statistically correlated to survival and can be used to guide clinical use
- Responders derive benefit that outweighs risk

Efficacy and Safety

Liarozole Fumarate





$C_{17}H_{13}ClN_4$-3/2$C_4H_4O_4$

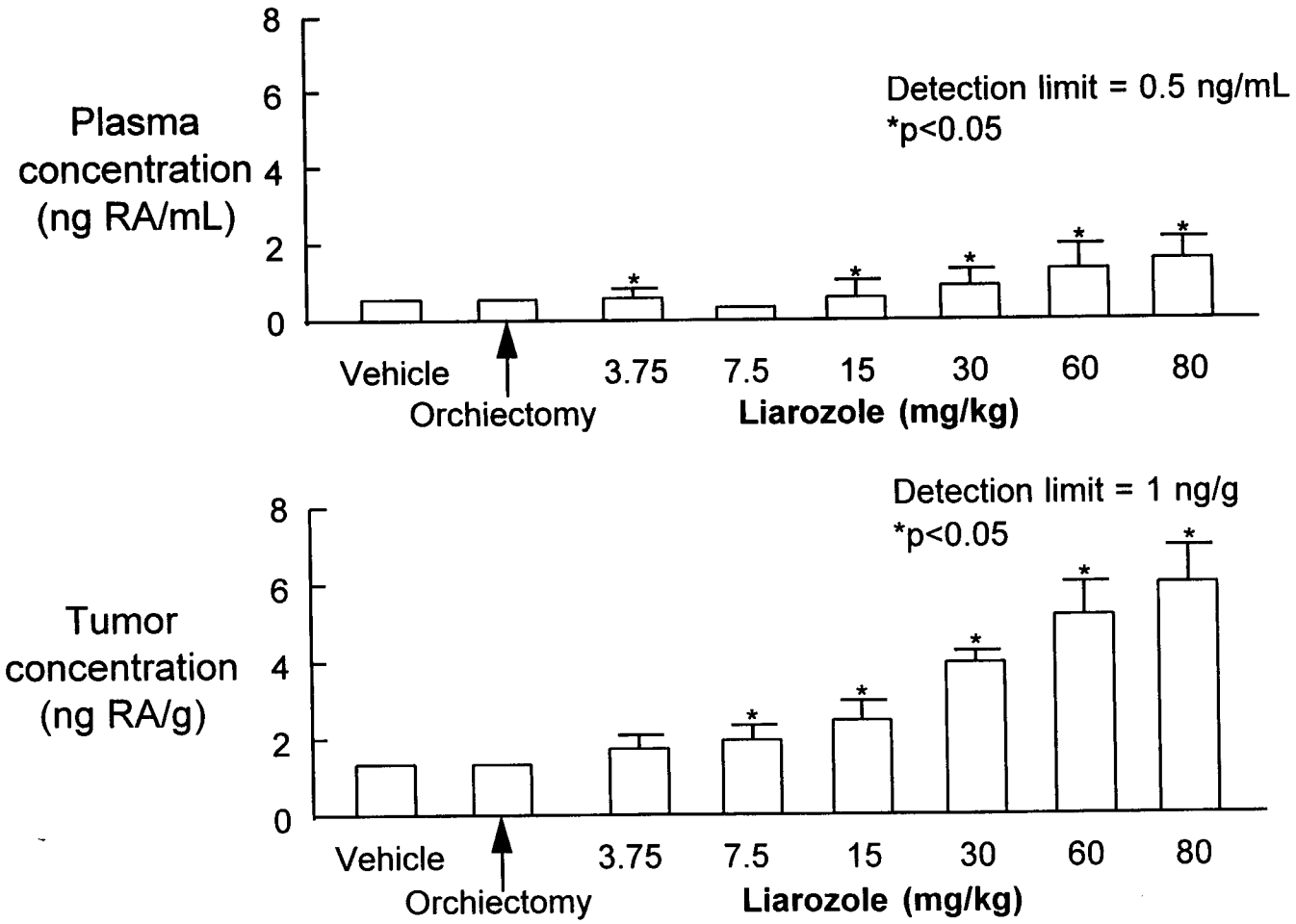
Mol wt: 482.88

Liarozole

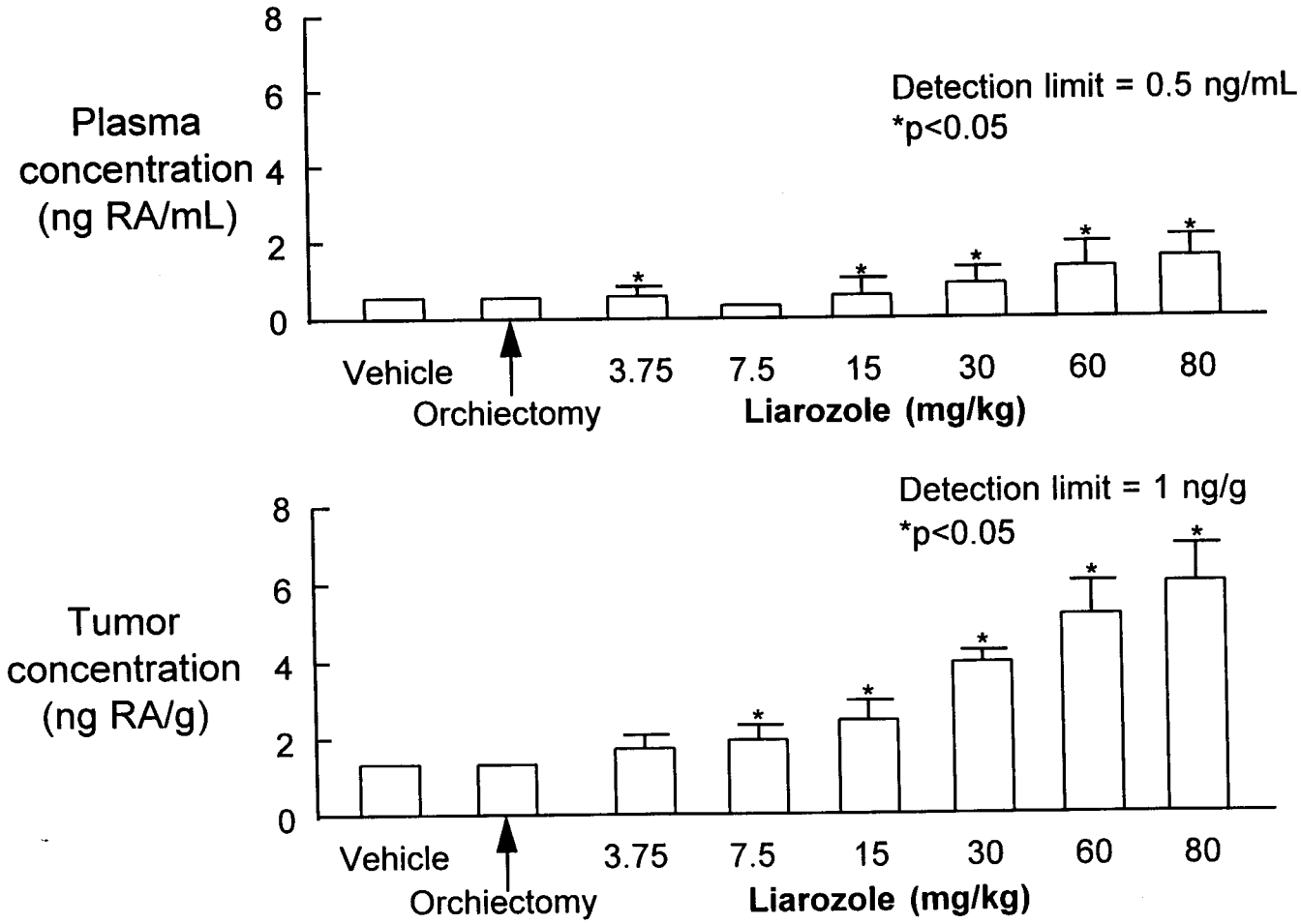
Mechanism of Action

- Novel class of differentiation agents
- Potent inhibitor of retinoic acid (RA) metabolism
- Increases intracellular levels of endogenous RA
- No induction of RA metabolism
- Demonstrates antiproliferative effect in prostate tumors and breast cancer cell lines

Liarozole Increases RA to a Greater Extent in Rat Tissues Than in Blood



Liarozole Increases RA to a Greater Extent in Rat Tissues Than in Blood



Mechanism of Action
What Liarozole Is Not

- Does not bind to androgen receptor
- Does not bind to retinoic acid receptor
- Does not block adrenal androgen production
- Does not chronically suppress testosterone
- Does not suppress PSA in LNCaP culture
- No direct cytotoxicity

Pharmacokinetics of Liarozole

- N-glucuronidation (27% to 46% of admin. dose)
- Not P-450 metabolized
- T_{max} ~ 0.5 to 2 hours postdose
- $T_{1/2\beta}$ ~ 8 hours
- No food effect
- Absolute oral bioavailability ~ 82%
- Steady state reached in 2 days

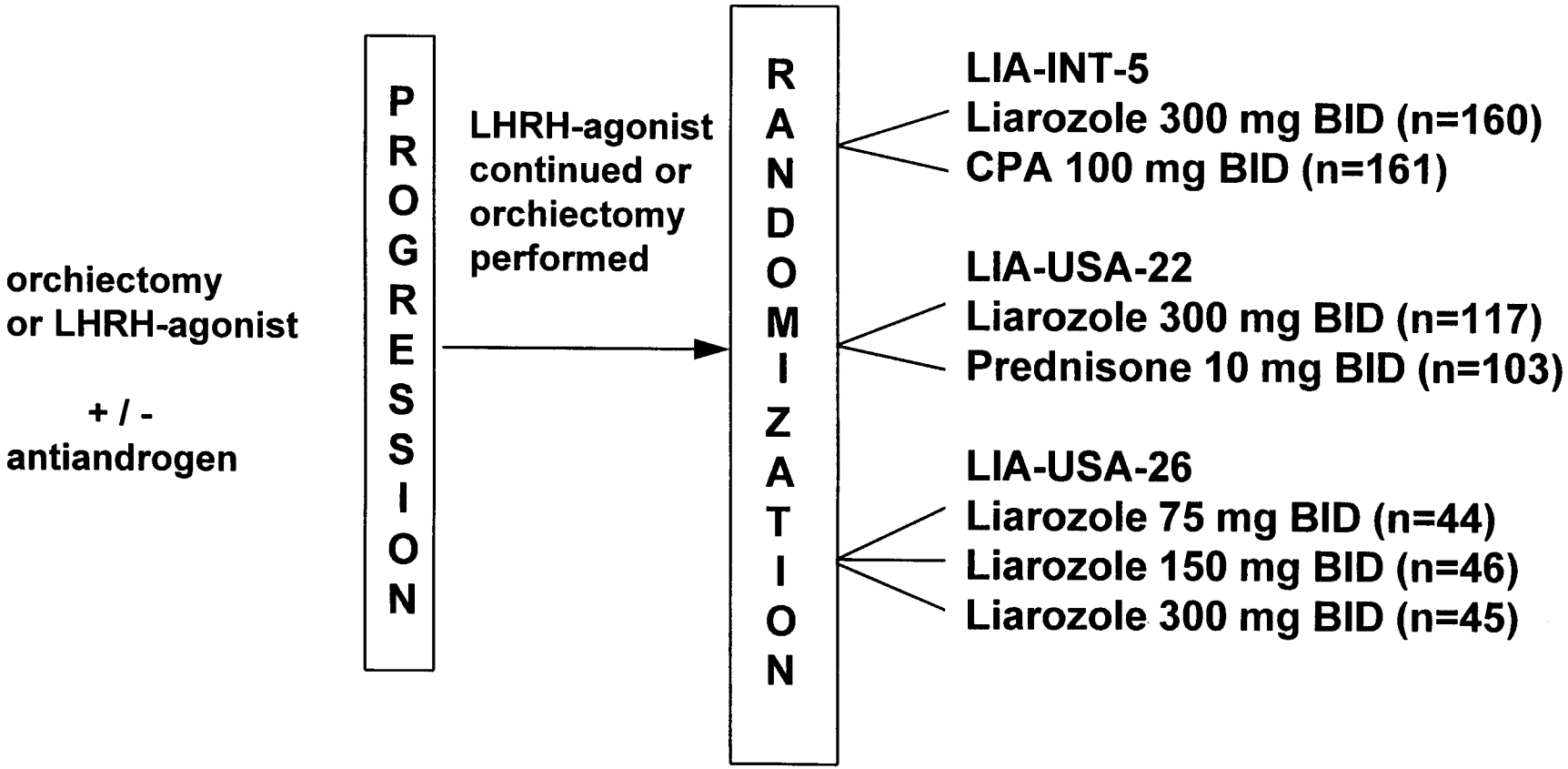
Extent of Exposure
Prostate Cancer Trials

	LIA 300 mg BID	All LIA doses
number of patients	383	575
mean exposure, days	146.8 ± 9.3	133.7 ± 6.9
total exposure, years	153.9	210.6

Liarozole in HRPC
Key Trials

Trial	Design	Number of Patients
LIA-USA-26	16-week, randomized, dose effect on PSA (75 mg, 150 mg, 300 mg BID)	135
LIA-INT-5	randomized, open-label, LIA 300 mg BID vs CPA stratified by ECOG, survival	321
LIA-USA-22	randomized, open-label, LIA 300 mg BID vs prednisone, survival	220
		Total: 676 Total Liarozole: 412

Liarozole in HRPC



LIA-USA-26
Summary

- Compared 75 mg, 150 mg, and 300 mg BID
- Dose-dependent PSA response rate
- Dose-dependent time to PSA progression
- Increase in liarozole dose correlates with a decrease in absolute PSA
- Flutamide withdrawal does not account for PSA response

Comparator Trials

Liarozole Comparator Trials
Final Amended Protocol

- Effectiveness based on:
  - Survival ($p \leq 0.05$)
  - Response rate, if linked to clinical benefit
  - Time to progression (PSA, radiologic, clinical)
    One at $p \leq 0.05$
    Second at $p \leq 0.10$
  - "Totality of the data"
- Log-rank for time to event
  - Cox regression, parameters unspecified
  - Post-hoc validation of Cox (suggested by FDA after analyses)

Response Rate
Tumor Response in HRPC

- Measurable disease is uncommon (~15% of patients)
- Bone lesions are not useful for response – osteoblastic, prolonged healing time
- Cannot determine response by bone scan
- PSA is the method used in the clinic for making treatment decisions

Response and Progression Criteria
LIA-USA-22

Original Protocol

NPCP Criteria

- Response
  - Measurable disease
  - Healing bone lesions
  - No accounting for PSA
- Progression
  - Symptoms not defined
  - No accounting for PSA
  - No accounting for differing time to progression events

Final Amended Protocol

- Response
  - Based on PSA
  - To be correlated with clinical benefit
- Progression
  - Symptoms defined as cancer related pain
  - Time to PSA, radiologic and clinical progression evaluated separately

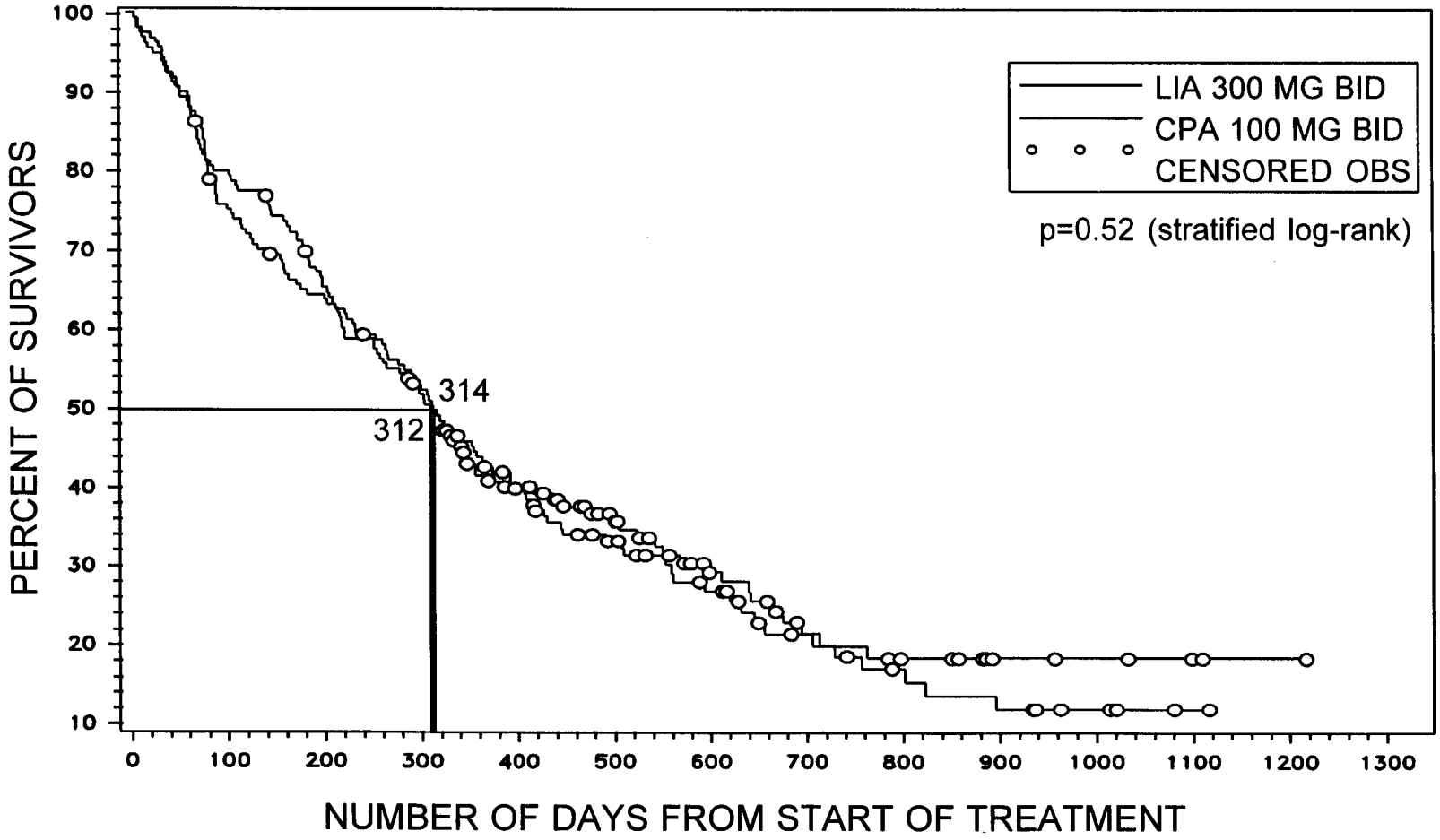
Comparator Trials
Results

- Survival – Log-rank analysis
- Baseline comparisons
- Survival – Cox regression analysis
- PSA response
- Time to progression
- QoL

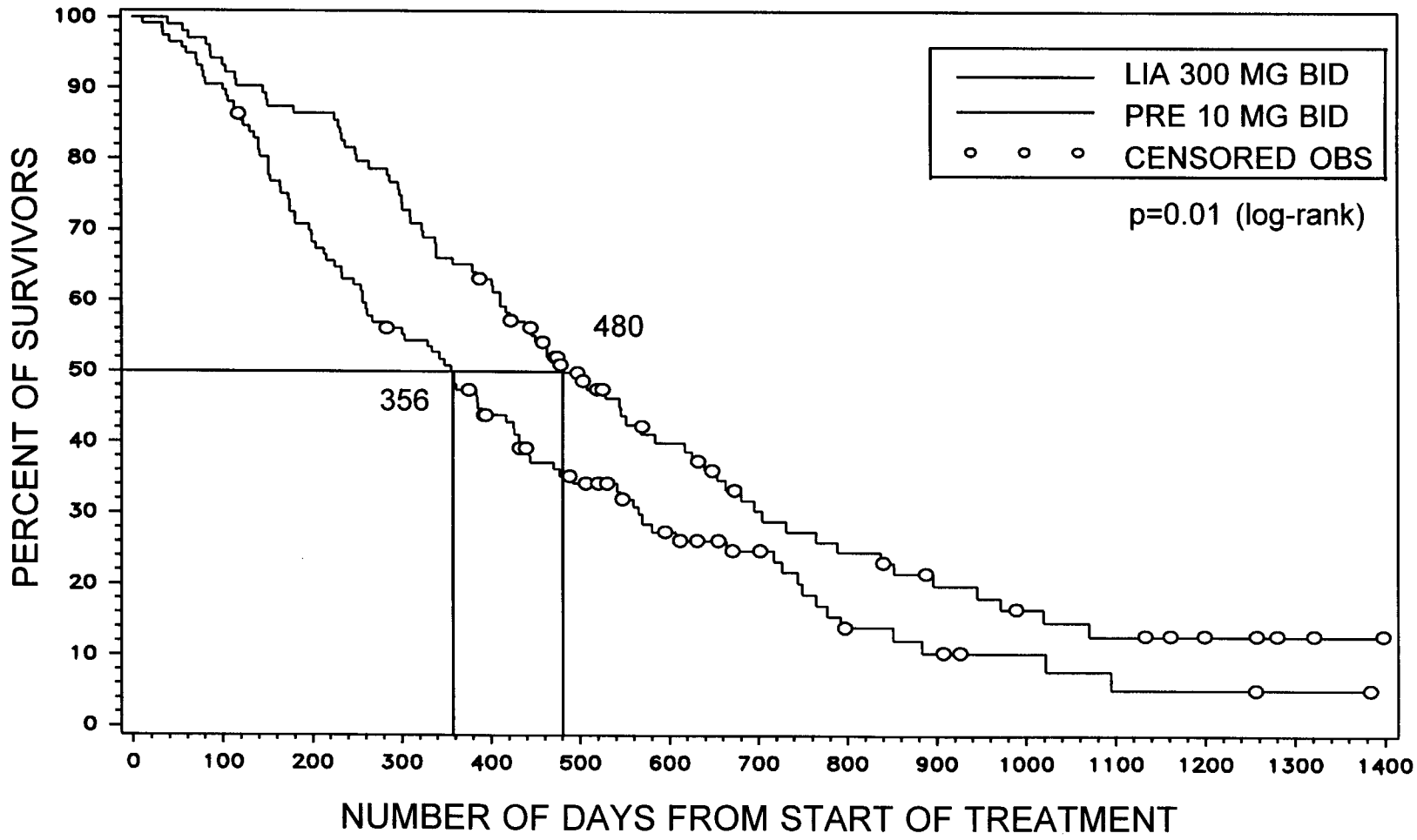
Comparator Trials
Results

- Survival – Log-rank analysis

LIA-INT-5
Survival Curves



LIA-USA-22
Survival Curves



Comparator Trials
Results

- Baseline comparisons
- Survival – Cox regression analysis

LIA-INT-5
Baseline Comparisons

Parameter		Liarozole (n=160)	CPA (n=161)	p-value
Performance score*	ECOG 0	43	36	
	1	67	78	0.09
	2	34	26	
	3	16	21	
Duration first-line response (mo)*		23.8	29.5	0.15
Hemoglobin (g/dL)*		12.1	12.3	0.17
PSA median (ng/mL)*		126	154	0.99
Alkaline phosphatase (U/L)*		460.5	445.7	0.77
Pain and Analgesic Use Score (0-4)*		2.0	1.0	0.04

* Prognostic value identified from univariate proportional hazards model.

LIA-USA-22
Significant Baseline Differences

Parameter		Liarozole (n=117)	Prednisone (n=103)	p-value
Performance score*	ECOG 0	37	46	0.008
	1	61	50	
	2	14	7	
	3	5	0	
LDH (U/L)*		264.5	204.9	0.010
Total FLIC score*		111.4	118.0	0.033
MPAC pain score		27.8	23.7	0.046

* Prognostic value identified from univariate proportional hazards model.

LIA-USA-22
Additional Baseline Comparisons

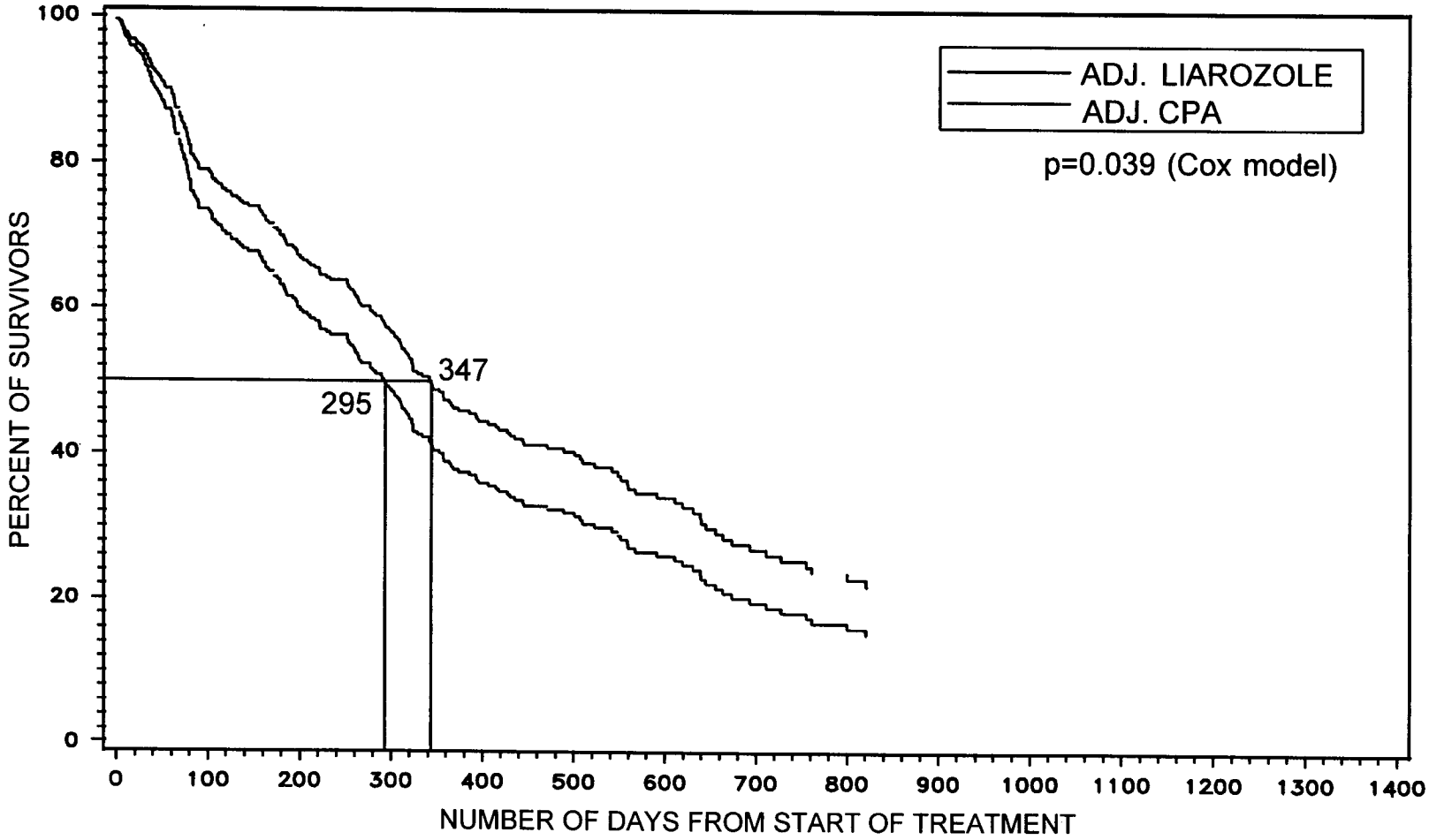
Parameter	Liarozole (n=117)	Prednisone (n=103)
PSA level, median (ng/mL)*	102.0	65.6
Duration of prostate cancer (diagnosis to study entry) (yrs)	3.8	4.3
Hemoglobin (g/dL)*	12.3	12.6
Alkaline phosphatase (U/L)*	278.7	234.0
% skeletal involvement	7.2	6.6
No. of bone lesions	69.6	59.6

* Prognostic value identified from univariate proportional hazards model.

Final Cox Model

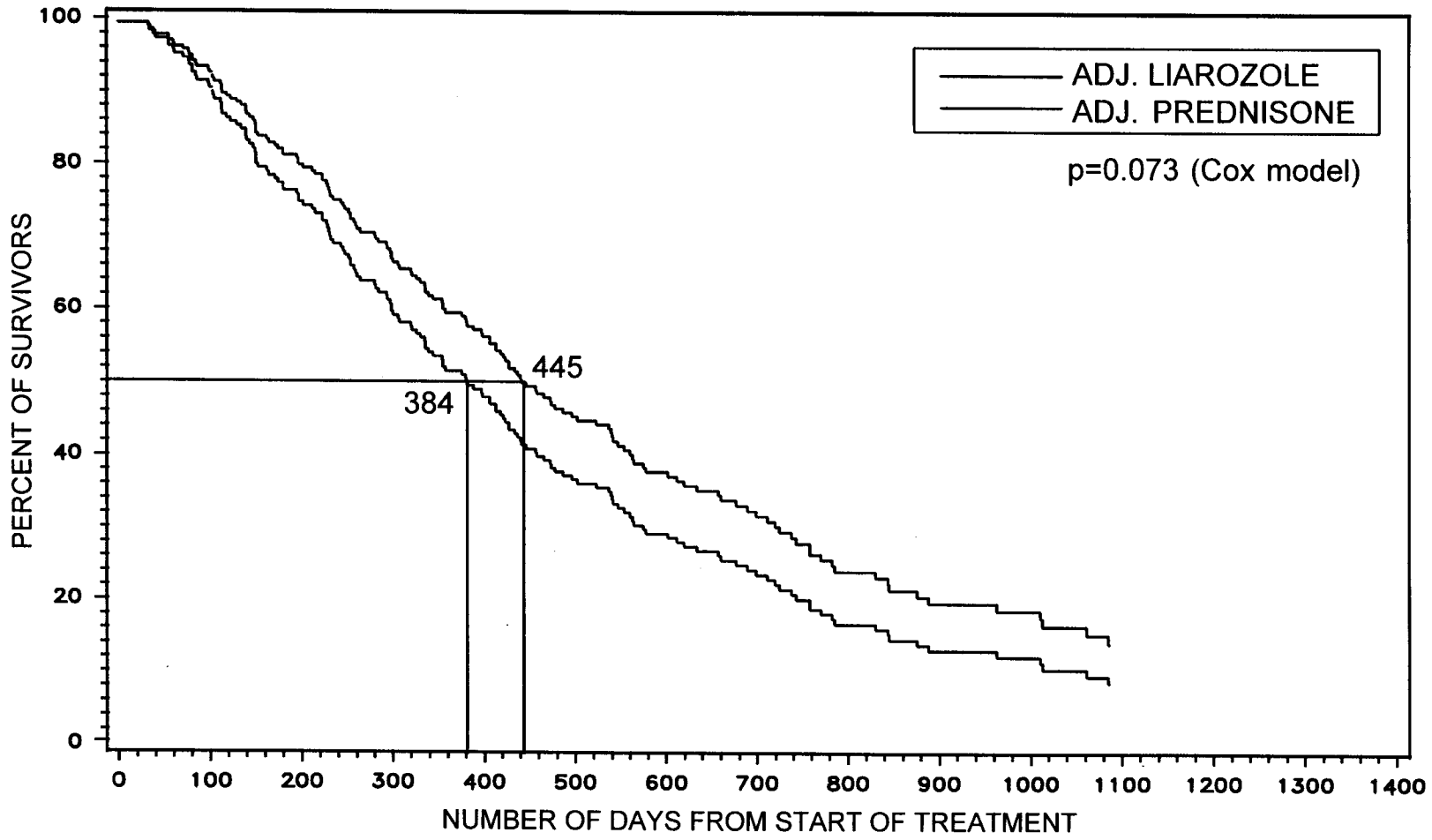
- Baseline prognostic factors:
  - ECOG performance status
  - Hemoglobin
  - Alkaline phosphatase
  - PSA
  - Duration of response to primary hormonal therapy (LIA-INT-5)
  - Time since primary hormonal therapy (LIA-USA-22)

LIA-INT-5
Survival Curves After Adjustment



LIA-USA-22

Survival Curves After Adjustment



LIA-INT-5 and LIA-USA-22

- Conclusions from the Cox model differ from the unadjusted analyses
  - Liarozole is superior to CPA
  - Differences from prednisone become statistically insignificant
- Validation of the Cox model

Validation of Cox Model

- Robust inference
- Bootstrap
- Outlier analysis

Validity of Cox Model

LIA-INT-5 and LIA-USA-22

Method	p-value LIA-INT-5 (n=290)	LIA-USA-22 (n=212)
Cox regression	*0.039*	*0.073*
Robust inference, Lin and Wei	0.046	0.080
Bootstrap‡	0.047	0.129
Collett 1_{max}		
Single patient	0.016	0.182
Multiple patients	0.011*	0.360†
Pettitt and Bin Daud		
Likelihood displacement	0.014	0.140

* 4 outliers.

† 2 outliers.

‡ Revised sampling algorithm.

Survival Analysis Summary

- Clinically important baseline differences exist
- Cox model is robust and valid
- After adjustment (Cox model)
  - Liarozole is superior to CPA
  - Differences from prednisone become statistically insignificant

PSA Effect

- Response
  - Correlation with survival

PSA and Outcome in HRPC

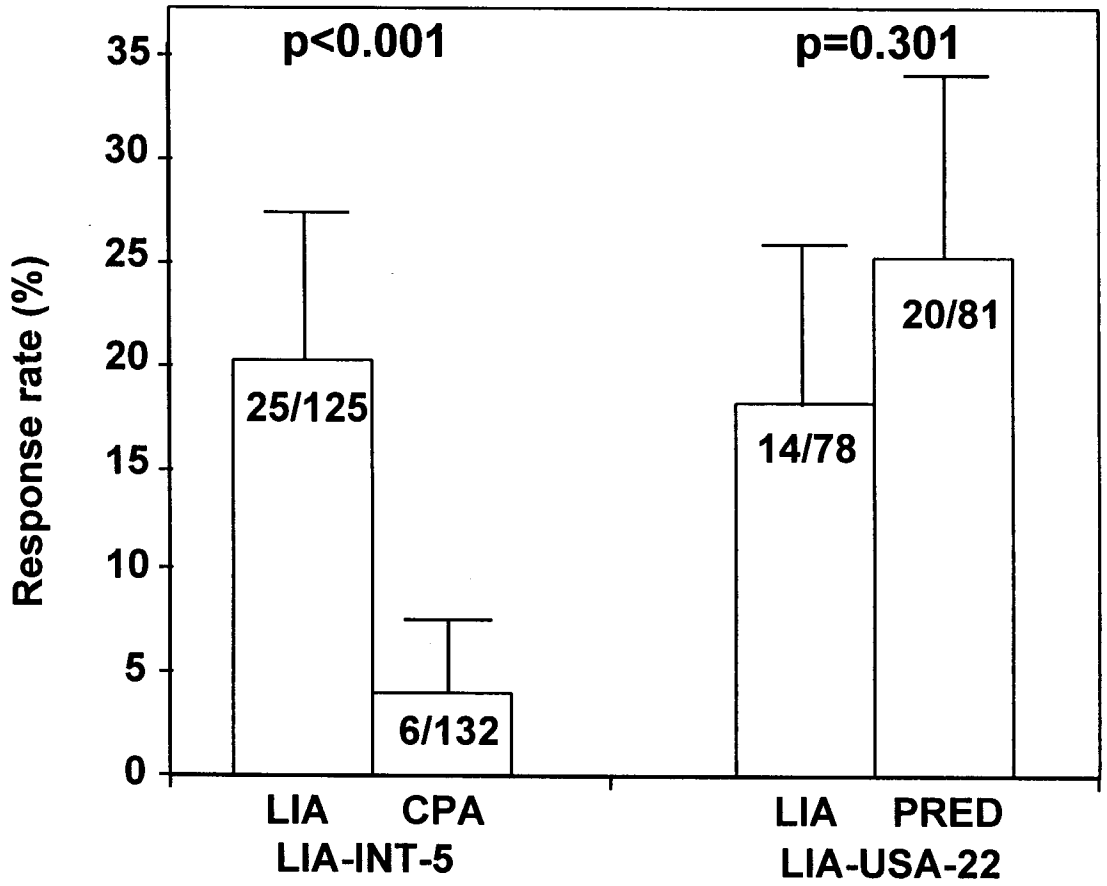
Source	Therapy	n	Outcome
Scher, 1990	Trimetrexate	31	≥ 50% increase in PSA linked to progression in measurable disease
Myers, 1992	Suramin	38	≥75% PSA decline at 8 weeks linked to survival
Kelly, 1993	Multiple Therapies	110	≥50% PSA decline at 60 days linked to survival
Sella, 1994	Ketoconazole/ Doxorubicin	39	CR/PR of measurable disease linked to 50% decline in PSA
Pienta, 1994	Estramustine/ etoposide	42	PSA decline ≥ 50% linked to survival
Sridhara, 1995	Suramin	103	PSA decline linked to survival
Sabbatini, 1996	Suramin	30	changes in PSA linked to bone scan
Small, 1996	Cyclophosphamide/ Doxorubicin	35	≥50% decline in PSA linked to survival
Iversen, 1997	Estramustine	131	≥50% decline in PSA linked to survival

PSA Response*

- CR: ≤4 ng/mL on 2 determinations ≥28 days apart
- PR: ≥50% decrease from baseline on 2 determinations ≥28 days apart
- PD: >50% increase over lowest prior moving average
- NC: Not CR, PR, PD

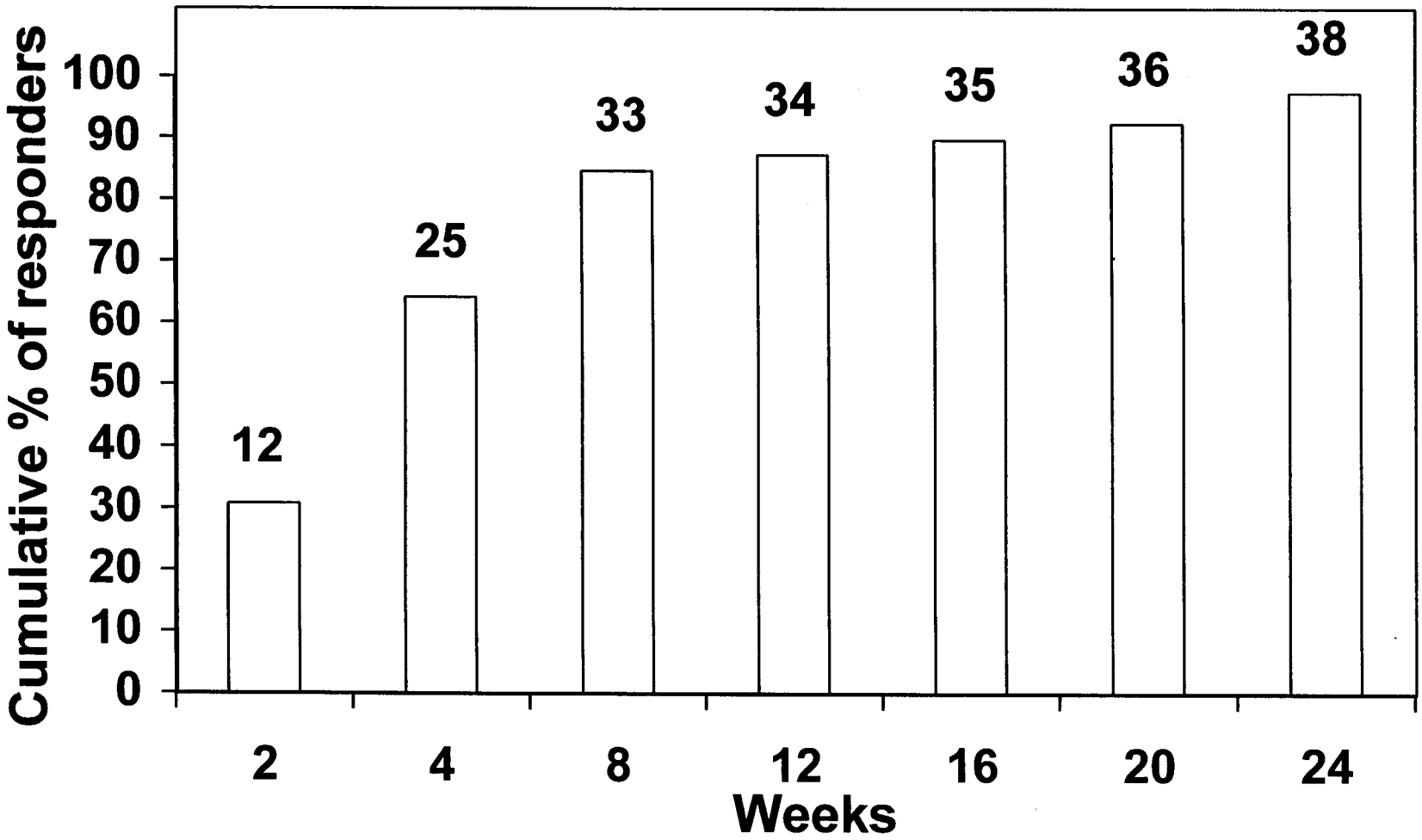
* Evaluable patients must have baseline PSA ≥20 ng/mL.

PSA Response Rate

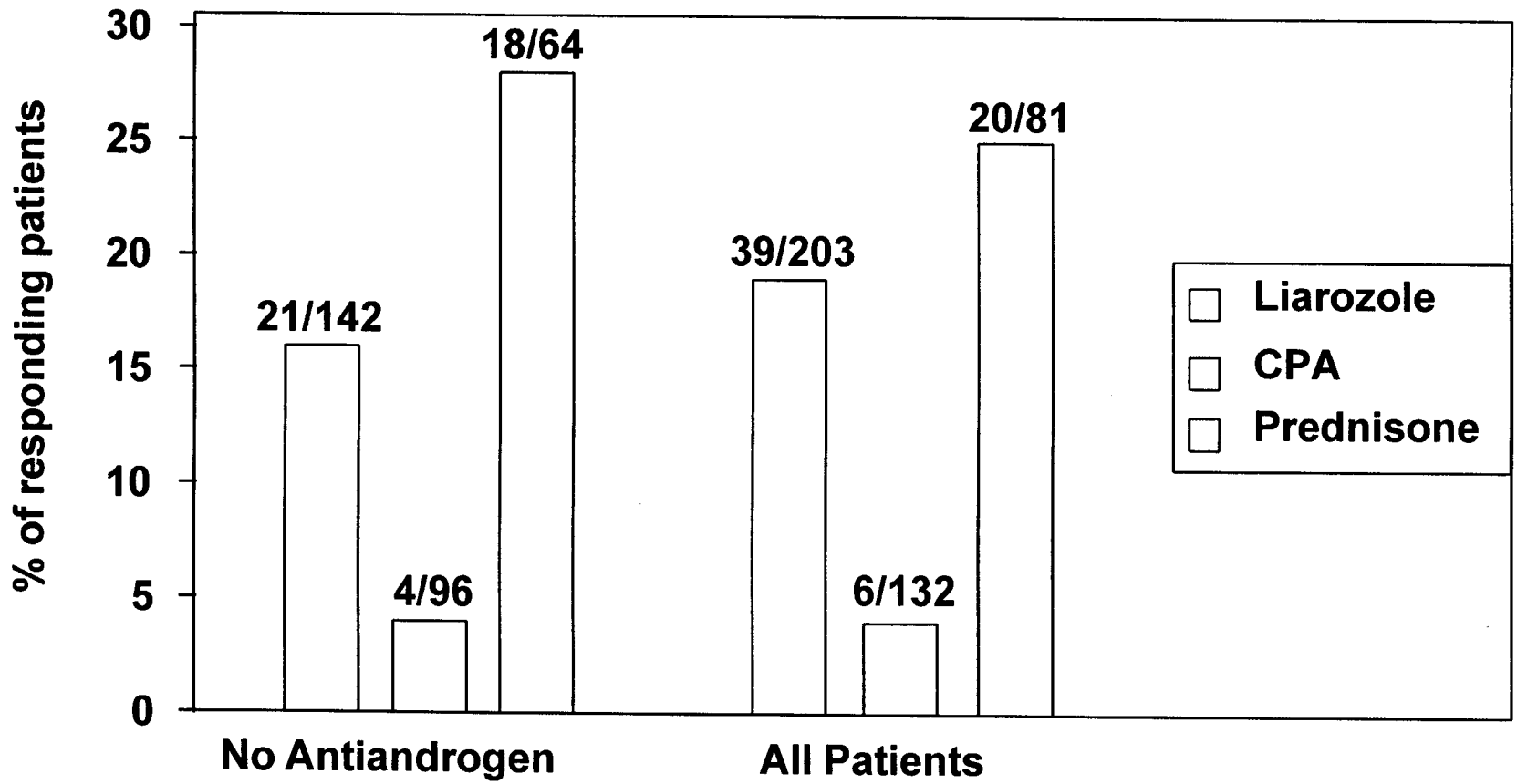


Distribution of Liarozole PSA Responders Over Time

LIA-INT-5 and LIA-USA-22



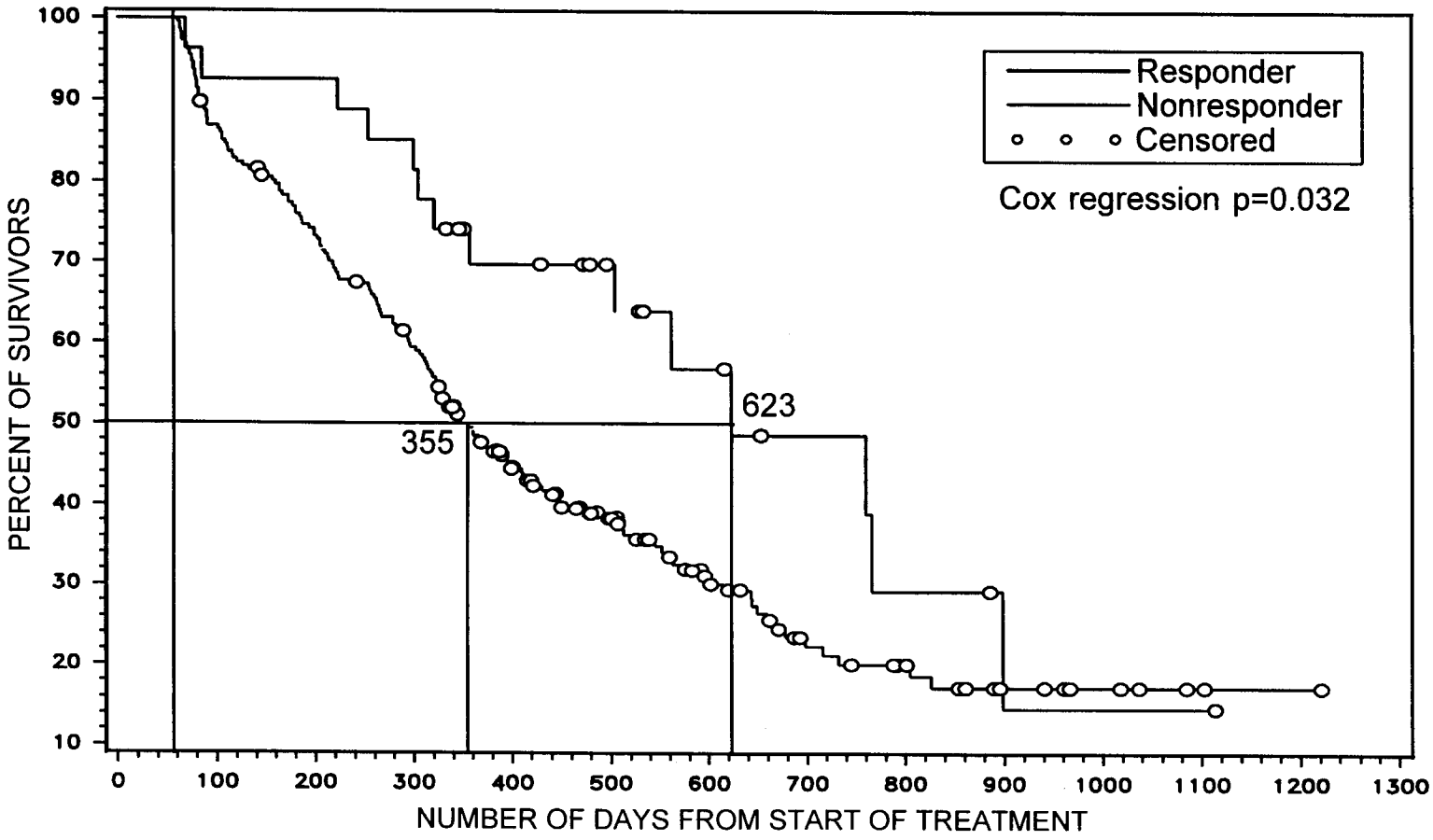
PSA Response Rates
Effect of Prior Antiandrogen Use
LIA-INT-5 and LIA-USA-22



LIA-INT-5

Survival by PSA Response

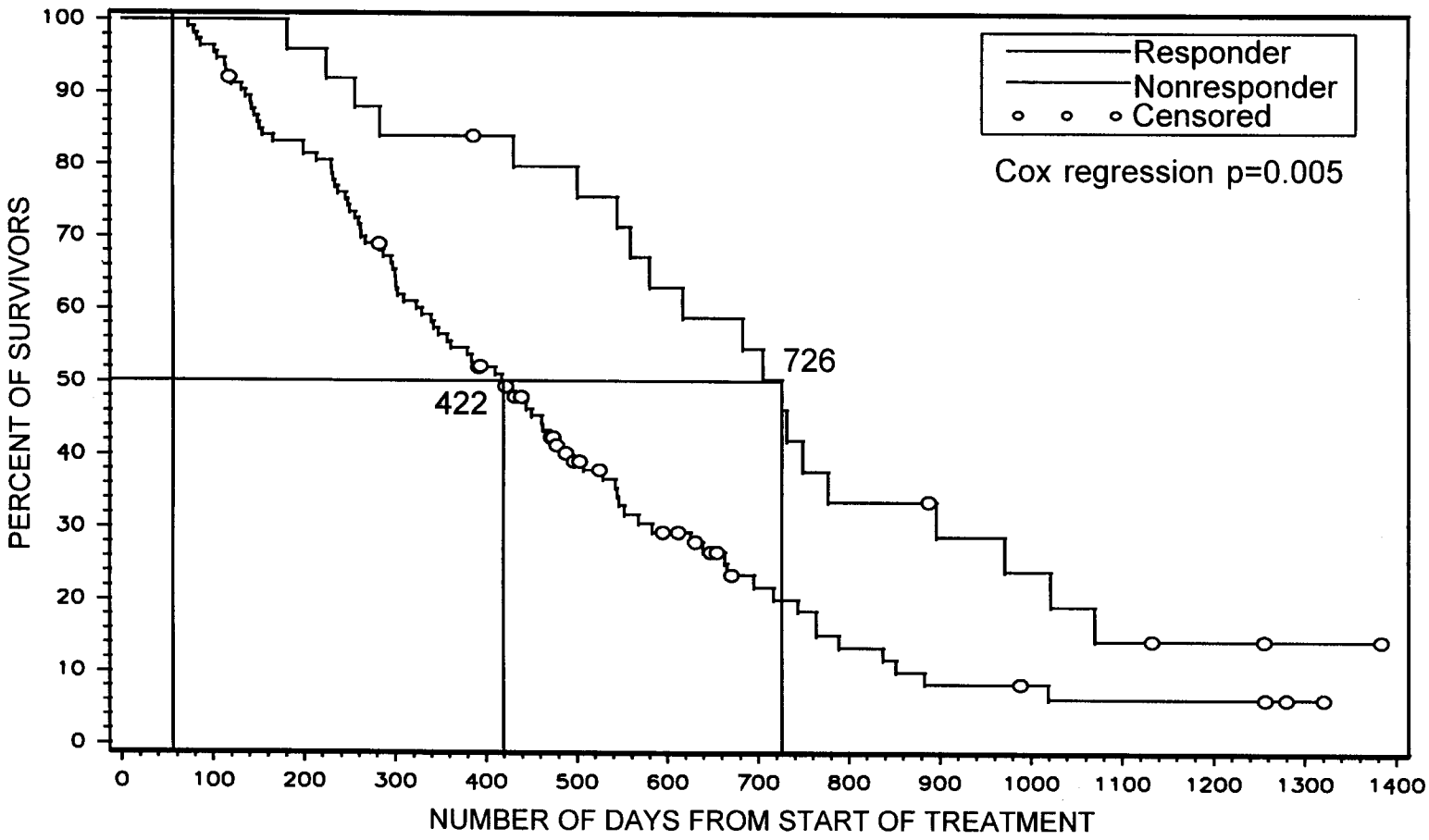
Landmark Analysis: Week 8



LIA-USA-22

Survival by PSA Response

Landmark Analysis: Week 8



Time-Dependent Covariate Analysis
Association Between PSA Response and Survival

All Treatment Groups

	Deaths/total patients	Hazards ratio 95% CI	p-value
LIA-INT-5	184/265	0.430 (0.253, 0.730)	0.002
LIA-USA-22	127/159	0.442 (0.281, 0.697)	<0.001

Correlation of PSA Response and Survival

- There is a strong statistically significant correlation between PSA response and survival
- This correlation cannot be attributed to baseline prognostic factors
- Not sensitive to landmark

Time to Progression (TTP)

Time to Progression (Months)

Study	Event	LIA	CPA	PRED	p-value
LIA-INT-5	PSA	4.6	3.6	–	0.019
	Radiology	–	–	–	–
	Clinical	4.9	4.6	–	0.630
LIA-USA-22	PSA	3.5	–	4.7	0.180
	Radiology	6.0	–	6.9	0.830
	Clinical	5.0	–	9.7	0.013

Comparison of Bone Scan Data Between Treatments
LIA-USA-22

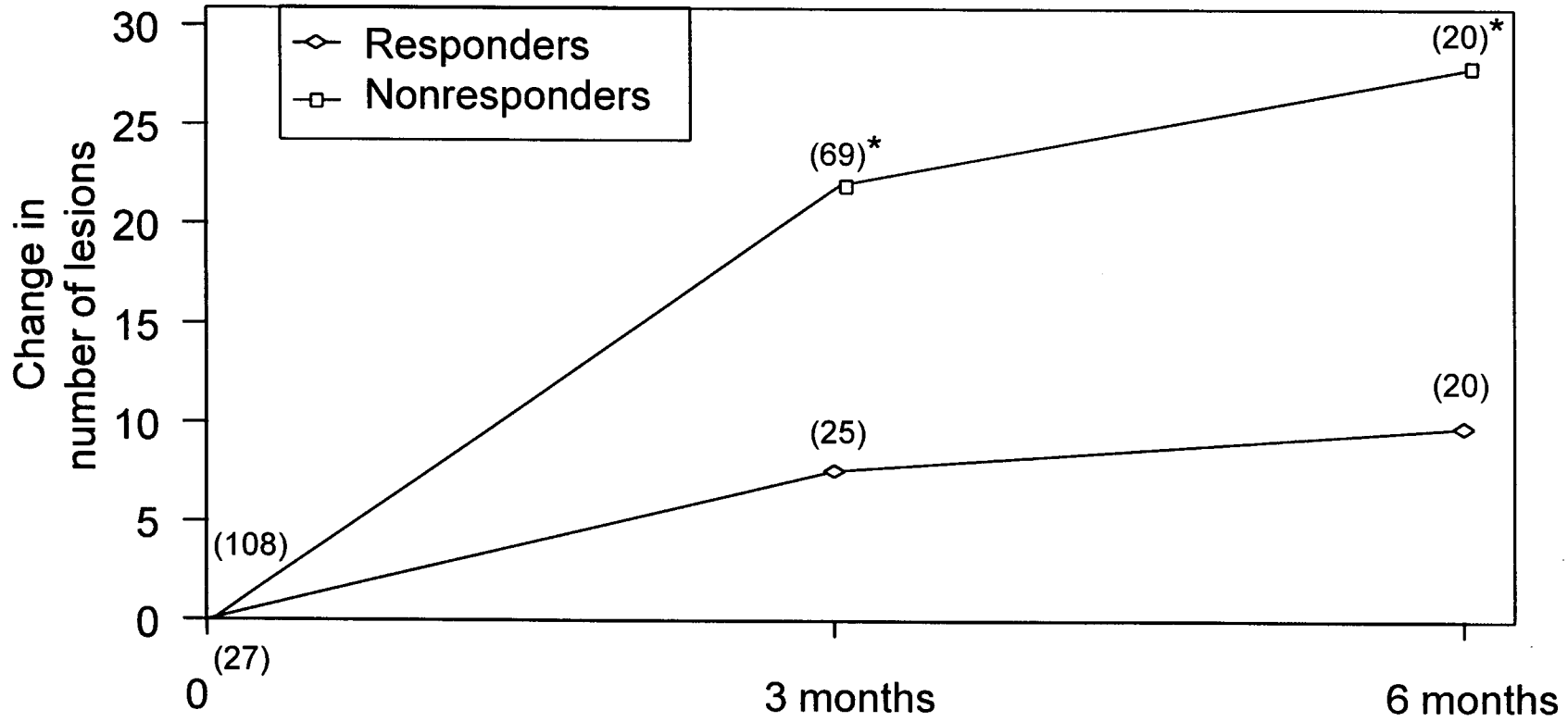
Summary of change from baseline in percentage of skeletal involvement

	Liarozole		Prednisone		
Visit	Mean	(n)	Mean	(n)	p-value
Baseline	7.2	(104)	6.6	(89)	0.908
Week 12	+2.6	(53)	+1.9	(67)	0.246
Month 6	+3.2	(21)	+2.3	(25)	-

Summary of change from baseline in number of bone scan lesions

	Liarozole		Prednisone		
Visit	Mean	(n)	Mean	(n)	p-value
Baseline	69.6	(104)	59.6	(89)	0.766
Week 12	+18.0	(53)	+13.2	(67)	0.548
Month 6	+23.1	(21)	+14.2	(25)	-

Bone Scan Changes by PSA Response (Liarozole and Prednisone)
LIA-USA-22



* Number is significant from baseline.

Time to Progression Summary

- For LIA-INT-5 and LIA-USA-22
  - 1 TTP was significant ($p < 0.05$)
  - No second event showed a trend ($p \leq 0.10$)
- No treatment arm was superior in time to progression
- Cox regression and competing risk analyses were consistent with this result

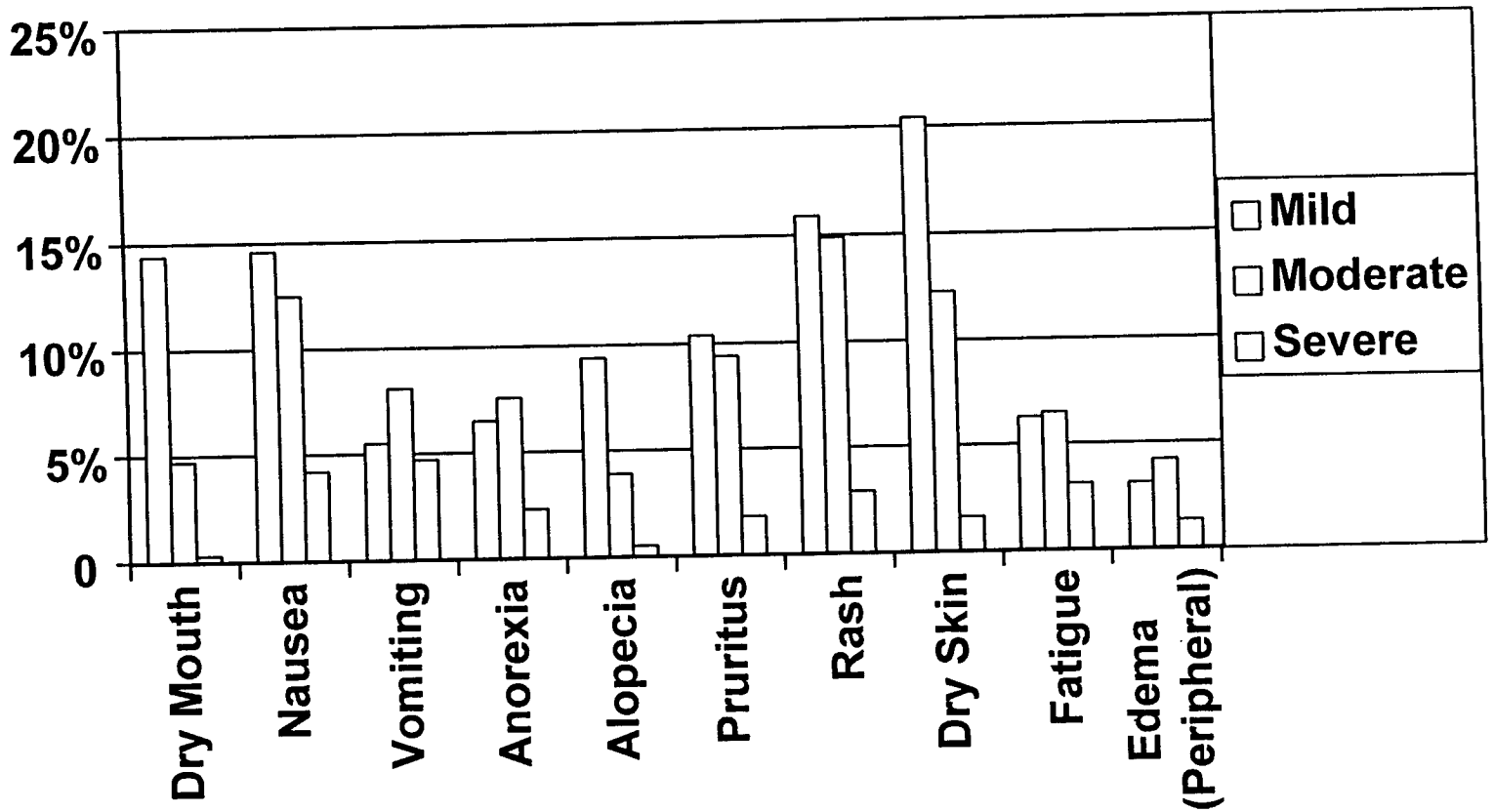
Quality of Life

Quality of Life

- Liarozole showed a significantly better pain profile than CPA
- Liarozole group began and ended with significantly worse QoL than the prednisone group
- PSA responders began and ended with significantly better QoL than PSA nonresponders

Safety

Most Frequent AEs
Prostate Cancer Trials – LIA 300 mg BID (n=383)



AE Discontinuations*

Prostate Cancer Trials

Drug	Dose	n	# of AE D/Cs (%)
LIA	300 mg BID	383	114 (30%)
PRED	10 mg BID	103	20 (19%)
CPA	100 mg BID	161	26 (16%)

* Excludes disease progression.

Incidence of AEs for Patients Who D/C Due to AEs

Prostate Cancer

WHO system/ Organ class	LIA 300 mg BID (n=383)	PRED 10 mg BID (n=103)	CPA 100 mg BID (n=161)
Skin and appendages	37 (10%)	0	0
Gastrointestinal	35 (9%)	4 (4%)	3 (2%)
Body as a whole	32 (8%)	5 (5%)	7 (4%)
Psychiatric disorder	23 (6%)	0	3 (2%)
Metabolic and nutritional	16 (4%)	7 (7%)	1 (1%)
Central & Peripheral nervous	12 (3%)	2 (2%)	1 (1%)
Respiratory	8 (2%)	3 (3%)	6 (4%)
Cardiovascular disorder	7 (2%)	3 (3%)	1 (1%)
Rhythm disorder	3 (1%)	0	2 (1%)
Vascular disorder	5 (1%)	0	4 (3%)
Urinary	7 (2%)	0	1 (1%)
Neoplasm	3 (1%)	2 (2%)	2 (1%)

Fluid and Electrolyte Balance

Prostate Cancer Trials

Diagnosis	LIA n=383	CPA n=161	PRED n=103
Edema, Dependent	32 (8%)	11 (7%)	10 (10%)
Edema, Peripheral	36 (9%)	8 (5%)	18 (18%)
Dyspnea	32 (8%)	23 (14%)	13 (13%)
Pleural Effusion	7 (2%)	0 (0%)	1(1%)
CHF*	28 (7%)	4 (3%)	3 (3%)
Hypokalemia	27 (7%)	1 (1%)	1 (1%)

* CHF significantly associated with anemia and ECOG PS.

Adverse Event Summary

- Most frequently occurring adverse events (GI/Skin) are consistent with mechanism of action
- These are mild to moderate in severity and manageable
- Excess discontinuations are mainly attributable to GI/Skin adverse events
- Safety profile is acceptable in relapsed cancer patients with monitoring for CHF

Efficacy Conclusions

- Liarozole produces longer survival, when baseline imbalance is accounted for than the comparator in one trial (vs CPA)
- PSA response is statistically correlated to survival and can be used to guide clinical use

Liarozole in HRPC
Risk/Benefit

- PSA responding patients obtain a significant benefit
  - Increased survival, 9 - 10 months
  - Slower progression of bone disease
  - Improved quality of life
- PSA monitoring detects patients who will benefit
- Most adverse events are acceptable and manageable

Liarozole in HRPC
Risk/Benefit

- Treatment options are limited in HRPC and survival is short
- Liarozole offers a new oral therapeutic option
- Responding patients derive benefit (survival) that outweighs risk

Value of Post-Therapy PSA Decline in Hormone-Resistant Prostate Cancer

Howard Scher, MD

Memorial Sloan Kettering Cancer Center

62

Rationale For Alternative Endpoints in Androgen-Independent Prostate Cancer

1. Measurable disease infrequent.
2. Soft-tissue response does not parallel bone.
3. Changes in bone lesions difficult to quantify in a reproducible way.
4. Prostate-specific antigen changes reflect total tumor burden.

Post-Therapy Change in PSA as an Endpoint

1. Rising PSA values antedate clinical or radiographic progression.

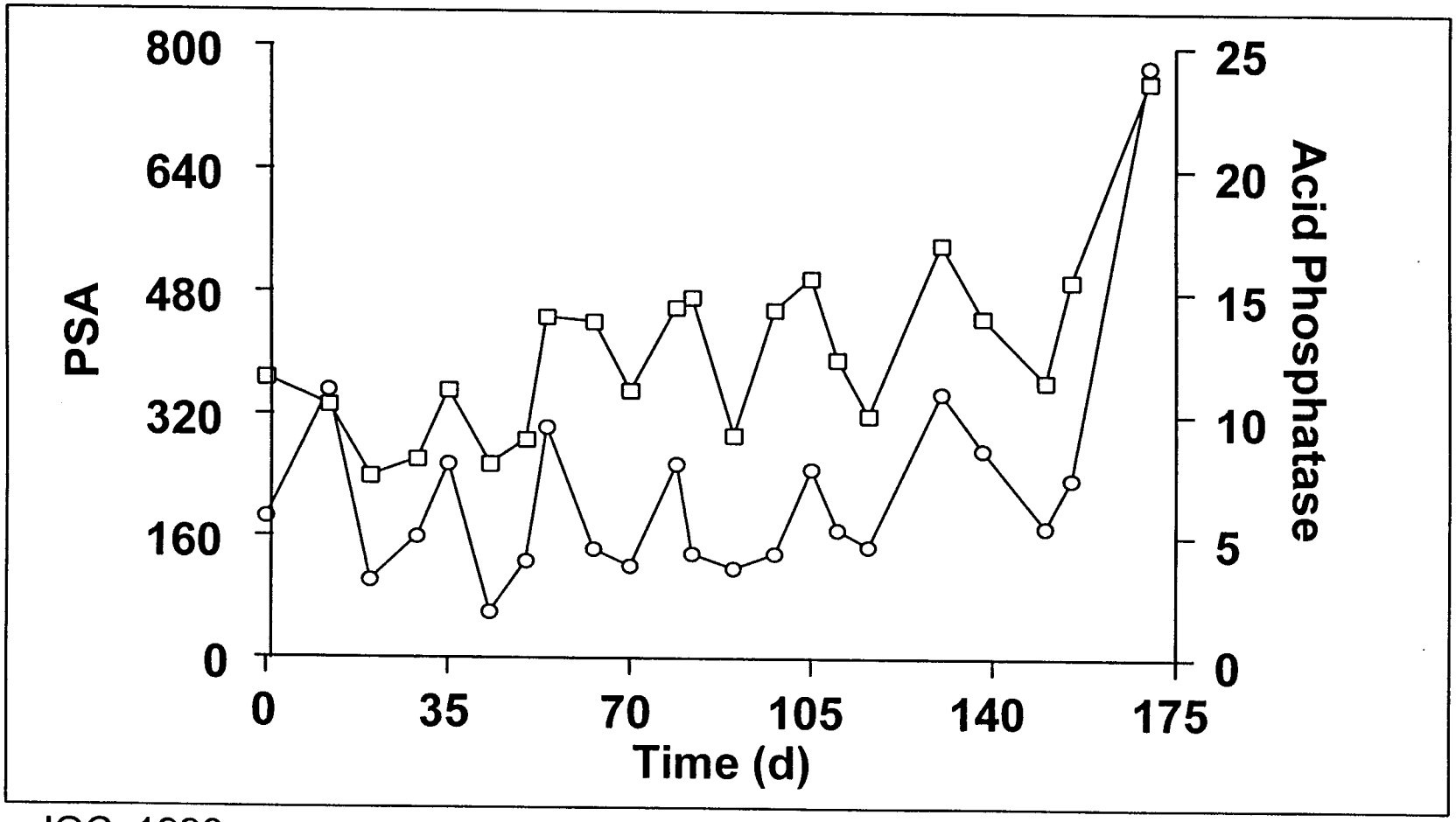
EORTC	30853
SWOG	INT-1

2. Easy to measure on a serial basis.
3. Allows rapid screening of new therapies.

Pitfalls in Use of Post-Therapy PSA Declines as a Clinical Trial Endpoint

1. Not all cells express PSA.
2. PSA subject to hormonal regulation.
3. PSA effects independent of cell kill.
4. Validity may vary as function of agent.

PSA in a Patient Treated with Trimetrexate



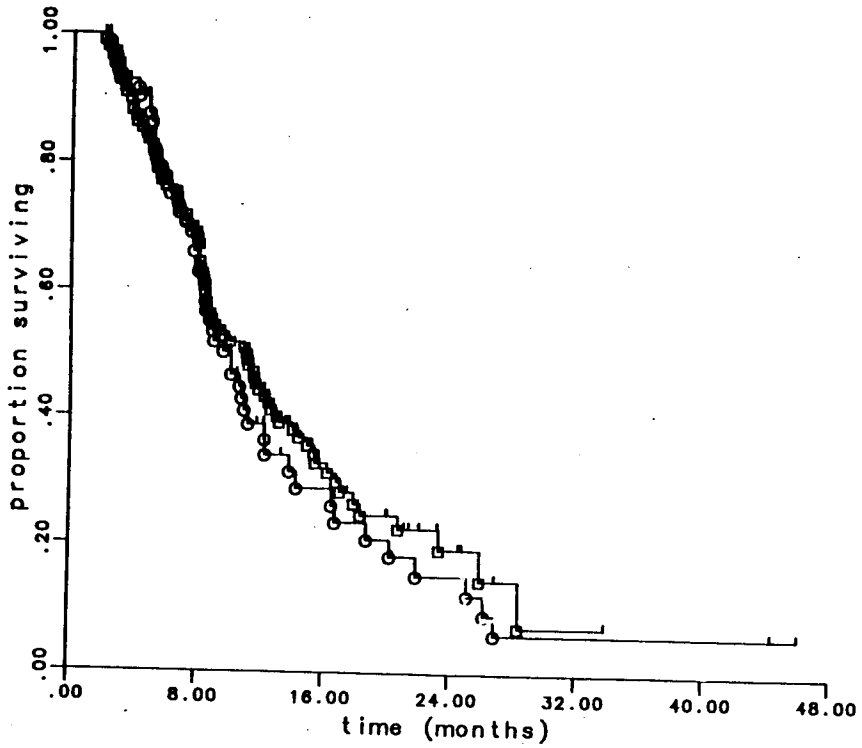
JOC, 1990

Post-Therapy Decline in PSA:
Multiple Therapies

1. MSKCC: 110 patients
   Multiple therapies
2. Methods: Life table analysis
   Proportional hazards
   Landmark Method
   (Anderson et al. 1983)
3. Validation with independent data set of patients from Norway.
4. Post-therapy decline of >50% was the most significant factor associated with survival.

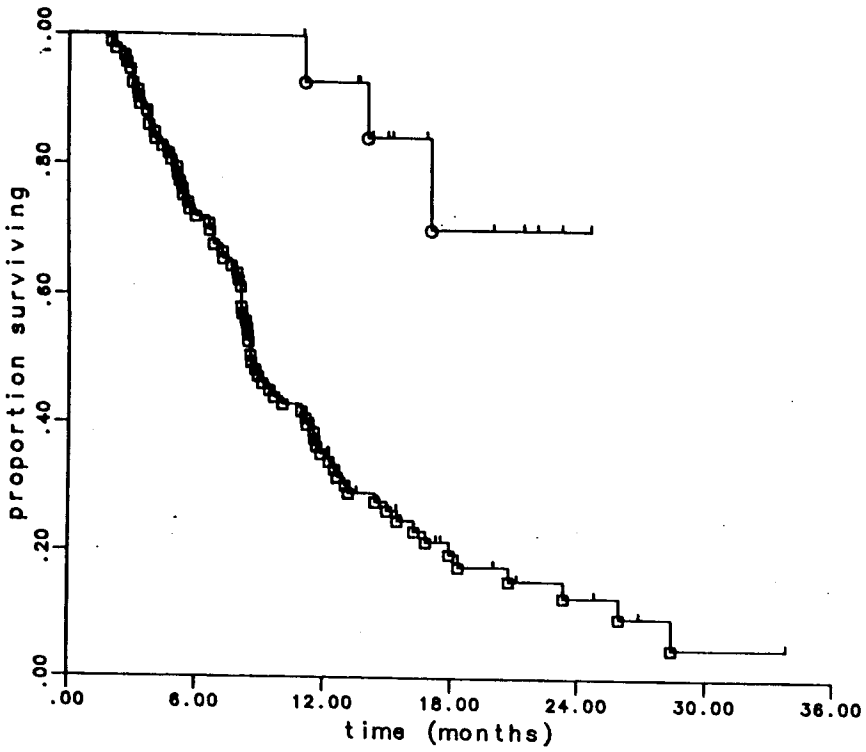
MSKCC, 1993

Comparative Survival of MSKCC and Norwegian Cohorts



JCO, 1993

Post-Therapy PSA Decline (>50%) and Survival



MSKCC, 1993

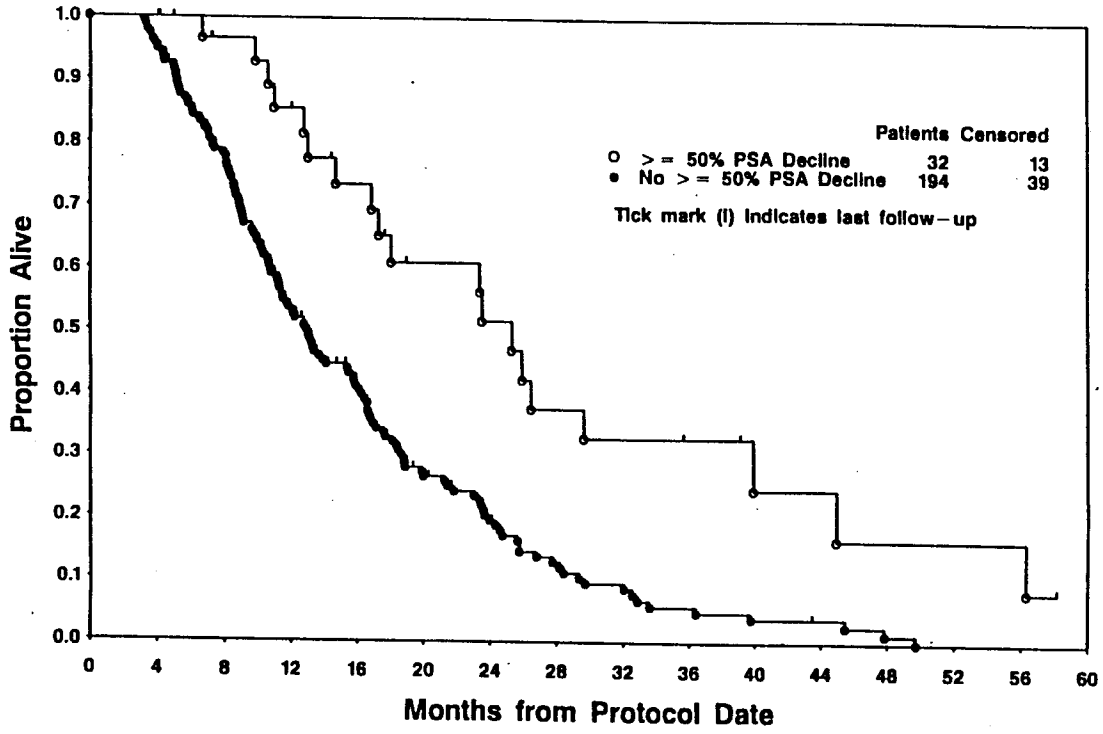
Refining Use of Post-Therapy PSA Declines

1. MSKCC Cohort: (254 patients)
   - Association between baseline variables and survival
   - PSA declines: 2 vs. 3 values
     - Monthly intervals
     - 60 or 90 day landmark
   - Multivariate prognostic model
2. Validation: (541 patients)
   - INT-5 Liarozole vs. cyproterone acetate
   - USA-22 Liarozole vs. prednisone

Demographics

	MSKCC	Combined Janssen Datasets
No. of patients	254	541
No. of deaths (%)	200 (79%)	403 (77%)
Survival		
Median in months	12.9	11.4
> 60 days	234 (92%)	428 (79%)
> 90 days	226 (89%)	409 (76%)
PSA decline >50% from baseline		
60 days	36 (11%)	58 (12%)
90 days	32 (14%)	64 (26%)

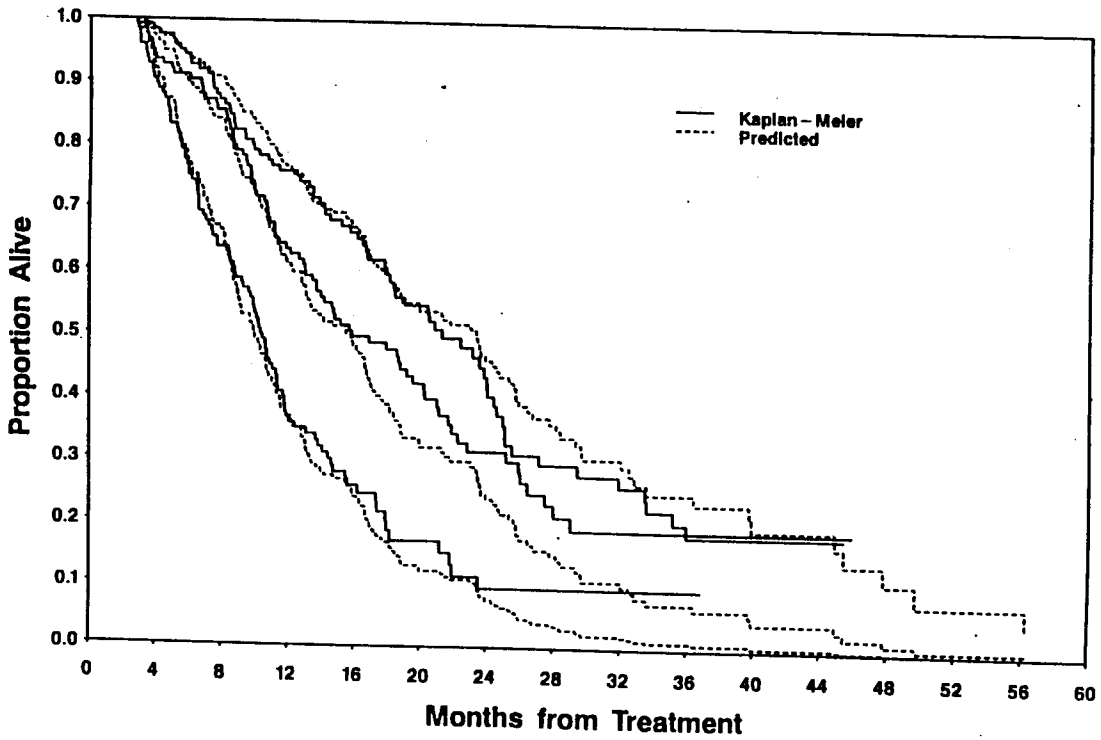
Survival
MSKCC Cohort



Observed and Predicted Survival in the Independent Data Set

		Survival Rate (%)		
		1-year	2-year	3-year
Low risk	Obs	0.76	0.44	0.18
	Exp	0.77	0.46	0.25
Intermediate risk	Obs	0.64	0.32	0.19
	Exp	0.62	0.24	0.07
High risk	Obs	0.37	0.10	0.10
	Exp	0.37	0.08	0.01

Predicted Against Observed Survival by Risk Group



Prentice Conditions for Surrogacy

1. The surrogate marker is affected by treatment.

Treatment and PSA decline

Relationship	Parameter	Relative Risk	95% CI	p-value
Prednisone		1.00		
Liarozole	-0.56	0.57	(0.29-1.13)	0.1085
CPA	-1.76	0.17	(0.06-0.51)	0.0016

2. The surrogate marker is prognostic.

No 50% PSA decline and survival

Relationship	Parameter	Relative Risk	95% CI	p-value
No 50% PSA decline within 12 weeks	0.49	1.64	(1.17-2.29)	0.004

3. The effect of the surrogate marker is independent of the treatment.

Treatment, PSA decline and survival

Relationship	Parameter	Relative Risk	95% CI	p-value
Prednisone		1.00		
Liarozole	0.27	1.31	(0.93-1.83)	0.12
CPA	0.27	1.31	(0.81-2.10)	0.27
No PSA decline within 12 weeks	0.48	1.62	(1.15-2.27)	0.006

Conclusions

1. Post-therapy PSA decline is a prognostic marker for survival.
2. Post-therapy PSA decline fulfills the conditions of surrogacy that were examined.

Value of Post-Therapy PSA Decline in Hormone-Resistant Prostate Cancer

Howard Scher, MD

Memorial Sloan Kettering Cancer Center

Rationale For Alternative Endpoints in Androgen-Independent Prostate Cancer

1. Measurable disease infrequent.
2. Soft-tissue response does not parallel bone.
3. Changes in bone lesions difficult to quantify in a reproducible way.
4. Prostate-specific antigen changes reflect total tumor burden.

Post-Therapy Change in PSA as an Endpoint

1. Rising PSA values antedate clinical or radiographic progression.

EORTC	30853
SWOG	INT-1

2. Easy to measure on a serial basis.
3. Allows rapid screening of new therapies.

Use of PSA in Phase II Trials

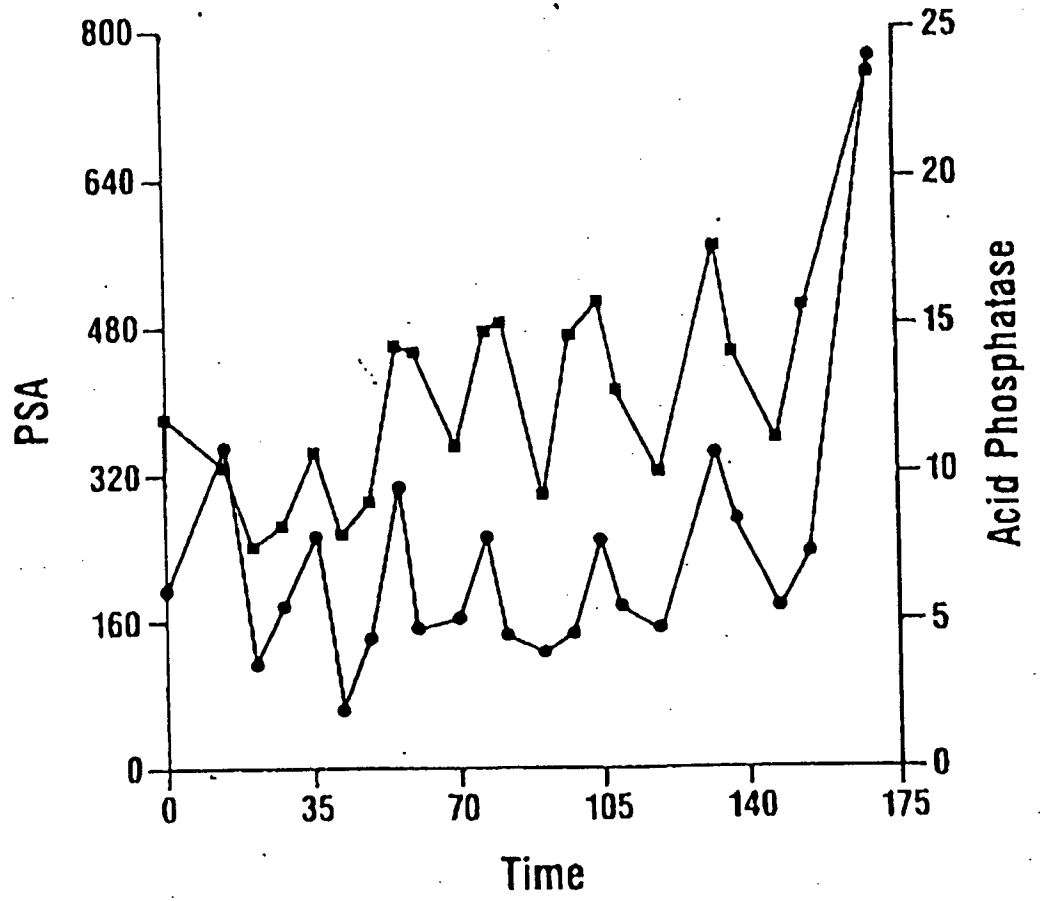
Agents that do not meet the criteria of a defined degree of decline for a defined duration are not worthy of further study.

Trimetrexate in Measurable Disease

1. Defined progression.
2. Recognized effect of treatment on PSA release without cell kill.
3. Proposed multidimensional outcomes:
    - Defined degree of decline
    - Defined duration
    - Repeated measures

MSKCC, 1990

PSA in a Patient Treated with Trimetrexate



JOC, 1990

Post-Therapy Decline in PSA:
Multiple Therapies

1. MSKCC: 116 patients
   Multiple therapies
2. Methods: Life table analysis
   Proportional hazards
   Landmark Method
   (Anderson et al. 1993)
3. Validation with independent data set of patients from Norway.
4. Post-therapy decline of >50% was the most significant factor associated with survival.

MSKCC, 1993

Post-Therapy PSA Declines:
Variable "Criteria"

1. Same patient population analyzed with different "criteria."
2. "Response" proportions range from 5-45%.

APPEARS THIS WAY
ON ORIGINAL

Refining Use of Post-Therapy PSA Declines

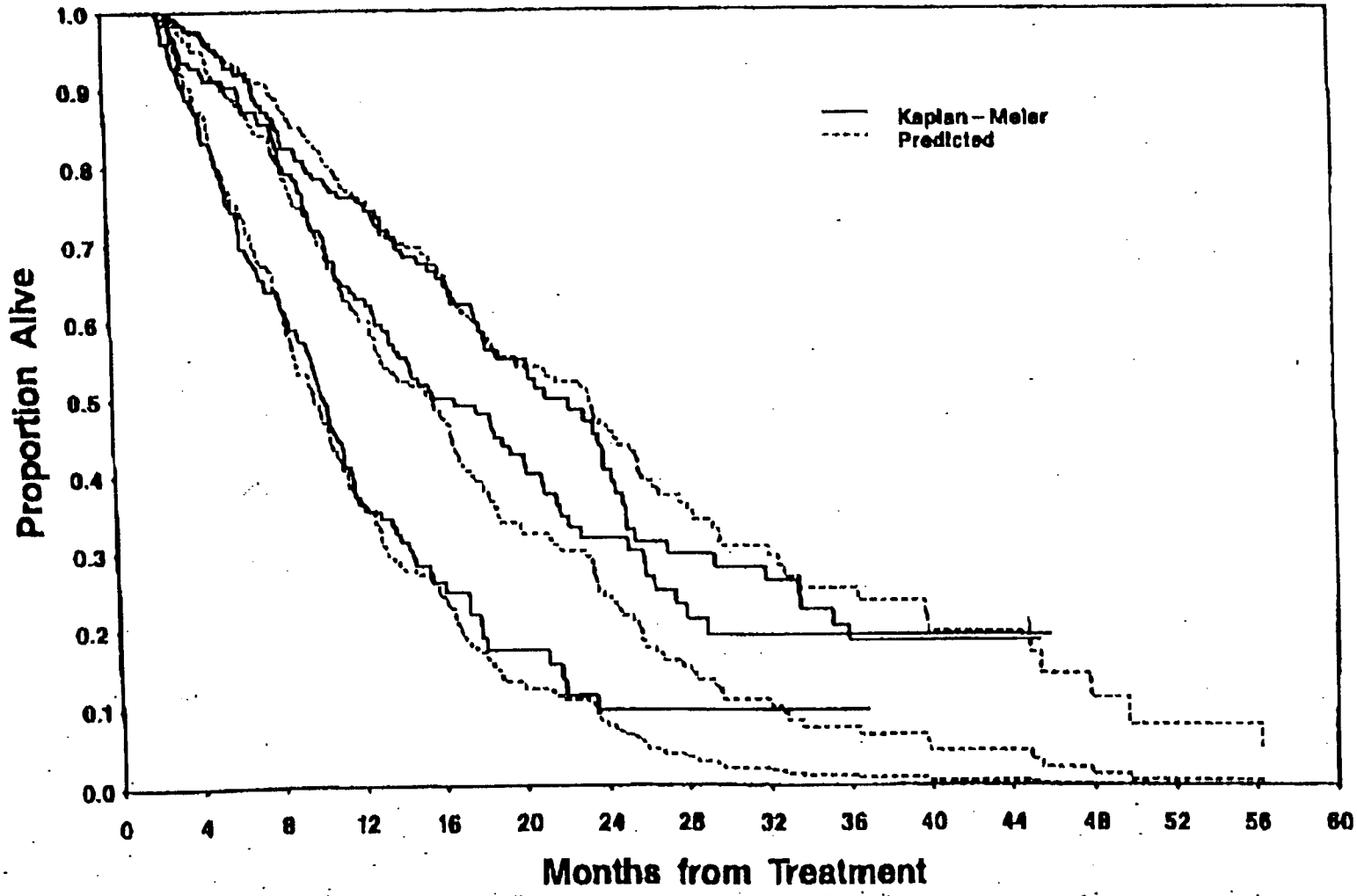
1. MSKCC Cohort: (254 patients)
   - Association between baseline variables and survival
   - PSA declines:
     - 2 vs. 3 values
     - Monthly intervals
     - 60 or 90 day landmark
   - Multivariate prognostic model

2. Validation: (541 patients)
   - INT-5 Liarozole vs. cyproterone acetate
   - USA-22 Liarozole vs. prednisone

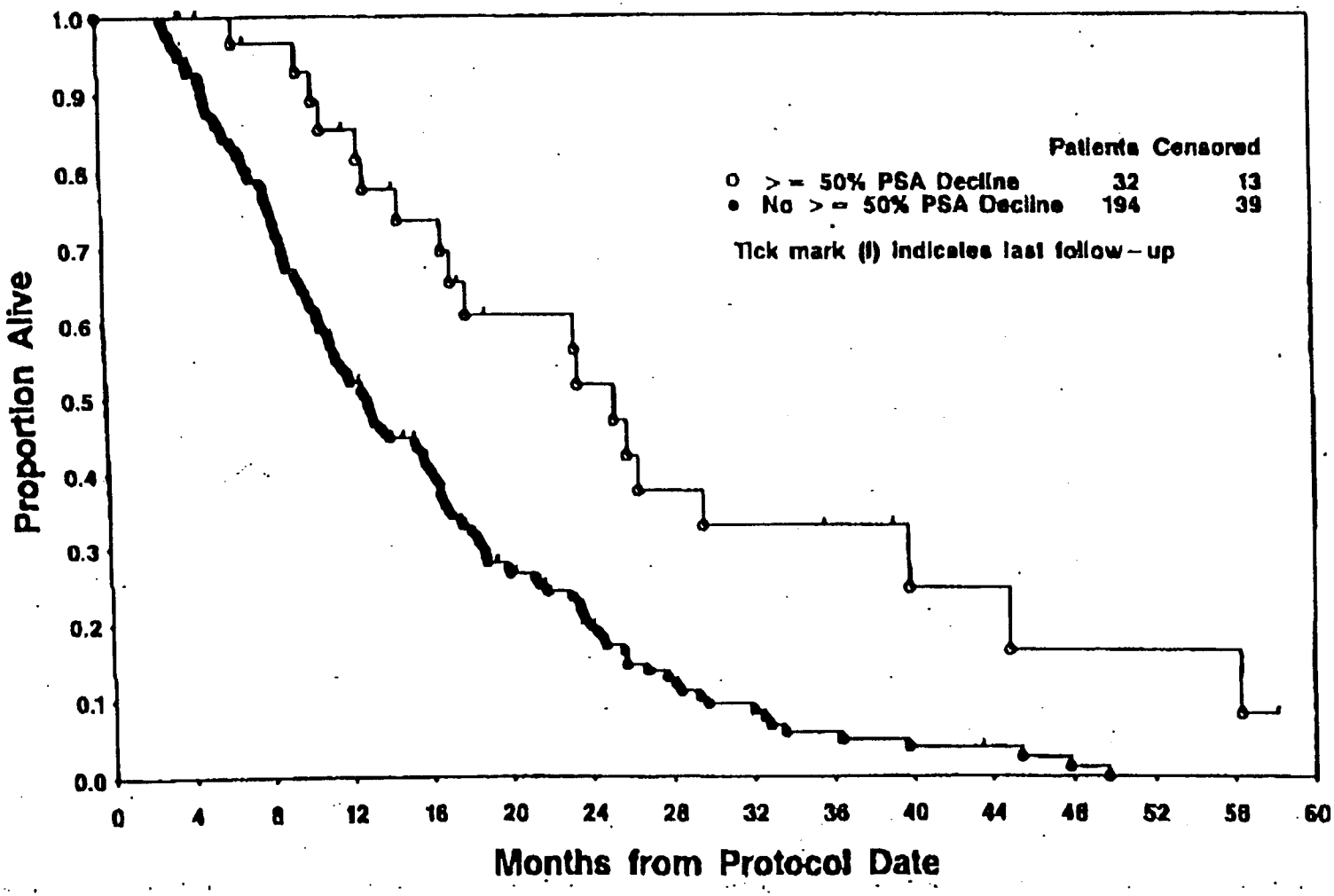
Demographics

	MSKCC	Combined Janssen Datasets
No. of patients	254	541
No. of deaths (%)	200 (79%)	403 (77%)
Survival		
Median in months	12.9	11.4
> 60 days	234 (92%)	428 (79%)
> 90 days	226 (89%)	409 (76%)
PSA decline >50% from baseline		
60 days	36 (11%)	58 (12%)
90 days	32 (14%)	64 (26%)

Predicted Against Observed Survival by Risk Group



Survival
MSKCC Cohort



Pitfalls in Use of Post-Therapy PSA Declines as a Clinical Trial Endpoint

1. Not all cells express PSA.
2. PSA subject to hormonal regulation.
3. PSA effects independent of cell kill.
4. Validity may vary as function of agent.

APPEARS THIS WAY
ON ORIGINAL

Prentice Conditions for Surrogacy

1. The surrogate marker is affected by treatment.
2. The surrogate marker is prognostic.
3. The effect of the surrogate marker is independent of the treatment.

Also, the observed treatment effect may be accounted for by the surrogate marker.

Prentice Conditions: 50% PSA Decline Within 12 Weeks as a Surrogate Marker for Survival

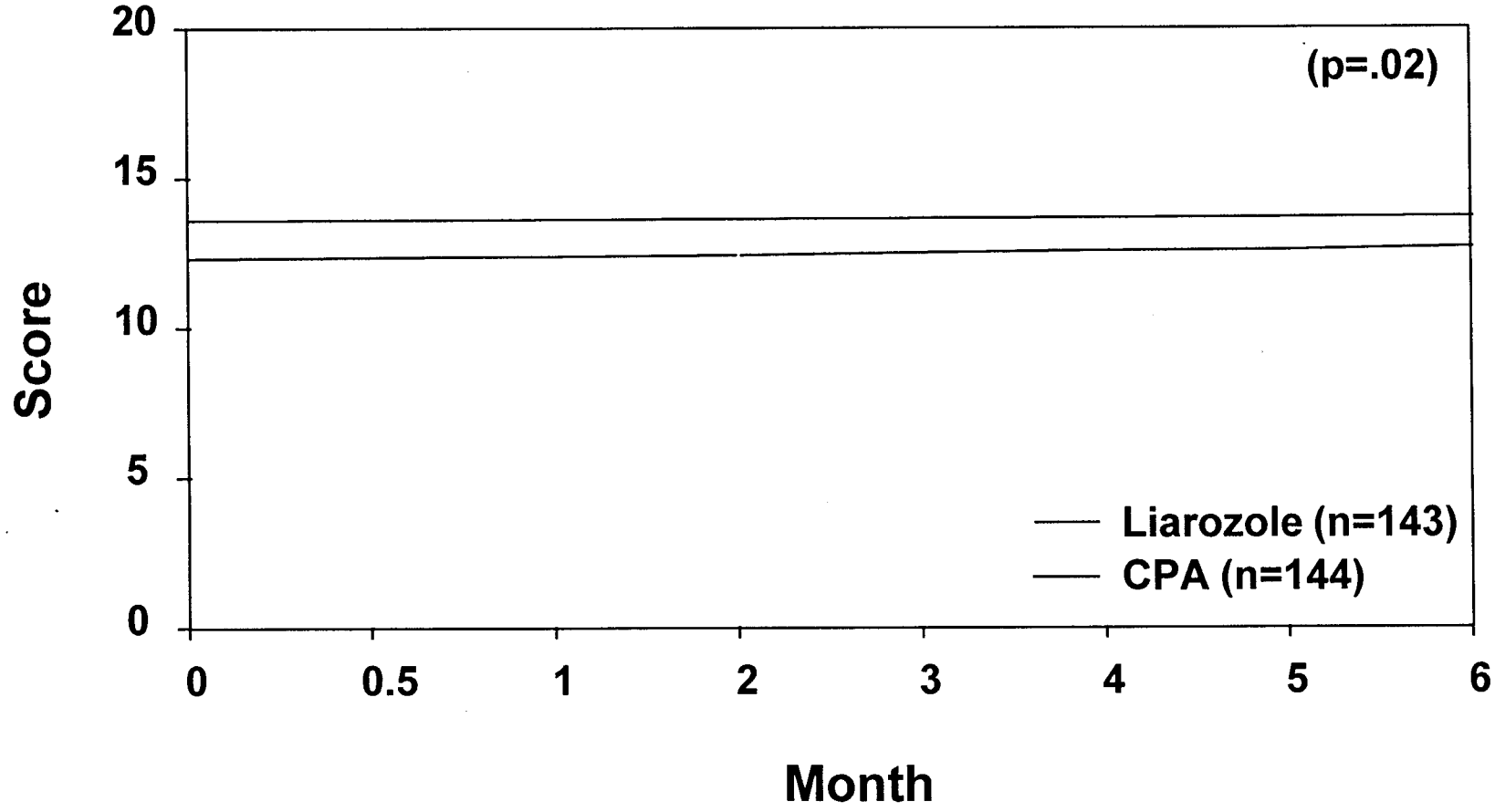
Relationship	Parameter	Relative Risk	95% CI	p-value
Prentice 1	**Treatment and PSA decline**			
Prednisone		1.00		
Liarozole	-0.56	0.57	(0.29-1.13)	0.1085
CPA	-1.76	0.17	(0.06-0.51)	0.0016
Prentice 2	**No 50% PSA decline and survival**			
No 50% PSA decline within 12 weeks	0.49	1.64	(1.17-2.29)	0.004
Prentice 3	**Treatment, PSA decline and survival**			
Prednisone		1.00		
Liarozole	0.27	1.31	(0.93-1.83)	0.12
CPA	0.27	1.31	(0.81-2.10)	0.27
No PSA decline within 12 weeks	0.48	1.62	(1.15-2.27)	0.006

The study population include those whose survival was longer than 12 weeks.

Conclusions

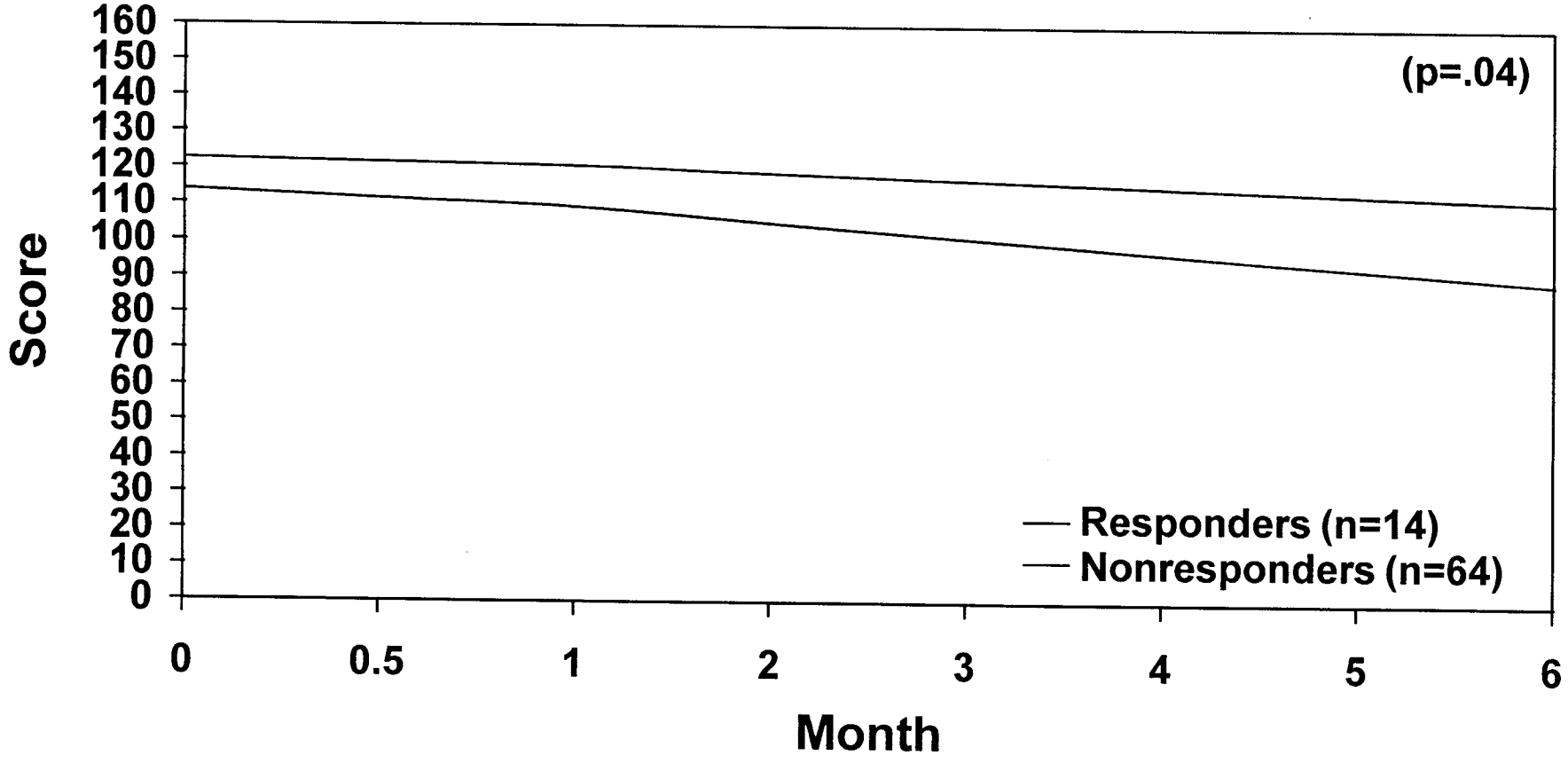
1. Post-therapy PSA decline is a prognostic marker for survival.
2. Post-therapy PSA decline fulfills the conditions of surrogacy that were examined.

FLIC Pain Scale
LIA-INT-5 (Modified ITT)



Scores ranged from 3 (most interference with function) to 21 (least interference).

Total FLIC
Liarozole PSA Responders vs Nonresponders
LIA-USA-22 (Modified ITT)



Scores range from 22 (worst function) to 154 (best function).

Total FLIC

LIA-USA-22 (Modified ITT)