ONCOLOGIC DRUGS ADVISORY COMMITTEE

MEETING # 52

12/±6/96

NOTE

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REQUESTS FOR INFORMATION ON THE PRODUCT REGULATED BY THE CENTER FOR BIOLOGICS EVALUATION AND RESEARCH WILL BE PROVIDED BY THAT CENTER.

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

Oncologic Drugs Advisory Committee
52nd Meeting
December 16, 1996
Double Tree Hotel, Rockville, MD
Plaza Ballroom I & II

AGENDA

Monday, December 16, 1996 **Open Session**

8:30 am- Call to Order and Opening remarks
Janice J. Dutcher, M.D., Chairman
Conflict of Interest Statement
LT Jannette O'Neill-Gonzalez, M.H.S.,
Health Scientist Administrator / Executive Secretary

8:35 am- Open Public Hearing. Half hour is allocated. The next agenda item will begin immediately if less than half hour is needed.

9:00 am- Sponsors presentation
NDA # 20-726 Femara™ Tablets (letrozole, CGS 20267, Ciba-Geigy Corporation), for the "treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, following antiestrogen therapy."

Ciba-Geigy Corporation

Overview :	Dr. John R. Hanagan
Pharmacodynamics :	Dr. Ajay Bhatnagar
Pharmacokinetics:	Dr. Christian Pfister
Clinical Efficacy: Clinical Safety Conclusion	Dr. Franzanne Vreeland

10:00 am- BREAK

	FDA Presentation	Dr. Genevieve Schechter
	ODAC Discussants	Dr. Sandra Swain Dr. Kim Margolin
	Committee Discussion	

12:00 pm- LUNCH

1:00 pm- Open Public Hearing. Half hour is allocated. The next agenda item will begin immediately if less than half hour is needed.

1:30 pm- Sponsors presentation
PLA # 92-0306 TICE® Product Licence Application (PLA) 92-0306 TICE® (BCG Vaccine, Organon Teknika Corporation), for "intravesical installation for prophylaxis against recurrent papillary carcinoma of the urinary bladder."

Organon Teknika Corporation

Introduction:	Dr. Michael Hanna
Overview and Presentation of Efficacy Data:	Dr. Donald Lamm
Presentation of Safety Data:	Dr. Donald Lamm
Synopsis of use of product:	Dr. Tom Delvers
Conclusions:	Dr. Donald Lamm

2:30 pm- BREAK

FDA Presentation Introduction:	Dr. Sheldon Morris Dr. Richard Steffen
ODAC Discussants	Dr. Derek Raghavan Dr. Craig F. Donatucci -Consultant
Committee Discussion	

4:30 pm- Adjourn

ONCOLOGIC DRUGS ADVISORY COMMITTEE

CHAIRMAN

Dutcher, Janice, M.D. 6/30/99
6/30/99
Professor of Medicine
Montefiore Medical Center
Albert Einstein Cancer Center
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and Therapeutics Research
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Duarte, California 91010

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Chief, Departments of Solid Tumor Oncology
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August 23, 1996

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Chicago, Illinois 60637

Consumer Representative
E. Carolyn Beaman, M.H.S. 6/30/99
President, Sisters Breast Cancer Network
123 Poinciana Street
Lake Jackson, Texas 77566

ONCOLOGY DRUGS ADVISORY COMMITTEE
December 16, 1996

Note: Please be advised you should not contact these people before the meeting, since, their participation in the meeting may be jeopardized.

GUESTS

Dr. Michael Cynamon (Speaker)
VA Medical Center
Syracuse, New York 13210

Dr. Craig F. Donatucci (Consultant)
Duke University Medical Center
Division of Urologic Surgery
Durham, NC 27710

Dr. Larry Schlesinger (Speaker)
The University of Iowa
Department of Internal Medicine
Division of Infectious Diseases
Iowa City, IA 52242

Dr. Steven M. Holland (Speaker)
Laboratory of Host Defenses
National Institute of Allergy and Infectious Diseases
National Institute of Health
Bethesda, MD 20892-1886

Dr. Robert R. DiLoreto (Consultant)
Regal Court Professional Building
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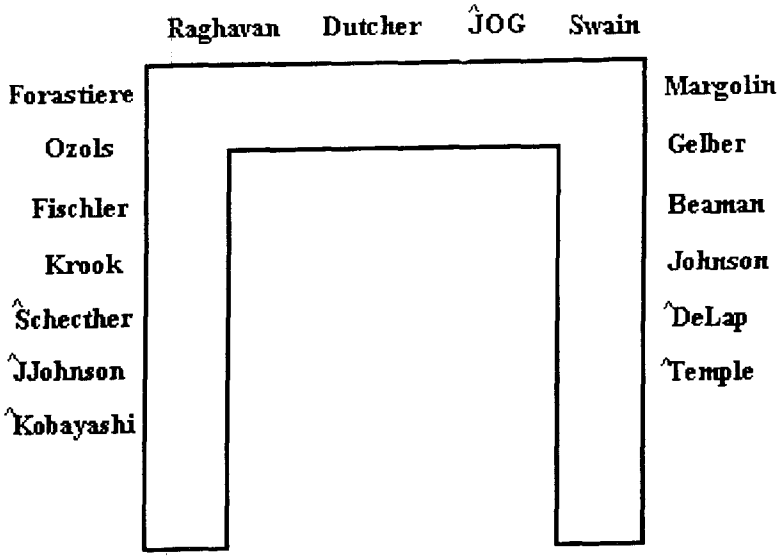
PATIENT REPRESENTATIVES

Colonel James Schultz (Retired)
Bladder Cancer Advocate
Organization: Walter Reed Medical Center
Moravia, MD

Ms. Sandra Zook-Fischler
Breast Cancer Advocate
Organization: SHARE Self-Help for women with breast cancer
New York, NY

CONSUMER REPRESENTATIVE

E. Carolyn Beaman, M.H.S.
President, Sisters Breast Cancer Network



^=FDA staff

Femara tablets

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

December 16 , 1996

Double Tree Hotel, Rockville, MD

Oncologic Drugs Advisory Committee
DRAFT Questions
Femara™Tablets

December 16, 1996

1. In the clinical trials patients were allowed to start treatment the day following antiestrogen discontinuation.

   a. What rate of tamoxifen withdrawal tumor responses might be expected?
   b. What impact should this have on our evaluation of the study results?
   c. In future studies of second line hormonal therapy of advanced breast cancer should protocols require an interval of at least 1 month between the last dose of the prior hormonal treatment and the baseline evaluation for the study?

2. Is Femara approvable for the treatment of advanced breast cancer after antiestrogen therapy in women with natural or artificially induced postmenopausal status who are hormone receptor status positive or unknown?

3. If so, what dose(s) of Femara should be approved?

   a. Femara PK data?
   b. Estradiol and Estrone blood levels?
   c. Results of clinical trials, i.e. response rate and duration, TTF, TTP and survival?

Femara™ Tablets
December 16, 1996
ODAC

	Q1a		Q1b		Q1c		Q2		Q3a		Q3b		Q3c	
Names	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Krook														
Fischler														
Ozols														
Forastiere														
Raghavan														
Dutcher														
Swain														
Margolin														
Gelber														
Beaman														
Johnson														
Total														

Agenda for Ciba's Presentation to the Oncology Drugs Advisory Committee

December 16, 1996

Femara ™

NDA 20-726

Treatment of Advanced Breast Cancer

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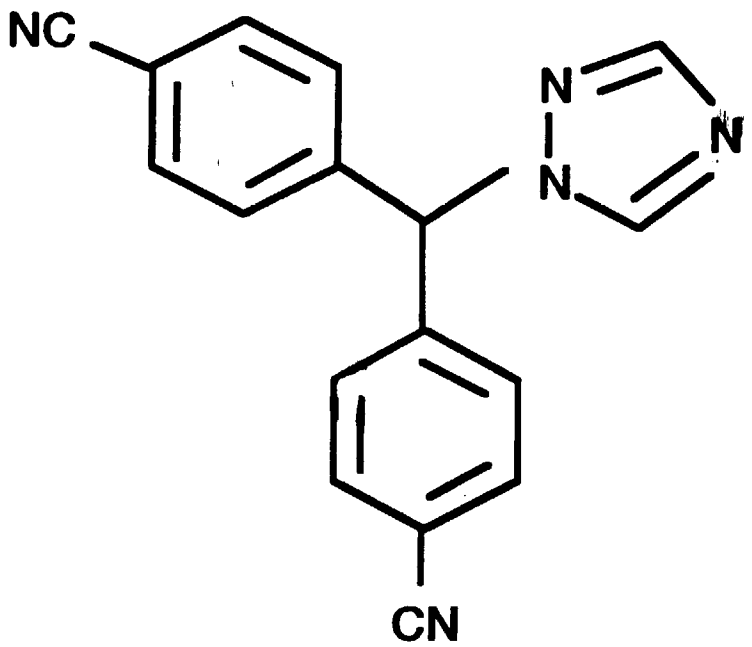
Opening Remarks

John Hanagan, MD
Vice President
Clinical Research
Ciba-Geigy

Femara™



4,4'[(1H-1,2,4-triazol-1yl)methylene]bisbenzonitrile

USAN, INN: Letrozole

Code No.: CGS 20267

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Agenda

Opening Remarks
John Hanagan, MD
Clinical Research

Pharmacodynamics of Femara
Ajay Bhatnagar, PhD
Pharma Research Dept.

Pharmacokinetics of Femara
Christian Pfister, PhD
Bioanalytics and Pharmacokinetics

Femara Efficacy and Safety
Franzanne Vreeland, MD
Clinical Research

Femara Overview (NDA 20-726)

- Femara is a potent and selective aromatase inhibitor
- Efficacy
  - Two pivotal trials demonstrate efficacy of Femara 2.5 mg compared to:
    - Megace® (MA)
    - Aminoglutethimide (AG)
- Safety
  - Equal tolerability between Femara doses
  - Superior tolerability to MA
  - Equal tolerability to AG + corticoid supplementation
- Femara 2.5 mg is indicated for treatment of advanced breast cancer in postmenopausal women with relapse or disease progression following anti-estrogen therapy

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Pharmacodynamics

Ajay S. Bhatnagar, PhD
Research Project Team Leader
Aromatase Inhibitors
Pharma Research
Ciba-Geigy

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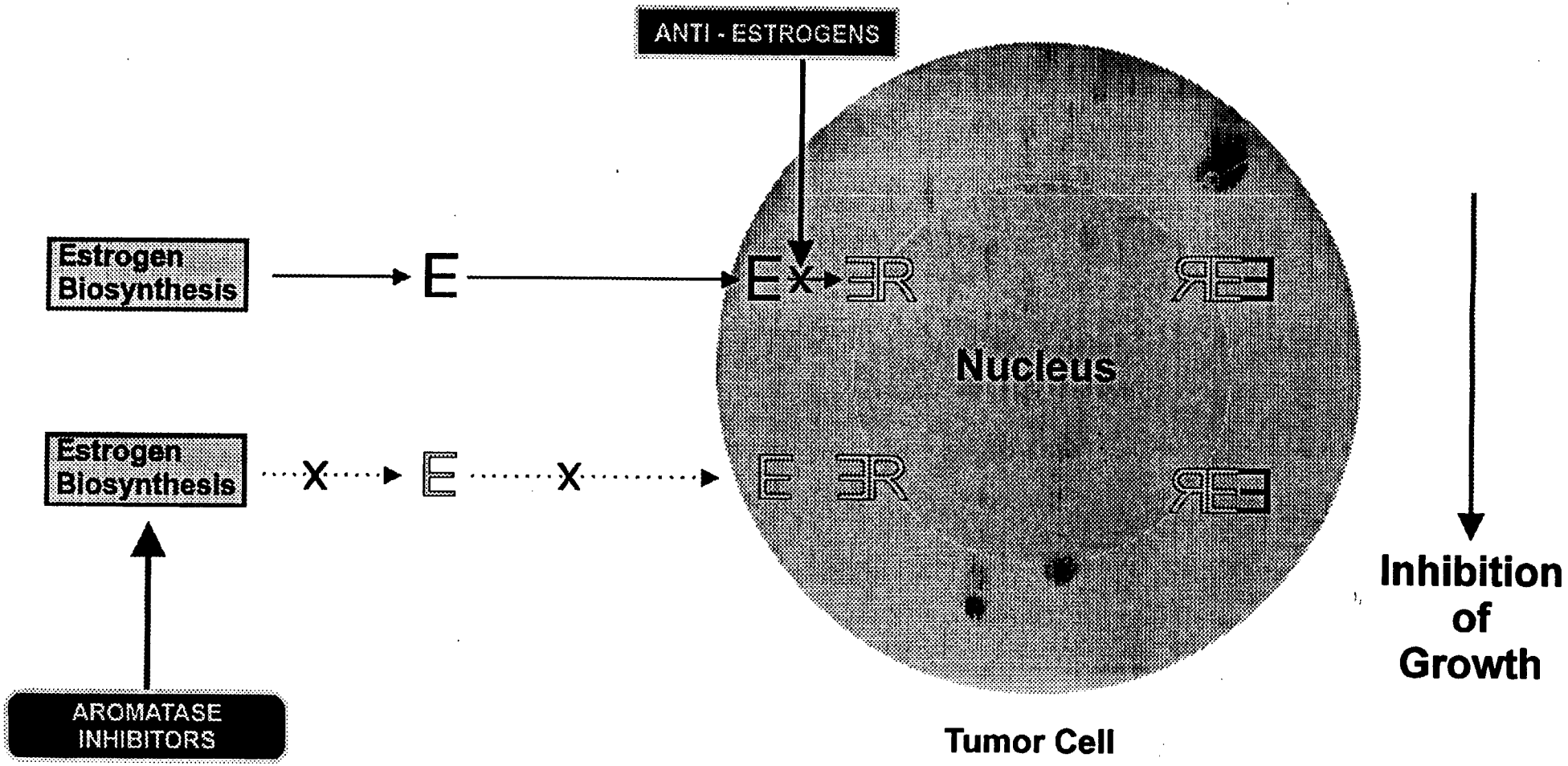
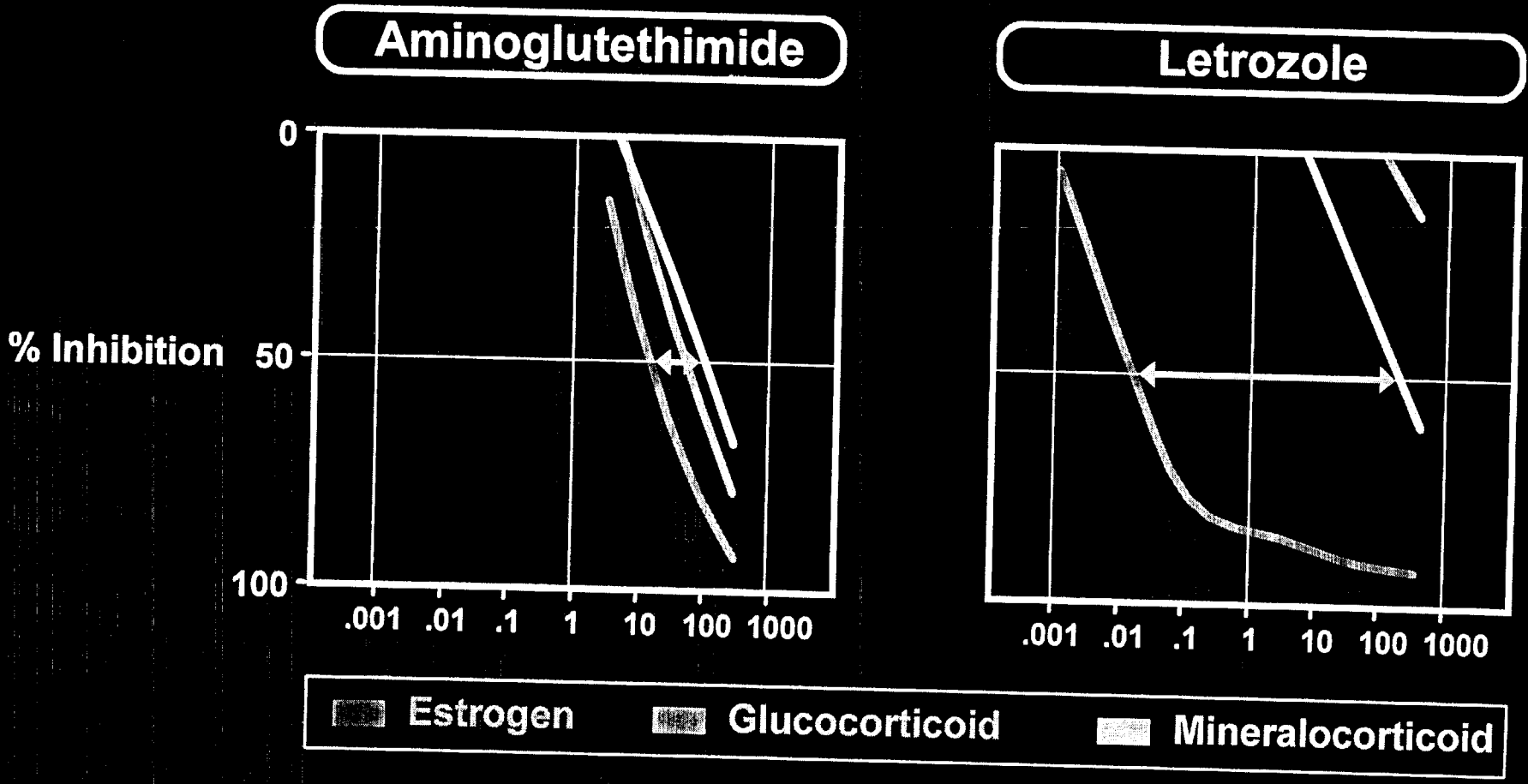
Inhibition of Estrogen-dependent Growth



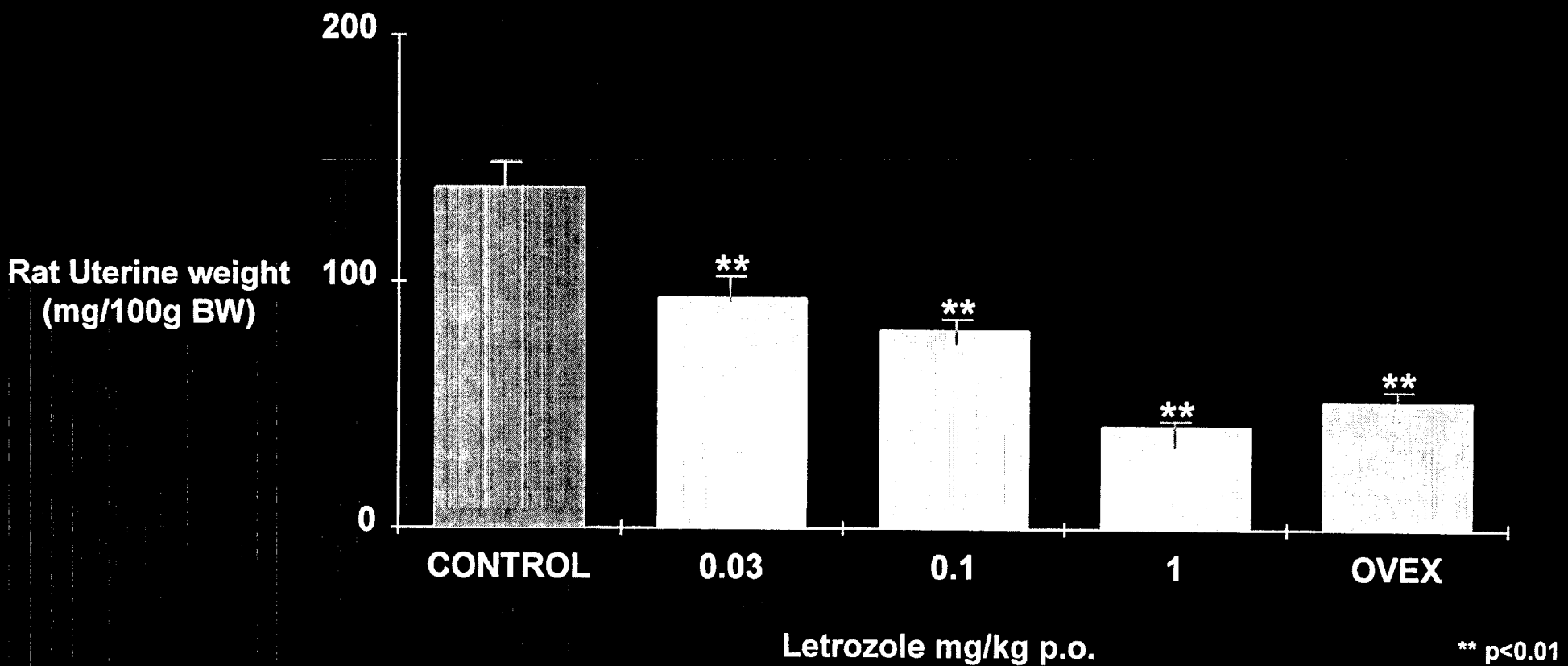
Inhibition of Aromatase

In vitro	Aminoglutethimide (AG)	Letrozole
IC50 nM	1900	11.5
Relative Potency	*1*	*165*
In vivo		
ED50 µg/kg p.o.	30,000	1 - 3
Relative Potency	*1*	*>10,000*

Selectivity in vitro

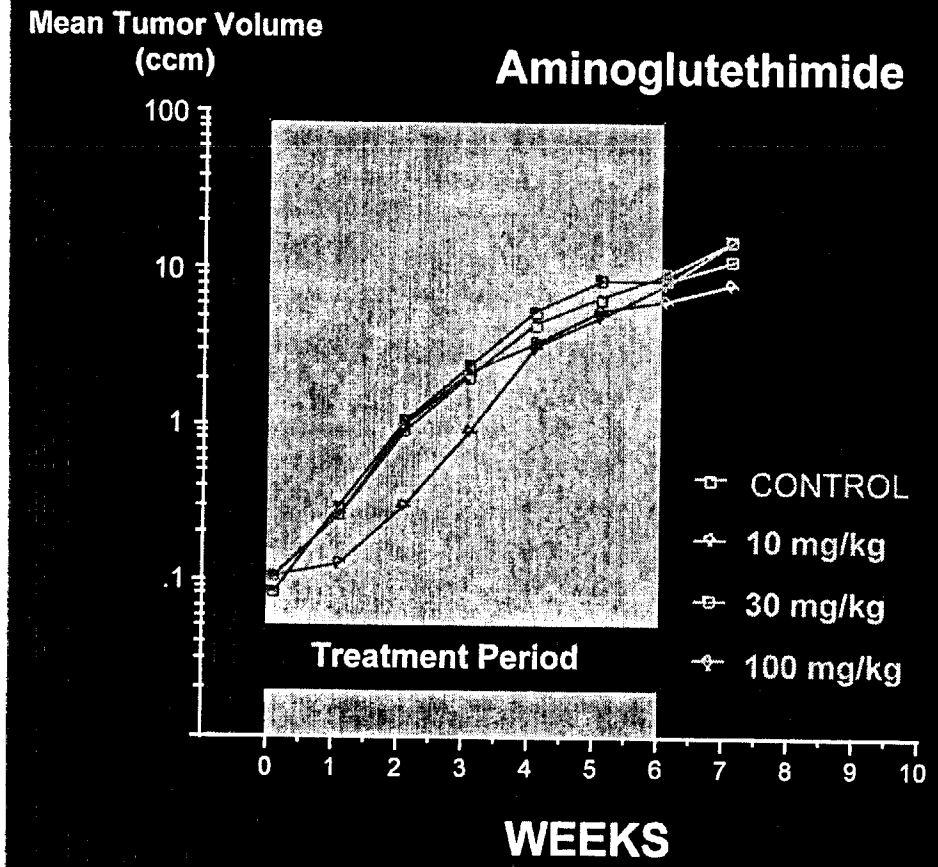


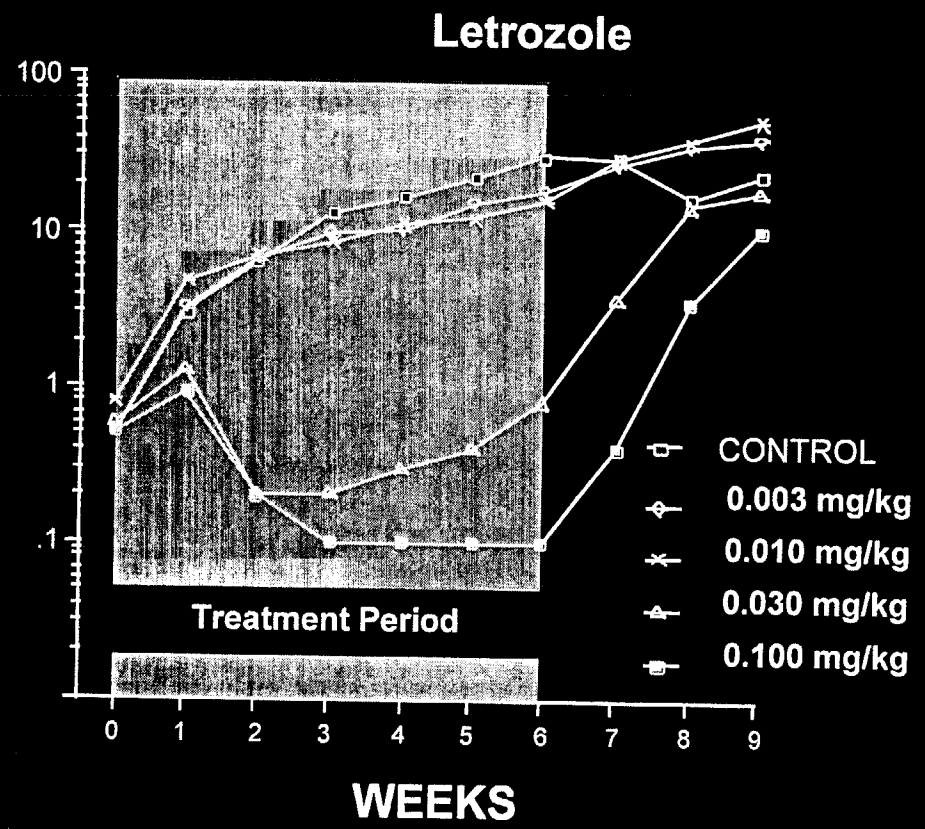
Endocrine Efficacy



Antitumor Efficacy

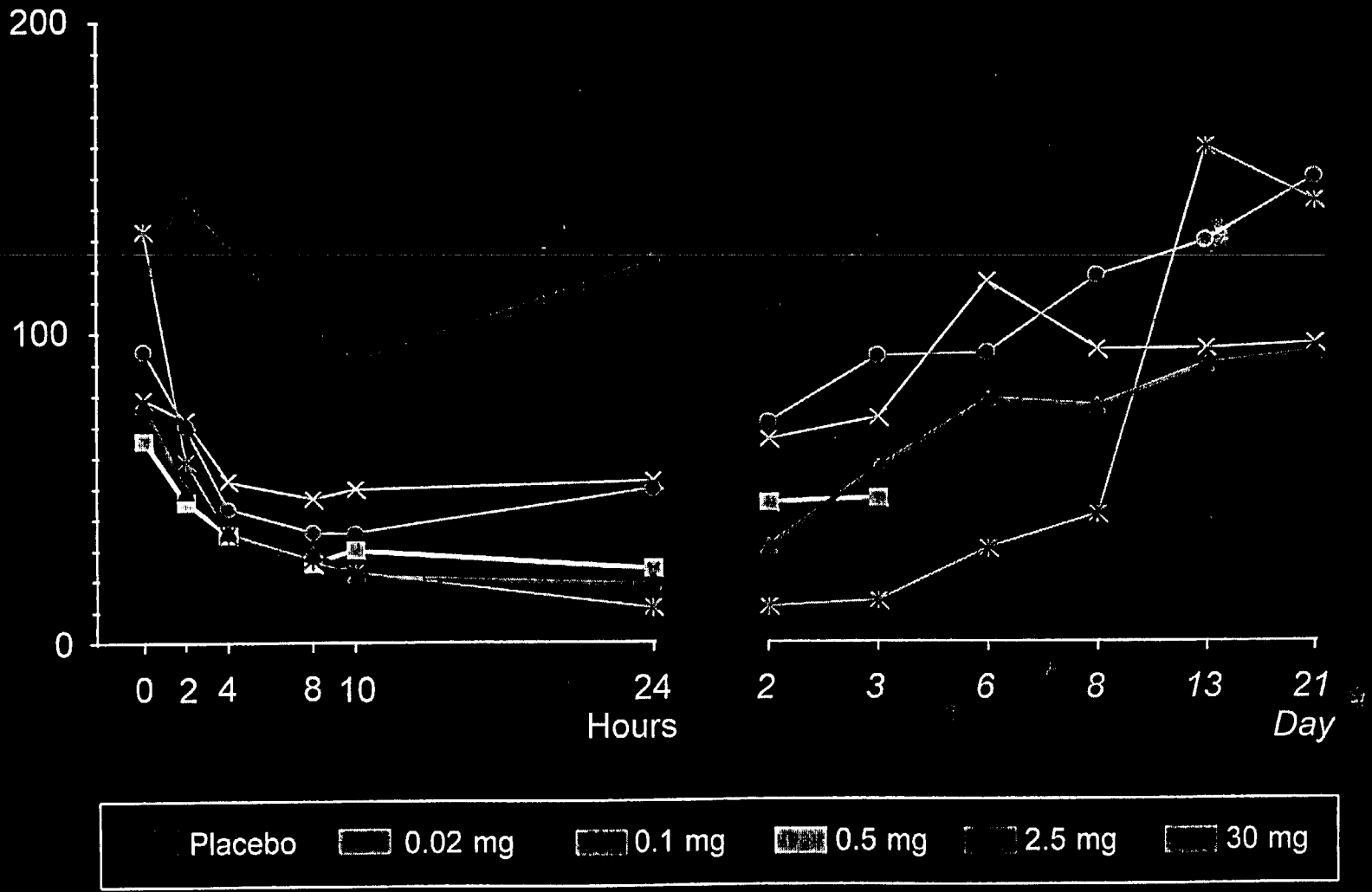
(DMBA model)





Serum Estradiol (pmol/L)

after a single dose in healthy volunteers



Rationale for Dose Selection in Pivotal Trials

- from single dose study:

  0.1mg 0.5mg 2.5mg

  chosen for multiple dose study

- from multiple dose study:

  0.1mg vs 0.5mg

  Statistical significance
  for more estrogen values
  below LOQ for 0.5mg

  0.5mg vs 2.5mg

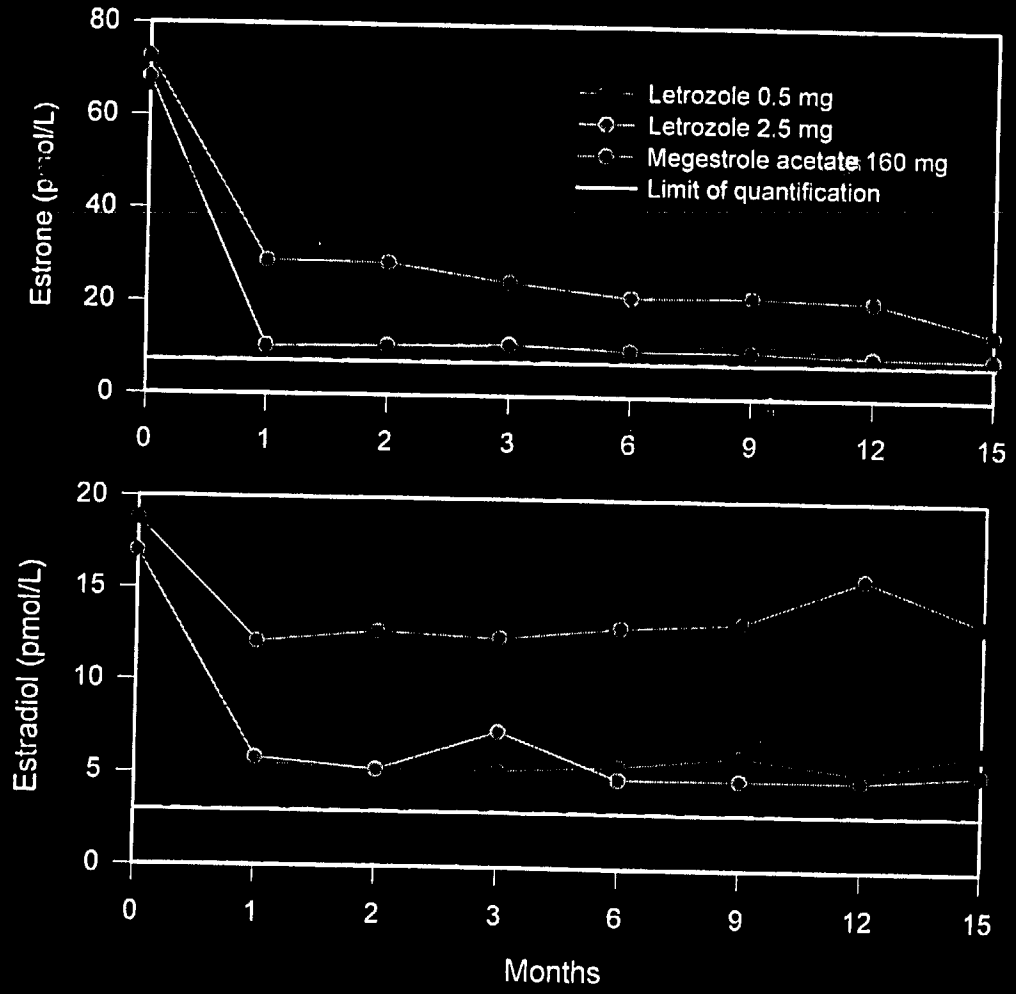
  No statistical significance
  for more estrogen values
  below LOQ

Rationale for Dose Selection in Pivotal Trials

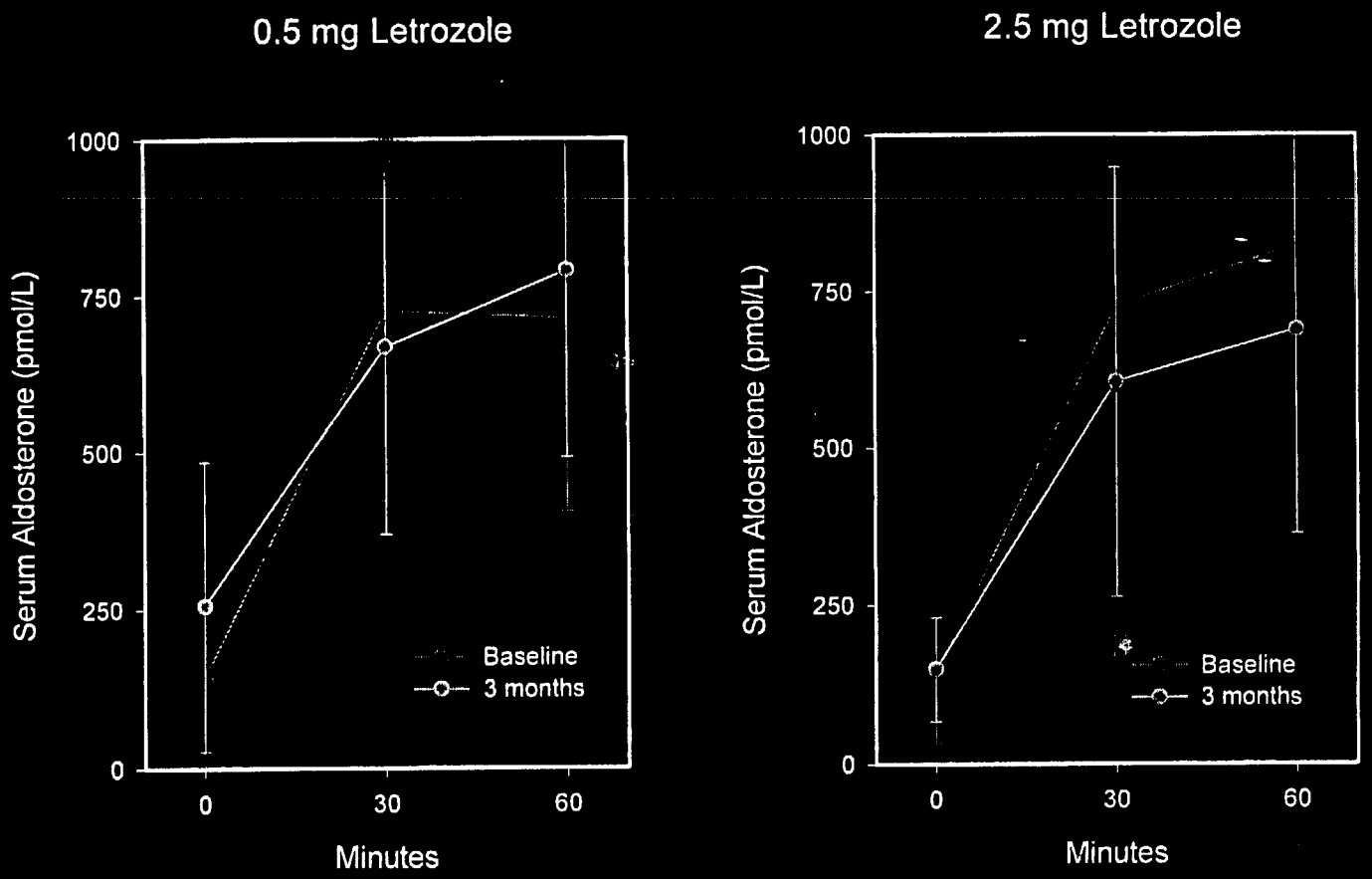
- 0.5mg — LOWEST dose which achieved MAXIMAL estrogen suppression
- 2.5mg — well-tolerated, selective, possibility of enhanced anti-tumor efficacy through increased inhibition of intra-tumoral aromatase

Serum Estrogens(pmol/L)

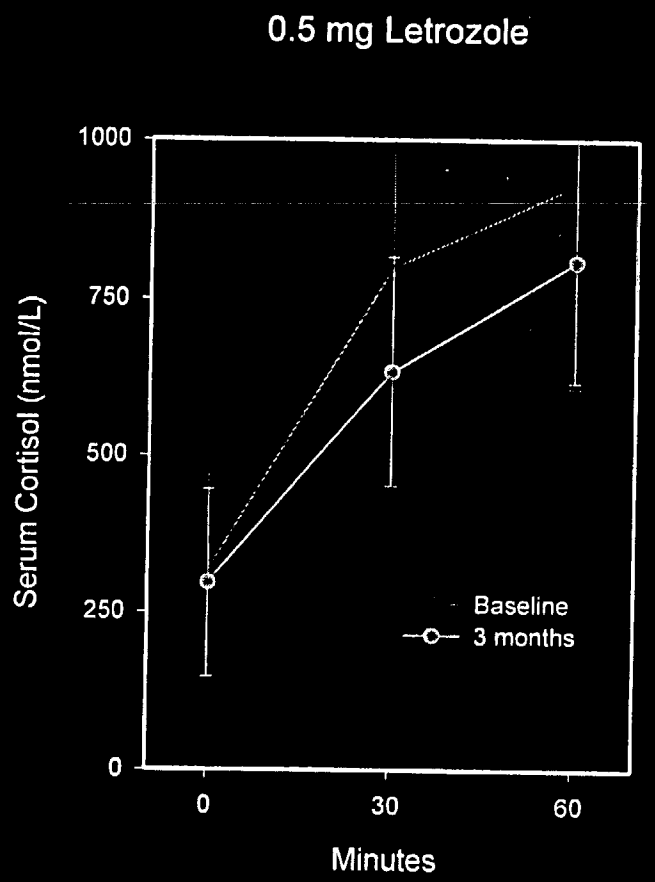
after multiple doses in patients (AR/BC2)

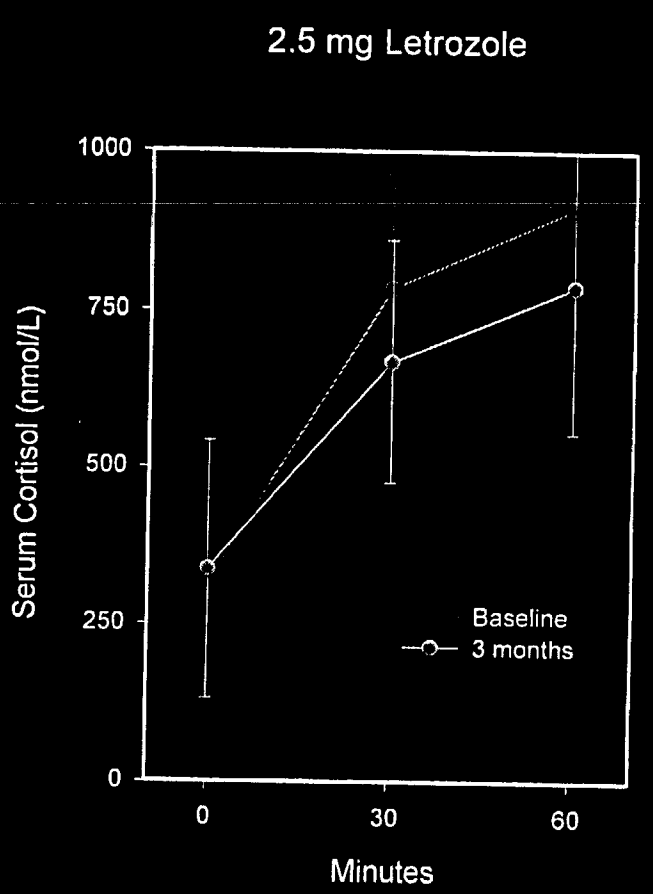


Synacthen® Test
(Aldosterone)



Synacthen® Test
(Cortisol)





Letrozole

- is a potent and selective aromatase inhibitor
- is as effective as ovariectomy in inducing estrogen deprivation
- shows maximal anti-tumor efficacy in the DMBA model
- potently and selectively reduces serum estrogens in humans

Pharmacokinetics

Christian U. Pfister, PhD
Bioanalytics & Pharmacokinetics
Pharma Research
Ciba-Geigy

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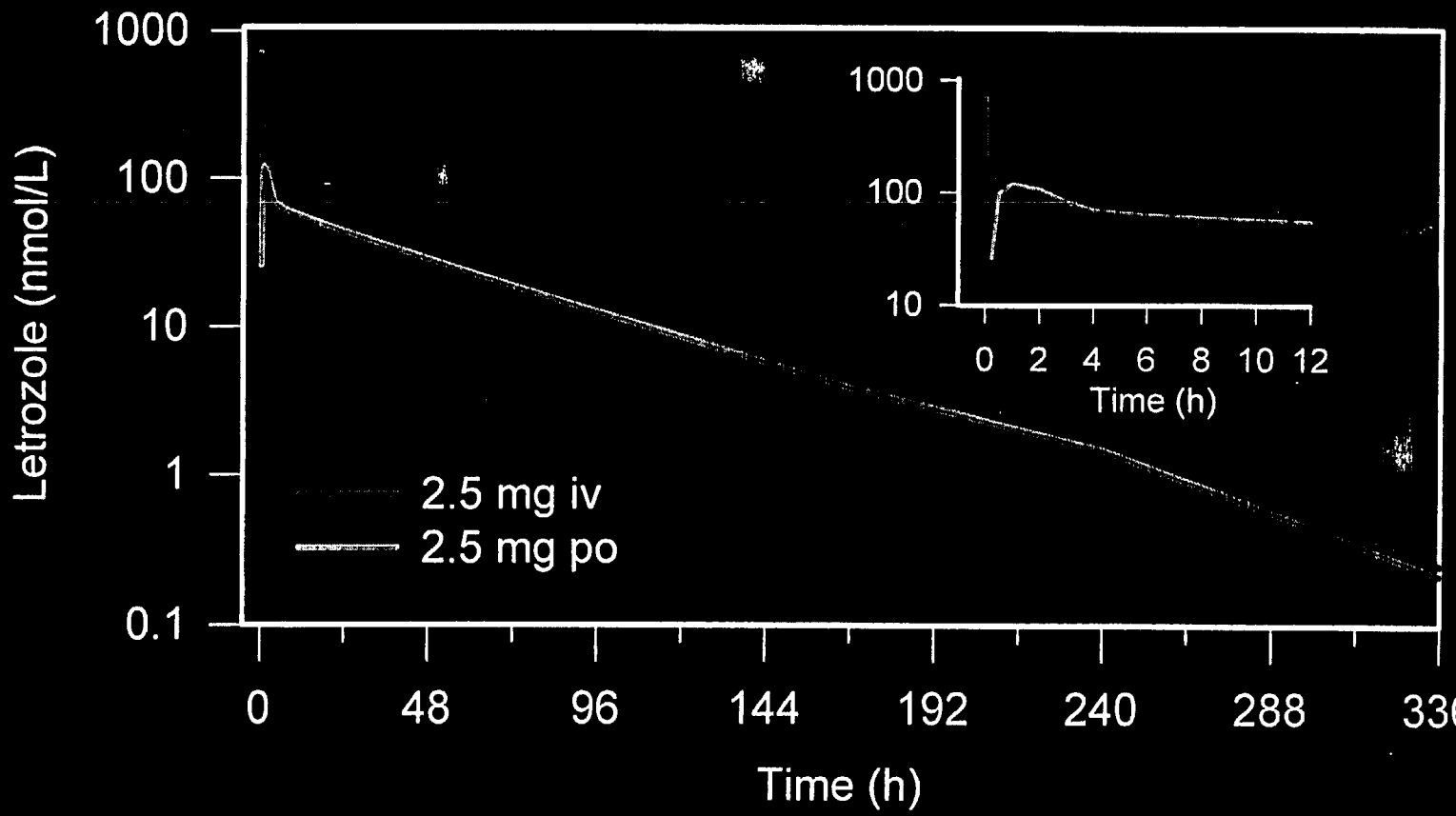
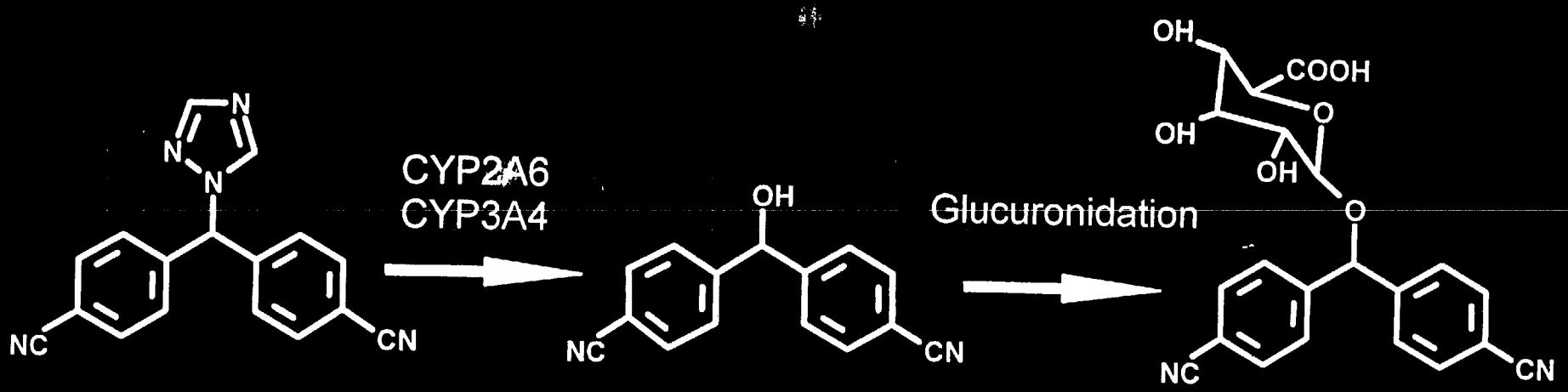
Absorption



BAV = 99.9%

$t_{1/2}$ = 46h

Metabolism and Excretion



Letrozole

CGP 44645

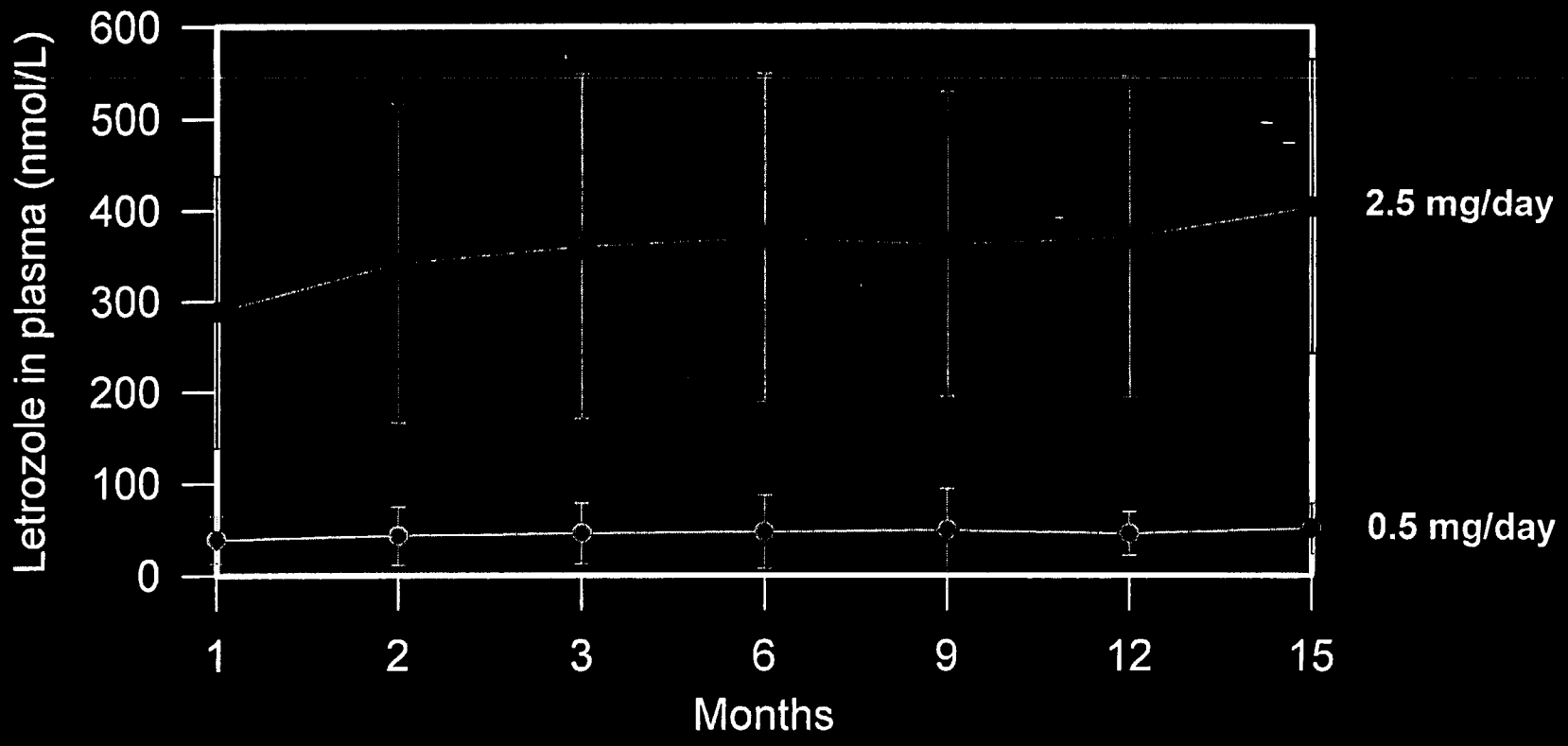
Renal excretion

5 %

Renal excretion

> 65 %

Steady State (AR/BC2)



Special Populations

No dose adjustment needed in

Elderly	No effect of age on letrozole plasma levels
Renally impaired	No correlation between renal function and letrozole kinetics (CLcr > 10 mL/min)
Hepatically impaired	Kinetic parameters within normal range in subjects with mild to moderate hepatic impairment (Child-Pugh score A and B)

Drug-drug Interactions

- No clinically significant interactions with cimetidine and warfarin
- Low potential for interaction via cytochrome P450 enzymes

Summary

- Fast and complete absorption
- Elimination mainly via metabolism
  (half-life approximately 2 days)
- Steady state attained despite
  slight non-linearity at 2.5 mg daily
- No dose adjustment required in:
  - Elderly
  - Renally impaired
  - Hepatically impaired (mild to moderate)
- No known clinically significant drug interactions

Clinical Efficacy/Clinical Safety

Franzanne Vreeland, MD
International Clinical Team Leader
Clinical Research
Ciba-Geigy

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Femara Pivotal Trials

AR/BC2	AR/BC3	P02
10 countries	11 countries	7 countries
91 centers	86 centers	119 centers
552 Patients	557 Patients	602 Patients
Results Submitted	Early results	Trial ongoing

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Design

Trial	Femara	Femara	
AR/BC2 double-blind	2.5 mg qd	0.5 mg qd	Megace 160 mg qd
AR/BC3 open-label (peer review blinded)	2.5 mg qd	0.5 mg qd	Aminoglutethimide 250 mg bid
PO2 double-blind	2.5 mg qd	0.5 mg qd	Megace 40 mg qid

Randomized (1:1:1)

Trial Population

Postmenopausal women with advanced breast cancer who have:

- Objective evidence of relapse on adjuvant or progression on therapeutic anti-estrogens
- Positive estrogen and/or progesterone receptors or both receptors unknown
- Measurable and/or evaluable disease

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Efficacy Endpoints

- Primary variable
  - Objective response rate (complete and partial)
  - Verified by independent blind external peer review by country
  - Used UICC criteria with confirmation of response at least 4 weeks from the first observed partial or complete response

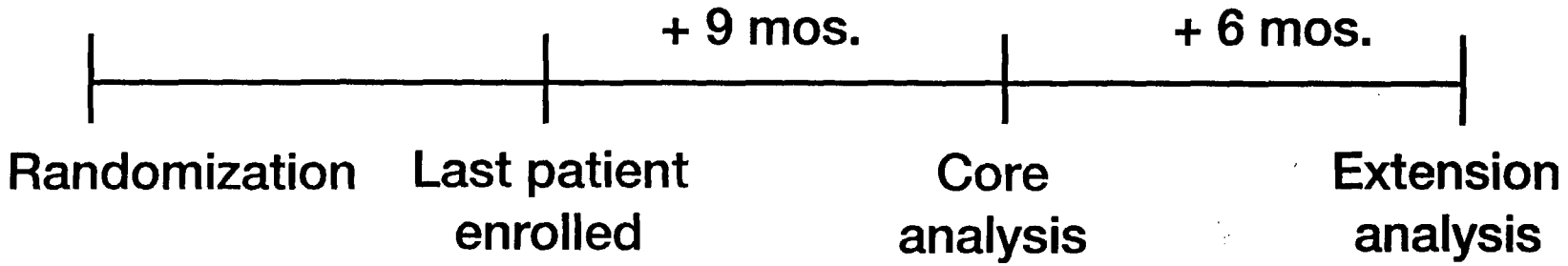
Efficacy Endpoints

- Secondary variables
  - Duration of response
  - Time to progression
  - Time to treatment failure
  - Survival (not mature for AR/BC3)
  - Quality of life

Baseline Prognostics

- Age class (≤ 55 years, 56-69 yrs, ≥ 70 yrs)
- Dominant site of disease
- Number of anatomical sites
- Disease-free interval
- Hormone receptor status
- Performance status
- Prior chemotherapy
- Prior anti-estrogen therapy
- Response to prior anti-estrogen therapy
- Previous or concomitant bisphosphonate use (AR/BC2 only)
- Body mass index

Trial Phases



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Protocol Specified Analysis Time Points

- Core analysis is the primary analysis for
  - Tumor response
  - Duration of response
  - Time to progression
  - Time to treatment failure
- Presented for AR/BC3
- Extension analysis presented for AR/BC2 because conclusions are identical to core analysis except for time to treatment failure

Protocol Specified Analysis Time Points

- Extension analysis is the primary analysis for survival
- AR/BC2 completed and will be presented
- AR/BC3 not yet completed: data immature

Treatment: Assignment, Analysis and Duration

	AR/BC2 Extension			AR/BC3		
	Femara 2.5 mg	Femara 0.5 mg	MA	Femara 2.5 mg	Femara 0.5 mg	AG
All randomized	174	188	190	185	193	179
Evaluable for efficacy	174	188	189	185	192	178
Evaluable for safety	174	188	189	185	192	178
Median duration of treatment in days	167	128	165	159	132	144

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Demography, Breast Cancer History, and Disease Status

In trials AR/BC2 extension and AR/BC3, patients in the different treatment groups within a trial generally were well matched for all prognostics and both trials had similar populations:

- Age class (≤ 55 years, 56-69 yrs, ≥ 70 yrs)
- Dominant site of disease
- Number of anatomical sites
- Disease-free interval
- Hormone receptor status
- Performance status
- Prior chemotherapy
- Prior anti-estrogen therapy
- Response to prior anti-estrogen therapy
- Previous or concomitant bisphosphonate use (AR/BC2 only)
- Body mass index

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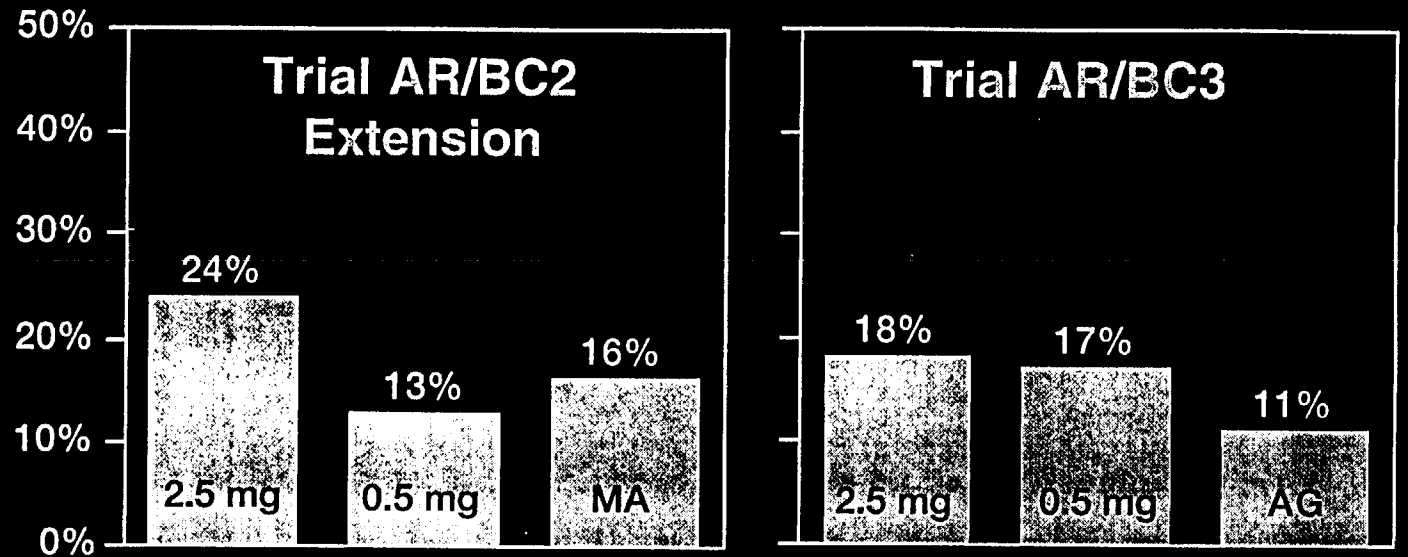
Objective Response Rate



Treatment comparisons	2.5/MA	2.5/0.5	0.5/MA	2.5/AG	2.5/0.5	0.5/AG
Odds Ratio	1.82	2.38	.60	1.78	1.01	1.97
P-value (adj)	.043	.004	.106	.092	.975	.051
P-value (unadj)	.087	.007	.317	.077	.764	.135

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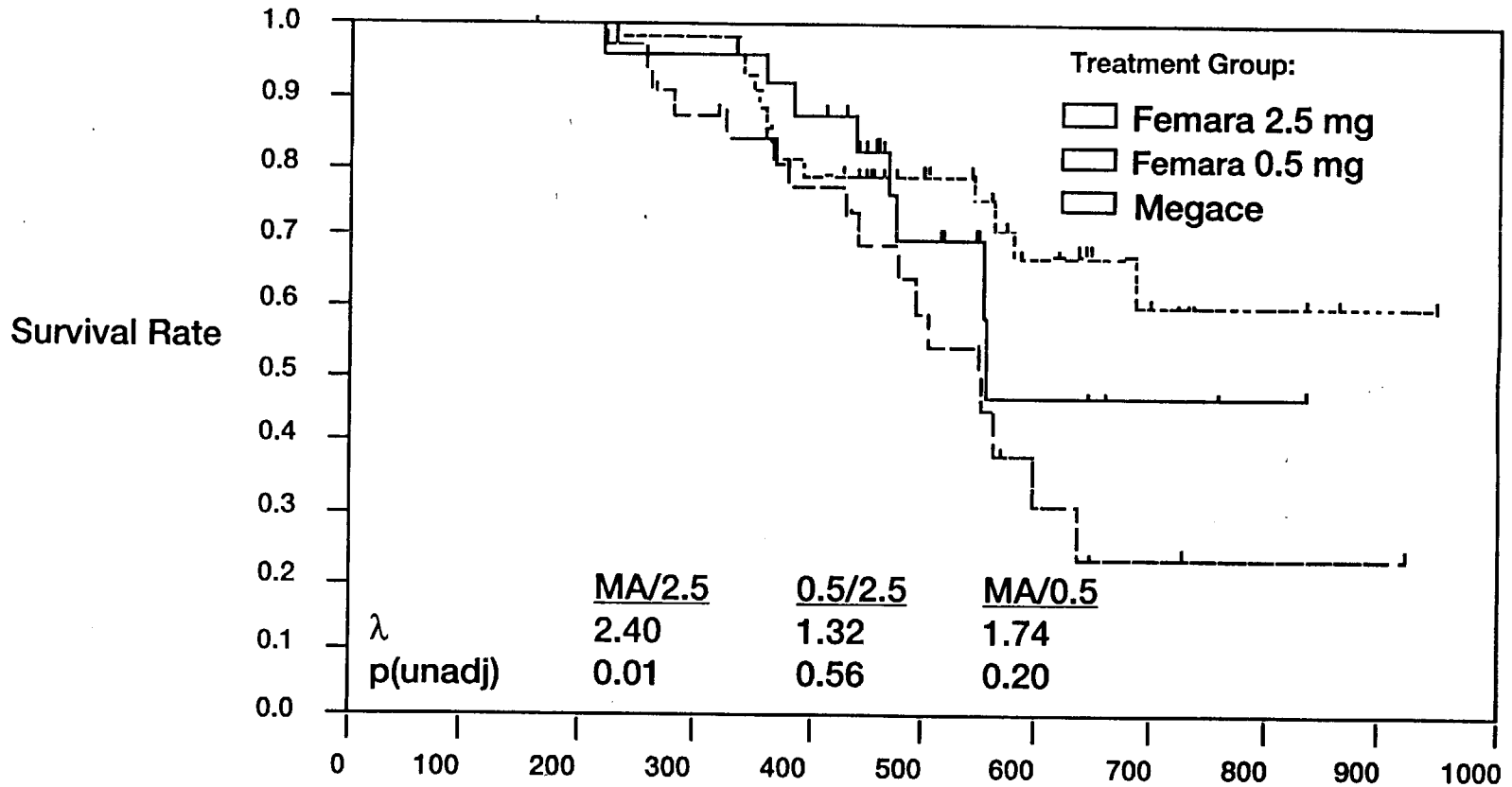
Duration of Response (AR/BC2 Extension)



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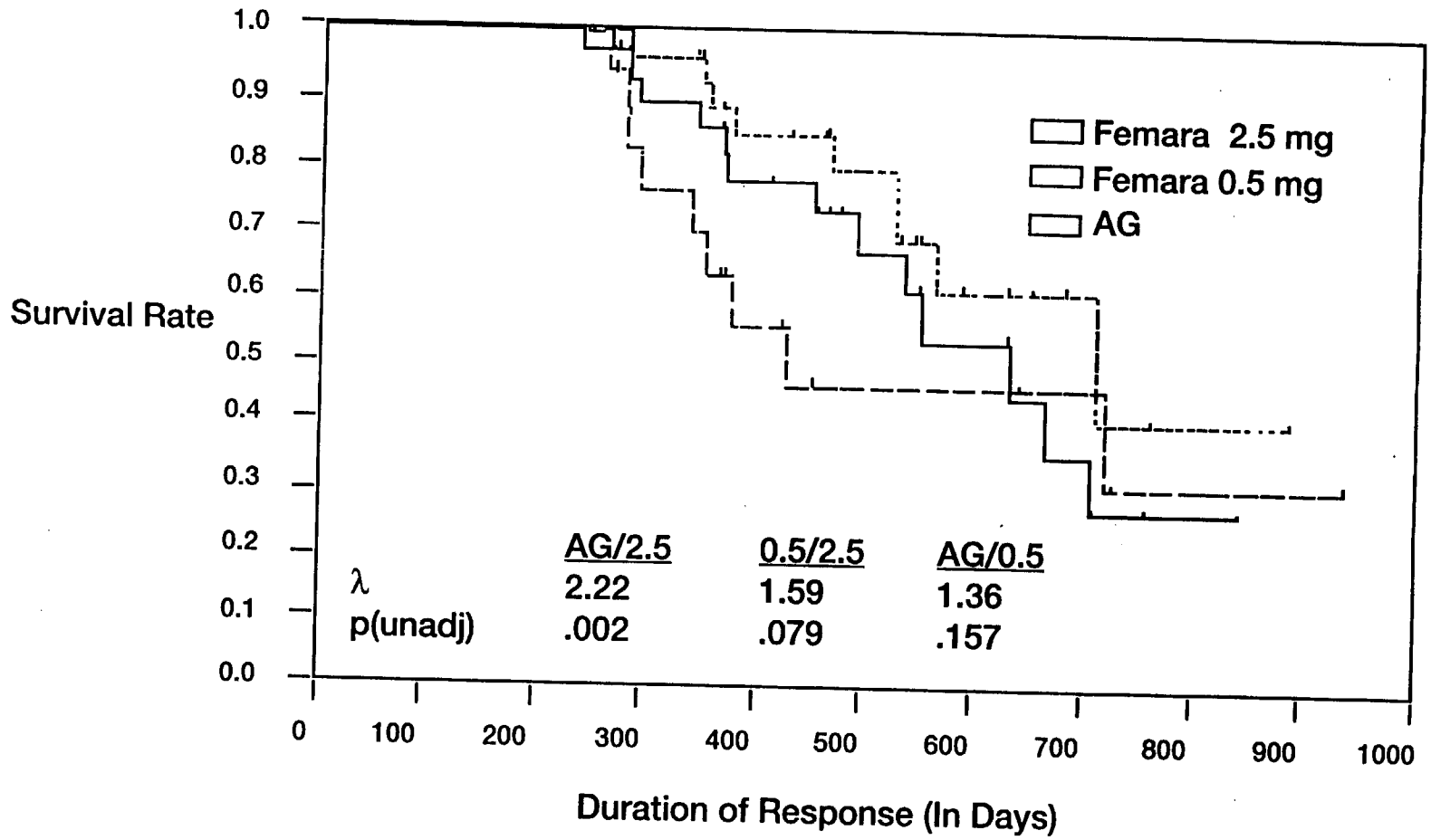
Duration of Response (AR/BC3)



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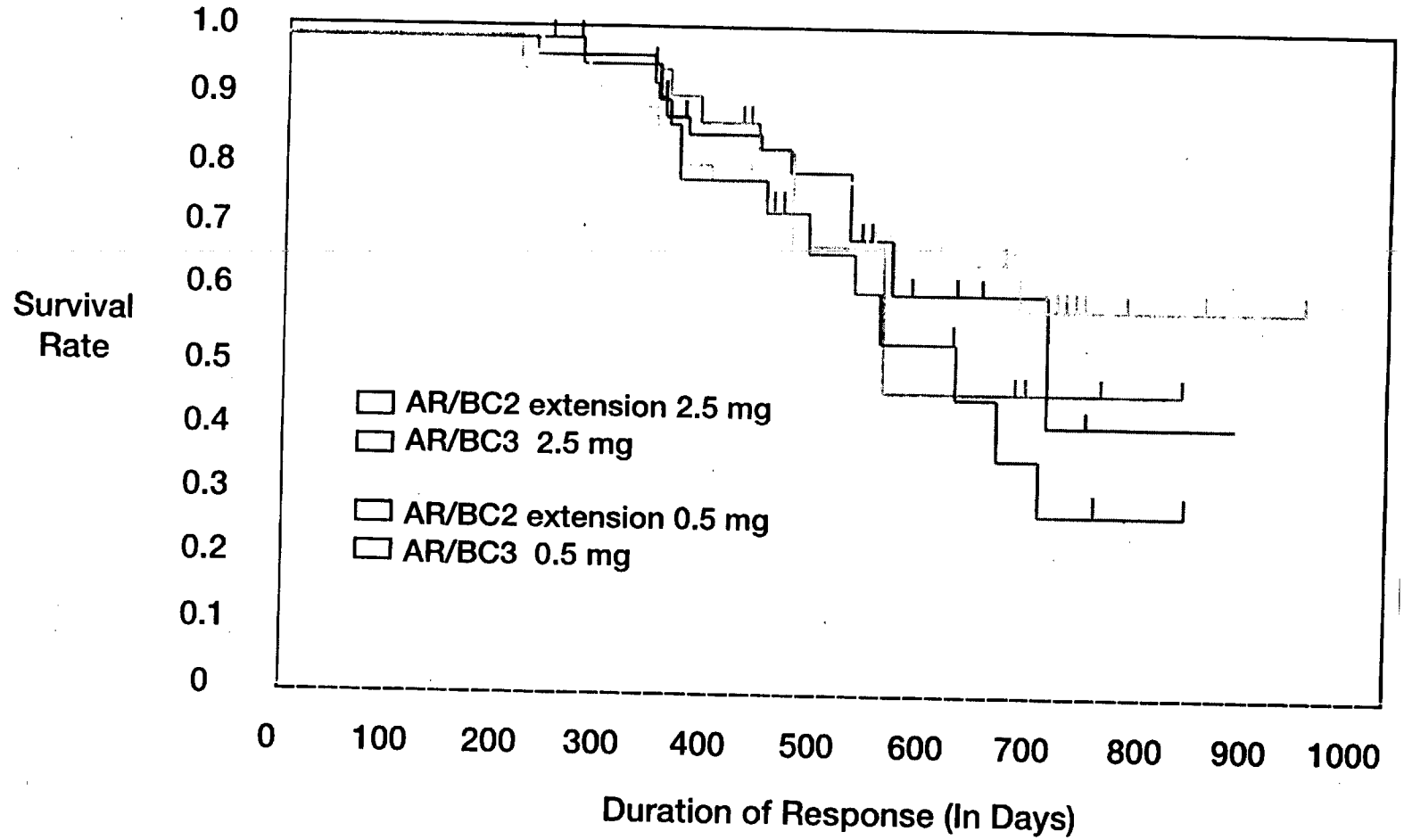
Duration of Response (AR/BC2 Extension + AR/BC3)



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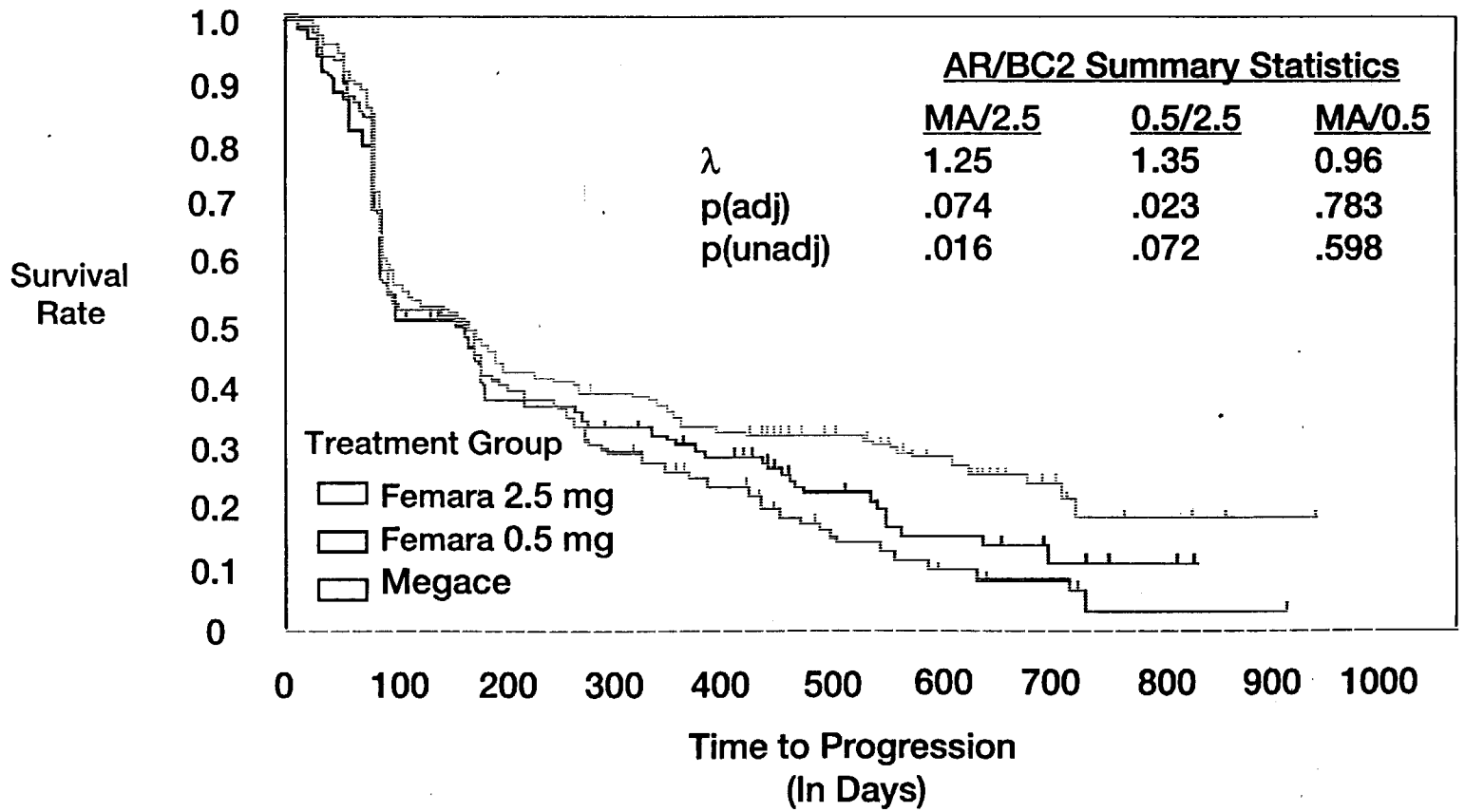
Time to Progression (AR/BC2 extension)



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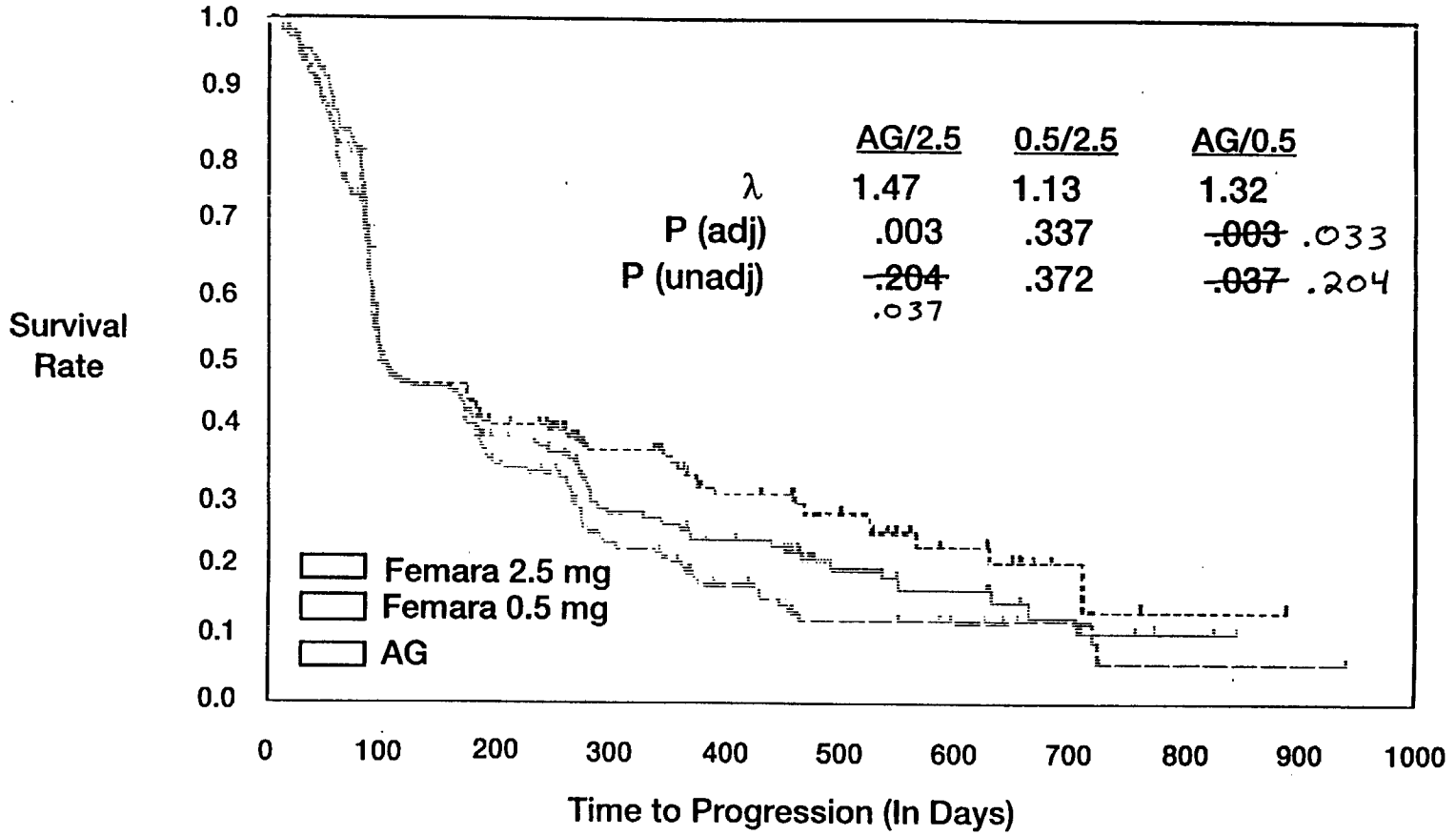
Time to Progression (AR/BC3)



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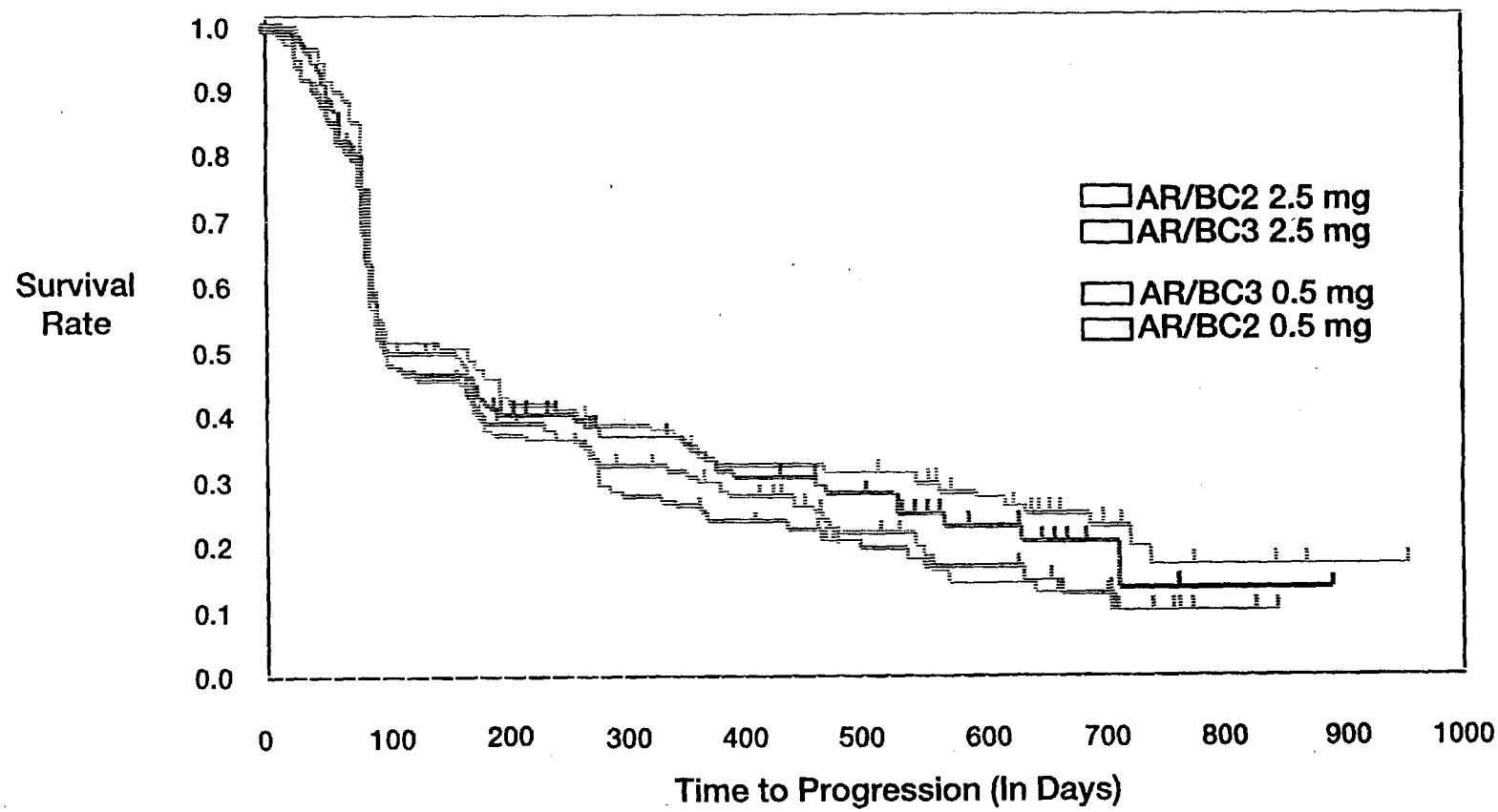
Time to Progression (AR/BC2 extension and AR/BC3)



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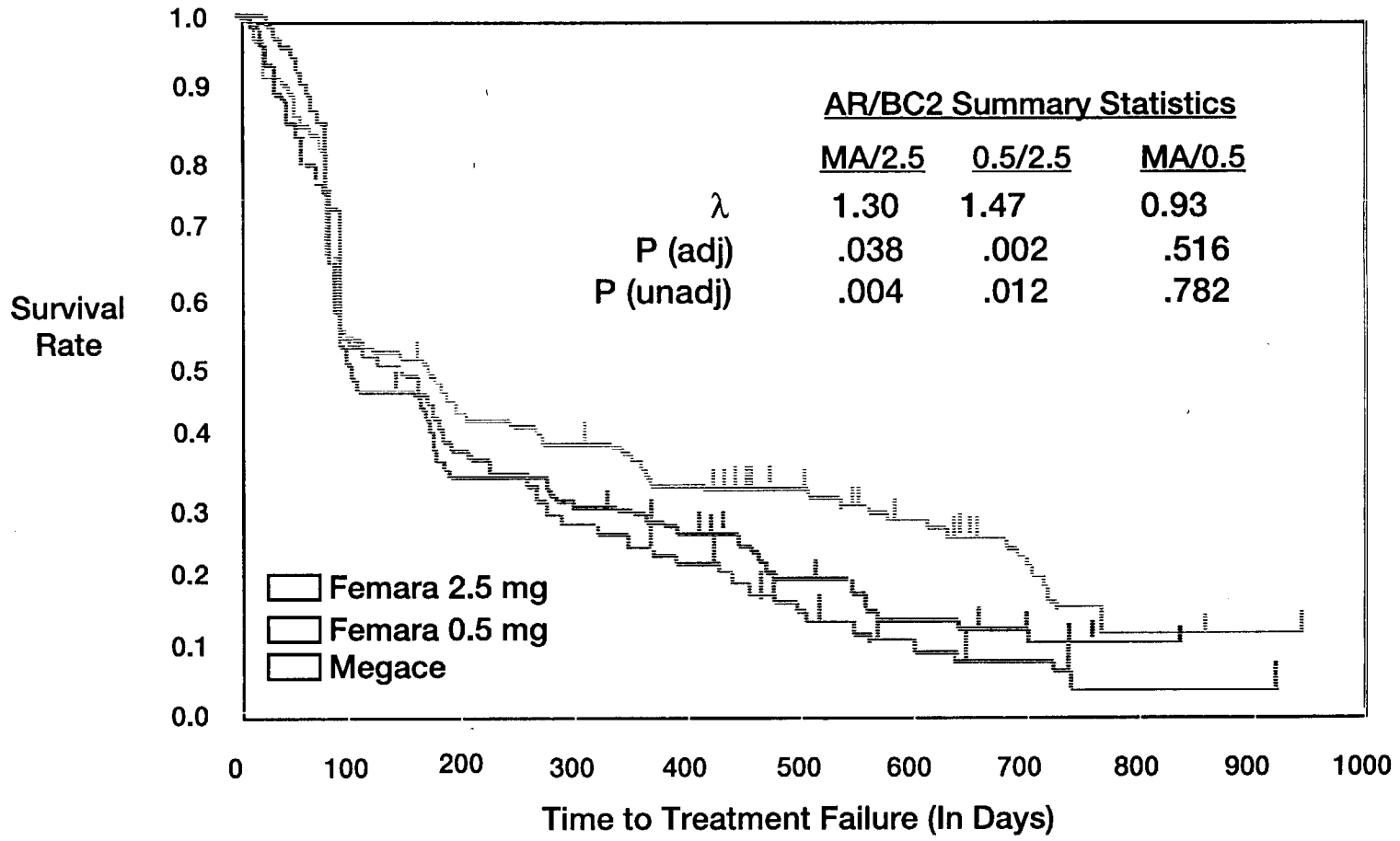
Time to Treatment Failure (AR/BC2 extension)



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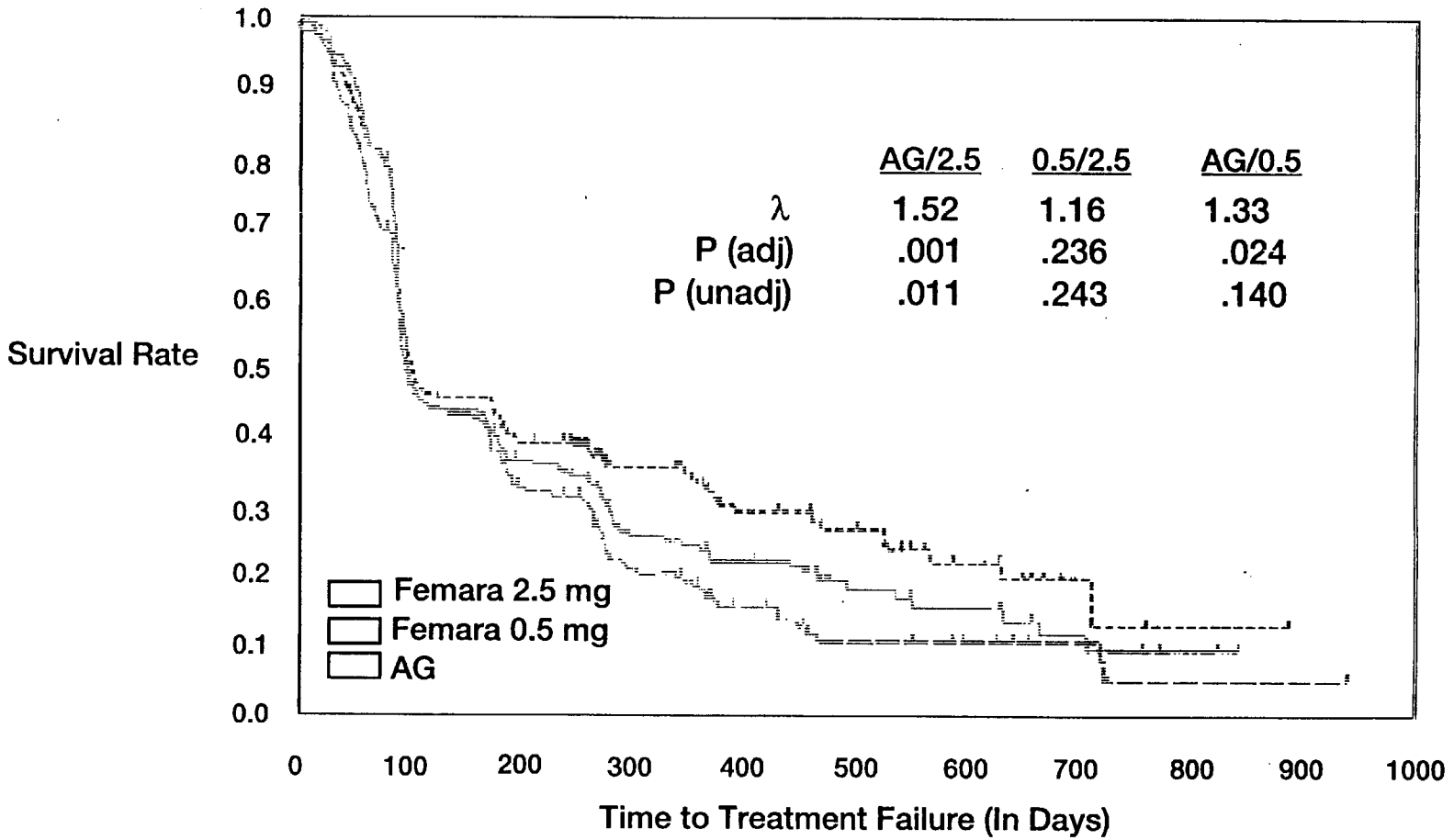
Time to Treatment Failure (AR/BC3)



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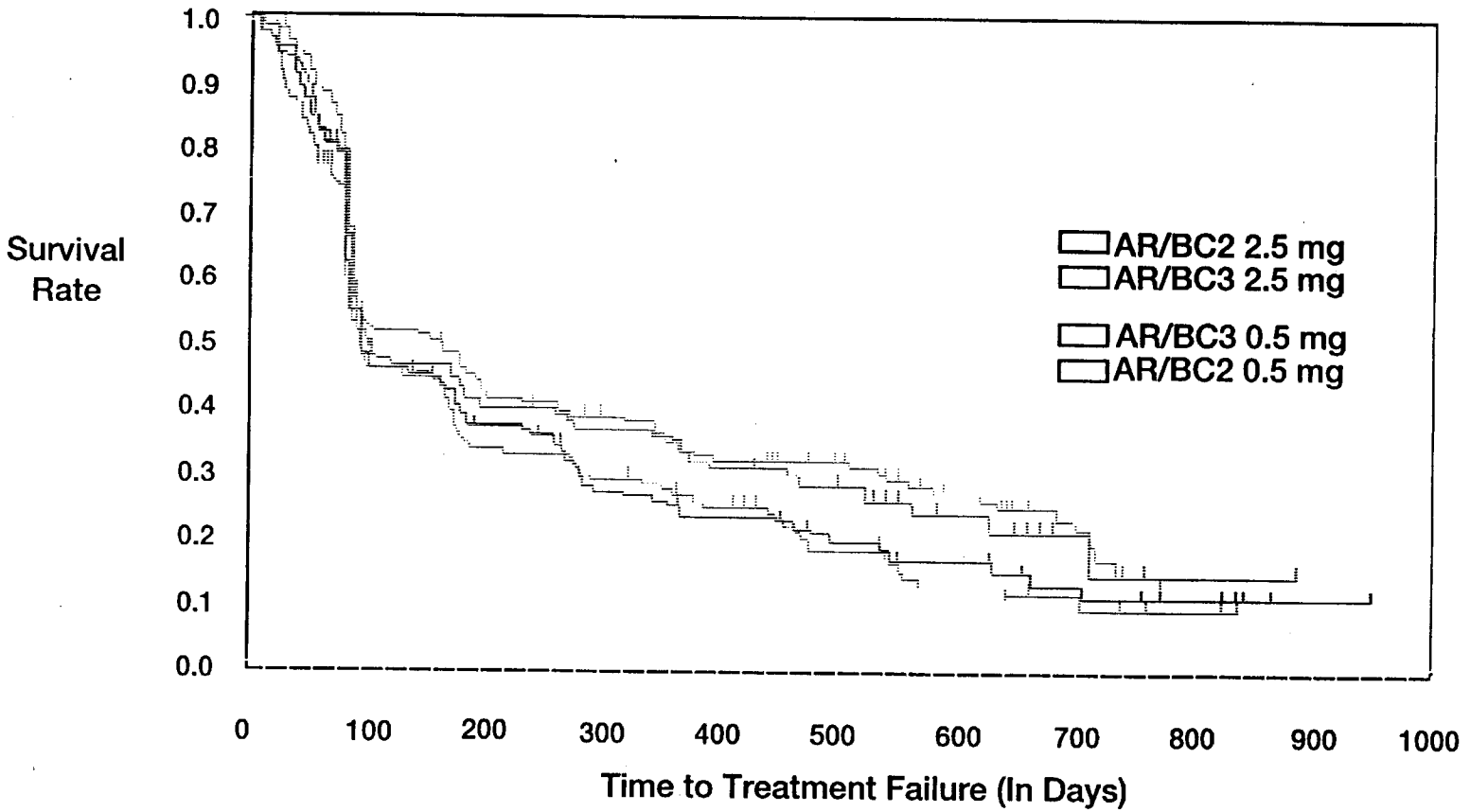
Treatment Time to Failure (AR/BC2 extension and AR/BC3)



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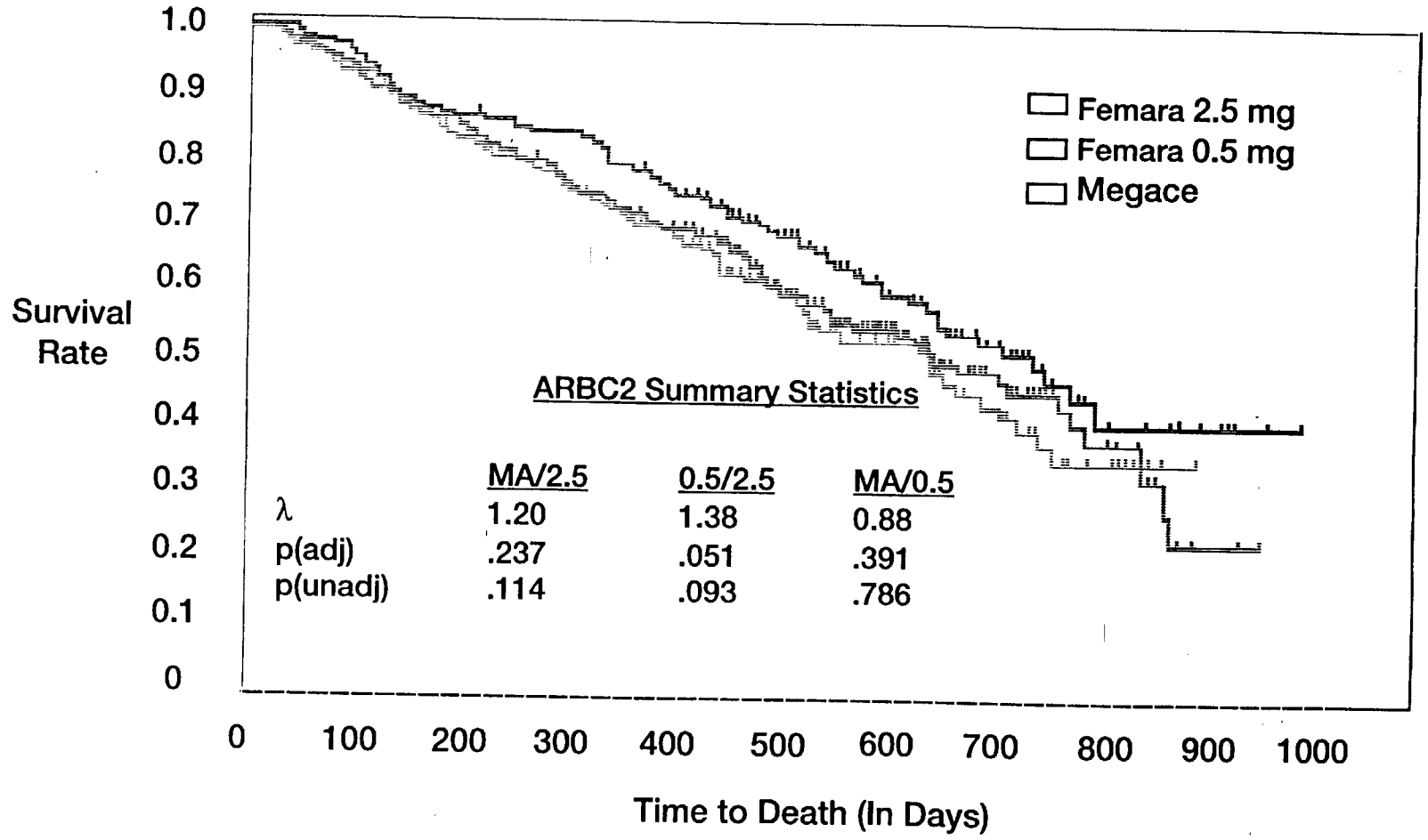
Survival (AR/BC2 extension)



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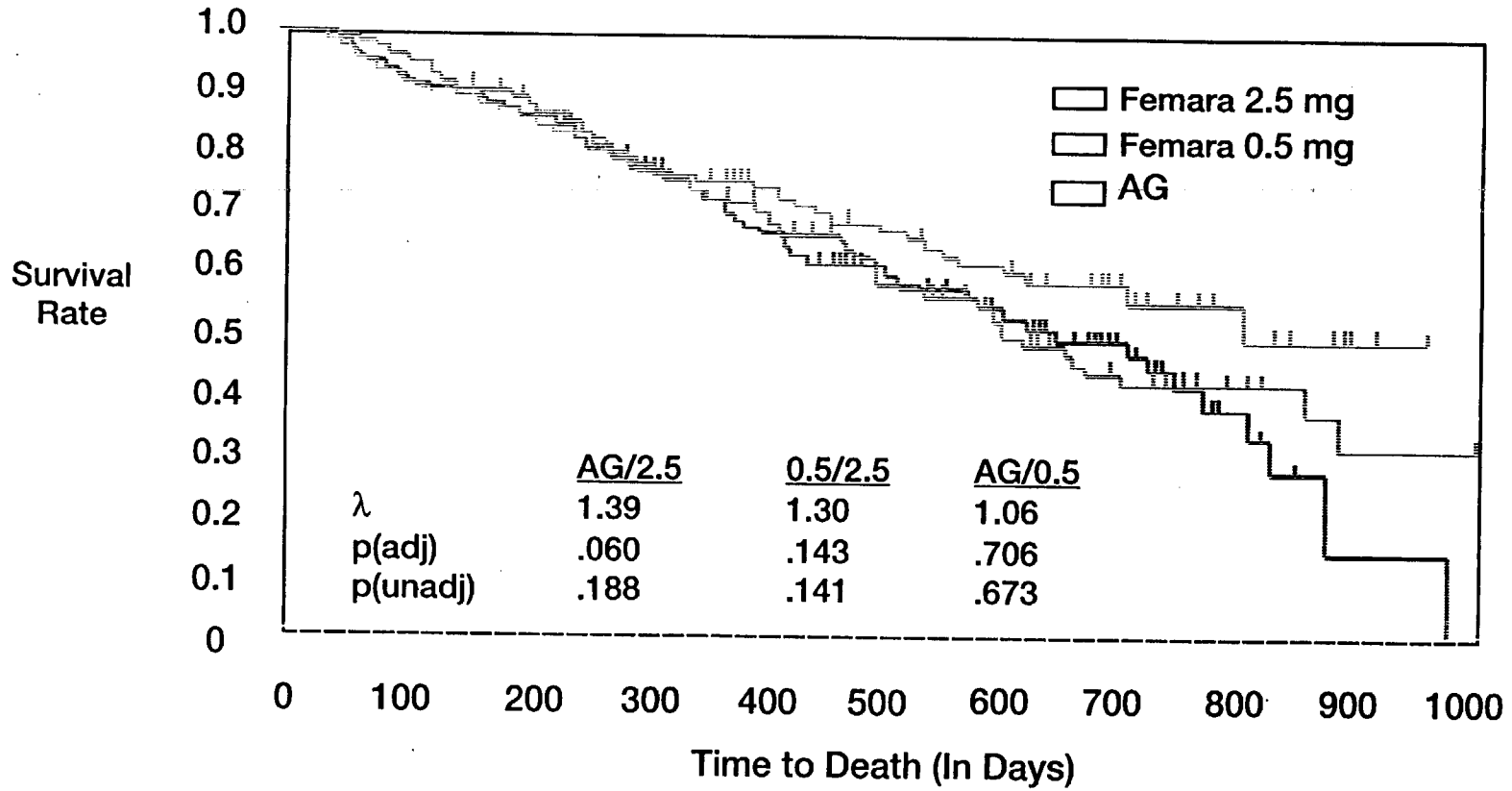
Survival (AR/BC3)



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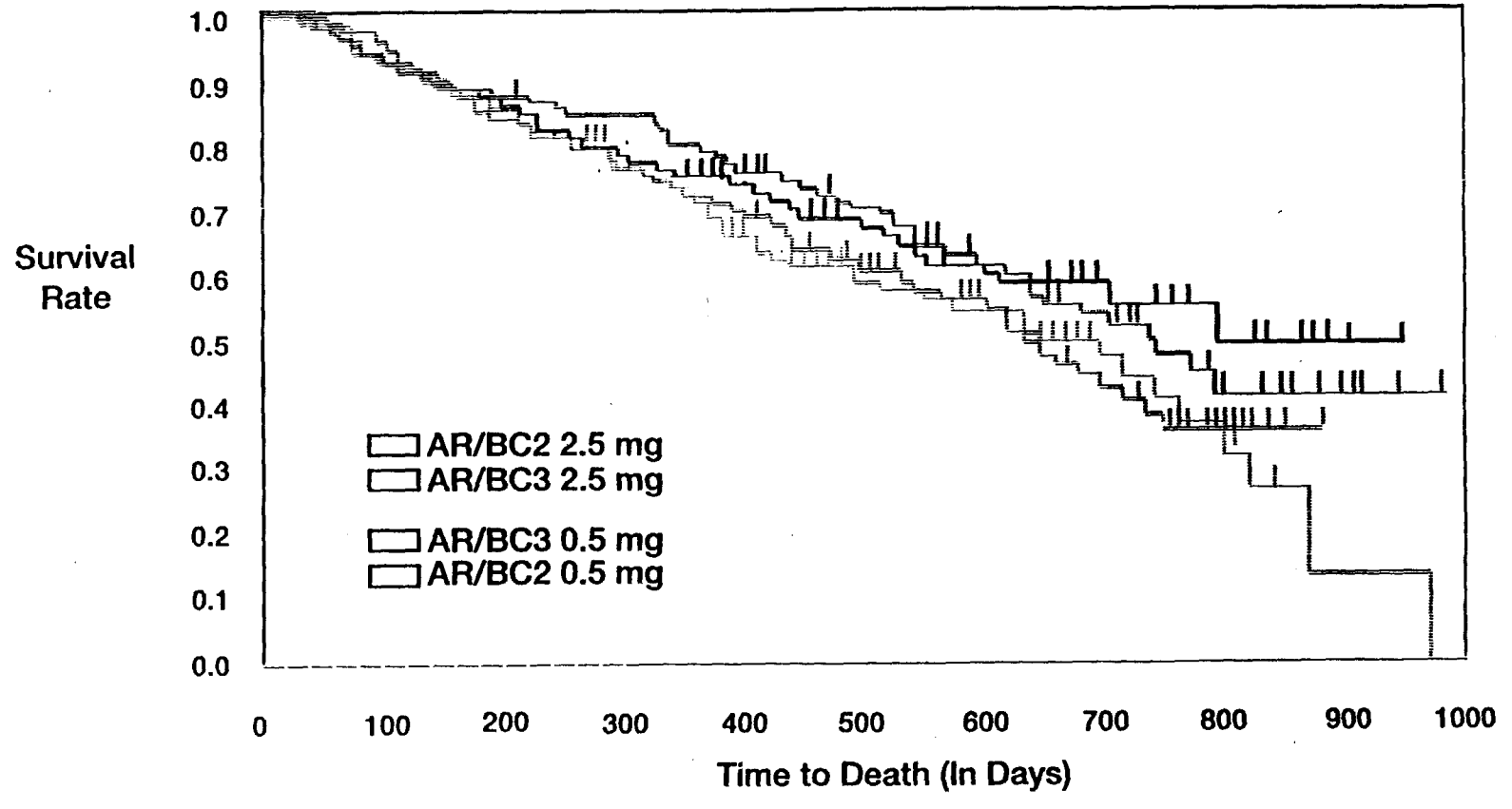
Survival (AR/BC2 extension and AR/BC3)



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Quality of Life (AR/BC2 Extension)

Endpoints:

- EORTC QLQ - C30 Questionnaire
- Pain scores
- WHO performance status

Results:

- No consistent evidence from EORTC questionnaire of significant differences between treatments
- Fewer patients on Femara 2.5 mg had deterioration of performance status than Megace (p =0.02)

Efficacy Summary

- In two adequate and well-controlled trials, Femara 2.5 mg daily was shown to be an effective hormonal therapy
- Favorable, statistically significant differences versus other hormone therapies
  - Objective response rate (MA)
  - Duration of response (MA)
  - Time to progression (AG)
  - Time to treatment failure (MA, AG)
- Superior to Femara 0.5 mg daily in AR/BC2

Reasons for Trial Discontinuation (%)

Reason	Trial AR/BC2 Extension			Trial AR/BC3		
	Femara 2.5 mg n=174	Femara 0.5 mg n=188	MA n=189	Femara 2.5 mg n=185	Femara 0.5 mg n=192	AG n=178
Adverse experience	3	5	9	3	2	5
Abnormal lab values	0	0	1	0	0	0
Death on trial	5	3	3	2	2	2
Therapy refusal	1	4	1	1	2	1
Unsatisfactory therapeutic effect	68	69	77	66	71	76
Other	3	6	2	3	3	4
Total percent	80	87	92	75	80	88

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General Safety Summary

	AR/BC2 Extension (%)			AR/BC3 (%)		
	Femara 2.5 mg n=174	Femara 0.5 mg n=188	MA n=189	Femara 2.5 mg n=185	Femara 0.5 mg n=192	AG n=178
Pts with AEs Irrespective of Drug Relationship	85	78	90	72	72	70
Pts with Drug - Related AEs	37	38	49	32	28	45
Pts with SAEs	10	15	29	15	9	11
Pts with Drug - Related SAEs	0	2	12	0	1	3
Patients Discontinued Due to AEs	3	5	9	3	2	5
Deaths on Trial or within 42 Days of Trial Discontinuation	9	9	11	11	7	11

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Adverse Experiences in ≥ 10% Patients Irrespective of Trial Drug Relationship

WHO Preferred Term	AR/BC2 Extension (%)			AR/BC3 (%)		
	Femara 2.5 mg	Femara 0.5 mg	MA	Femara 2.5 mg	Femara 0.5 mg	AG
	(%)			(%)		
Musculoskeletal Pain*	27	26	30	20	20	17
Headache	13	13	9	6	10	7
Arthralgia	13	9	8	4	7	3
Nausea	11	19	9	16	11	14
Fatigue	11	6	11	4	5	3
Dyspnea	9	11	16	5	7	5
Rash*	6	4	3	4	3	13
Hypertension	4	5	5	7	10	6

* Includes several related terms

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Femara Tolerability Comparisons to Megace (%)

AR/BC2 Extension	Femara 2.5 mg n = 174	Femara 0.5 mg n = 188	MA n = 189
Serious adverse experiences	**10**	15	**29**
Serious adverse experiences related to cardiovascular system	**2**	2	**10**
Discontinuation due to poor tolerability	**3**	5	**9**
Dyspnea	**9**	**11**	**16**
Nausea	**11**	**19**	**9**
Weight gain ≥5% from baseline	**19**	**14**	**30**

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Hematology (AR/BC2 Extension)

	Grade 3-4 (%)		
	Femara 2.5 mg	Femara 0.5 mg	MA
Anemia	0	1	1
Leukopenia	0	0	0
Granulocytopenia	0	0	0
Lymphocytopenia	8	6	2
Thrombocytopenia	0	1	0

Patients who had Grade 0 at Baseline

Other Laboratory (AR/BC2 Extension)

	Grade 3-4 (%)		
	Femara 2.5 mg	Femara 0.5 mg	MA
Creatinine	0	0	0
SGOT	0	1	1
SGPT	1	0	1
Alkaline Phos.	1	1	1
Bilirubin	4	2	5
Gamma GT	2	2	7

Patients who had Grade 0 at Baseline

Safety Summary

- Femara 2.5 mg compared to Megace had significantly
  - Fewer SAEs
  - Fewer cardiovascular events
  - Fewer discontinuations
  - Lower incidence of weight gain
- No dose-related increase in toxicity endpoints
- Femara 2.5 mg was equally well-tolerated in both pivotal trials

Overall Conclusions

- Femara is a potent and selective aromatase inhibitor
- Femara 2.5 mg:
  - Is an effective hormonal therapy as demonstrated in two pivotal trials
  - Is at least as effective as two other standard hormonal therapies
  - Is superior to Femara 0.5 mg in AR/BC2

Overall Conclusions

- Femara 2.5 mg shows:
  - Superior tolerability to MA
  - Equal tolerability to AG + corticoid supplementation
  - Equal tolerability to Femara 0.5 mg

Overall Conclusions

- Femara 2.5 mg is indicated for the treatment of advanced breast cancer in postmenopausal women with relapse or disease progression following anti-estrogen therapy

Letrozole

ODAC PRESENTATION
DECEMBER 16, 1996

NDA 20-726
Femara™ (Letrozole)

- Indication: Treatment of advanced breast cancer in women with naturally or artificially induced postmenopausal status following antiestrogen therapy

FDA Team

• Team Leader:	John Johnson, M.D.
• Project Manager:	Daine Spillman, CSO
• Statistical Reviewer:	Masa Takeuchi, Ph.D.
	Rosewitha Kelly, M.S.
• Pharmacology Reviewer:	Margo Brower, Ph.D.
• Biopharm Reveiwer:	Gene Williams, Ph.D.
• Chemistry Reviewer:	Lang Zhan, Ph.D.
	Paul Dietze, Ph.D.
• Techical Support:	Gary Gensinger, MBA
• Medical Reviewer:	Genny Schechter, M.D.

History

- IND 37443: July 29,1991
- "End of Phase II Meeting": March 11, 1994
- Pre-NDA Meeting Request: January, 1996
- NDA Submission: July 25, 1996

Comparative Trials

- AR/BC2: Pivotal Trial
  - Comparator Arm: Megestrol
- AR/BC3: Preliminary Study Report
  - Comparator Arm: Aminoglutethimide
- Protocol 02: Enrollment Completed
  - Comparator Arm: Megestrol

Pharmacokinetics

- $T_{max:}$ 1- 2 hours
- VD_{ss} 1.87 L/kg
  - Protein binding ~ 60%
- $T_{1/2B}$ ~ 2 days
- Major Metabolite:
  - 4,4'-methanolbisbenzonitrile
  - Metabolically inactive
  - Uurinary excretion

Pharmacokinetics

- AUC:
  - Greater than proportional increase with letrozole doses $\geq$ 2.5 mgs
  - Increased with hepatic impairment
- Plasma Concentration:
  - No change with increasing age
  - No change with renal impairment
- No drug-drug interactions reported

Second Line Therapies (Literature Survey)

- Megestrol, Aminoglutethimide, Anastrozole
- Response Rates: 5 - 48%
- Median Duration of Response: 7 - 15 mos.

AR/BC2:
Primary Objectives

- Objective tumor response
- Duration of tumor response
- Time to treatment failure
- Time to Progression

AR/BC2:
Secondary Objectives

- Tolerability and Toxicity of each study drug
  - Performance Status
  - Pain Control
  - Quality of Life
  - Adverse Event Profile
- Evaluation of estrone, estradiol suppression
- Plasma letrozole concentrations on study

AR/BC2: Population Demographics

- Age:
  - ~ 20% $\leq$ 55yrs
  - ~ 50% 56 - 70 yrs
  - ~ 30% > age 70
- WHO Performance Status:
  - Grade 0: 50%
  - Grade 1: 35-45%
  - Grade 2: 9-15%

Population Demographics

- Sites of Disease
  - One Site Only: 50 - 60%
    - Soft Tissue : 25 - 30%
    - Bone: ~20%
    - Visceral: 8 - 15%
  - More than one site: 35 - 46%
    - Three sites: 6 - 9%
  - None: 2%

Demographics

- Previous Hormone Therapy
  - Adjuvant only: 32 - 34%
  - Therapeutic only: 53 - 57%
  - Adjuvant and Therapeutic: 8 - 14%
- Previous Chemotherapy
  - None 59 - 69%
  - Adjuvant Chemo ~ 21%
  - Therapeutic 7.5 - 15%

Demographics

- Stage of Disease at Initial Presentation
  - Stage IV at presentation: 7 - 12%
  - DFI < 24 months: 13 - 30%
  - DFI > 24 months 58 - 63%
- Receptor Status
  - Positive 55 - 59%
  - Unknown 41 - 45%

AR/BC2
Objective Responses by Arm

- Letrozole 0.5 mg: 22/188 (11.7%)
- Letrozole 2.5 mg: 41/174 (23.6%)
- Megestrol: 31/190 (16.3%)
- $OR_{L0.5:L2.5} = 0.43$ [95% CI: 0.24, 0.76; P= 0.004*]
- $OR_{L0.5:M} = 0.68$ [95% CI: 0.38, 1.22; P=0.191*]
- $OR_{L2.5:M} = 1.57$ [95% CI: 0.93, 2.64; P=0.089*]

*unadjusted

AR/BC2:
Response Rates - Receptor Status

	Letrozole 0.5 mg	Letrozole 2.5 mg	Megestrol
Receptor Positive	6/104 (5.8%)	23/100 (23.0%)	19/112 (17.0%)
ER+, PR+	5/69 (7.2%)	16/57 (28.1%)	10/70 (14.3%)
ER or PR +	1/35 (2.9%)	7/43 (16.3%)	9/41 (22.0%)
Receptor Unknown	16/84 (19%)	18/74 (24.3%)	12/78 (15.4%)

AR/BC2:
Objective Response in Patients Treated with Previous Antiestrogen Therapy Only

[redacted]	Letrozole 0.5 (N = 114)	Letrozole 2.5 (N = 120)	Megestrol (N = 113)
Prior Adjuvant Therapy Only	4/50 (8.0%)	7/39 (17.9%)	6/39 (15.4%)
Prior Therapy - Metastatic Disease	12/57 (21.0%)	12/64 (18.8%)	17/55 (30.9%)
Both Adjuvant and Therapeutic Rx	0/7 (0.0)	0/17 (0.0)	4/19 (21.0)

AR/BC2:
Objective Response: Adjuvant Chemotherapy and Prior Antiestrogen Therapy

	Letrozole 0.5 mg (N = 41)	Letrozole 2.5 mg (N = 36)	Megestrol (N = 41)
Adjuvant AntiE2 Only	0/14 (0.0)	4/16 (25.0%)	2/17 (11.8%)
AntiE2 Rx for Advanced Disease	3/21 (14.3%)	3/16 (18.8%)	3/21 (14.3%)
Both Adjuvant & Therapeutic AntiE2	1/6 (16.7%)	0/4 (0.0)	2/3 (66.7%)

AR/BC2:
Objective Response: Chemotherapy for Advanced Disease and Prior Antiestrogens

	Letrozole 0.5 mg (N = 29)	Letrozole 2.5 mg (N = 13)	Megestrol (N = 25)
Adjuvant AntiE2 Therapy	0/1 (0.0)	0/2 (0.0)	0/4 (0.0)
AntiE2 Rx Advanced Disease	2/26 (7.7%)	3/9 (33.3%)	6/21 (28.6%)
Adjuvant and Therapeutic AntiE2	0/2 (0.0)	1 /2 (50.0%)	0/2 (0.0)

AR/BC2:
Objective Response > Three Therapies

- Letrozole 0.5 mg arm: 0/4 patients
- Letrozole 2.5 mg arm: 1/5 patients
- Megestrol arm: 1/9 patients

AR/BC2:
Objective Response to Study Drug and Antiestrogen Withdrawal Response

Treatment Arm	AntiE2 Discontinued > 60 Days before Entry (CR + PR)	AntiE2 Discontinued < 60 Days before Entry (CR + PR)
Letrozole 0.5 mg	3/16 (18.8%)	19/172 (11.0%)
Letrozole 2.5 mg	4/12 (33.0%)	37/162 (22.8%)
Megestrol	4/21 (19.0%)	27/169 (16.0%)

AR/BC2:
Response in Patients Not at Risk for AntiE2 Withdrawal

- All adjuvant only patients
- Patients who did not response (PD < 6 months, Unknowns)
- Patients who completed antiestrogen therapy > sixty days before trial enrollment

AR/BC2:
Objective Risk: Patients NOT at Risk of Antiestrogen Withdrawal Response

• Letrozole 0.5 mg:	5/99	(5.1%)
• Letrozole 2.5 mg:	17/88	(19.3%)
• Megestrol	19/97	(19.6%)

AR/BC2:
Median Duration of Response

- Letrozole 0.5 mg arm
  - Median Duration: 552 days
  - 7/22 (31.8%) progressed
- Letrozole 2.5 mg arm
  - Median Duration not reached
  - 14/41 (34.1%) progressed
- Megestrol
  - Median Duration: 561 days
  - 14/31 (45.2%) progressed

AR/BC2
Median Time to Progression

- Letrozole 0.5 mg: 154 days (93, 175)
- Letrozole 2.5 mg: 170 days (94, 200)
- Megestrol 168 days (112,183)
- $RR_{L0.5:L2.5} = 1.24$ (95% CI:0.97, 1.59), p = 0.09*
- $RR_{L2.5:M} = 0.77$ (95% CI: 0.60, 0.98), p = 0.03*
- $RR_{L0.5:M} = 0.97$ (95% CI: 0.76, 1.23), p = 0.77*

* Unadjusted

AR/BC2:
MedianTime to Progression: Patients with Previous Hormone Therapy Only

[redacted]	Letrozole 0.5 (N = 114)		Letrozole 2.5 (N = 120)		Megestrol (N = 113)	
	Adjuv. Only (N = 50)	Therap +/ - Adj (N = 64)	Adjuv Only (N = 39)	Therap. +/- Adj (N = 81)	Adjuvant Only (N = 39)	Therap. +/- Adj (N = 74)
No.Patients Progressed	24 (48%)	21 (32.8%)	21 (53.8%)	31 (38.3%)	16 (41%)	34 (45.9%)
TTP (days) 95% CI	98 (84, 171)	88 (100, 469)	102 (88,181)	193 (91,365)	182 (100,433)	167 (91,220)

AR/BC2:
Median Time to Treatment Failure

- Letrozole 0.5 mg 91 days
- Letrozole 2.5 mg 102 days
- Megestrol 120 days
- $RR_{L0.5:L2.5} = 1.41$ [95% CI: 0.83, 1.57; P = 0.003*]
- $RR_{L2.5:M} = 0.72$ [95% CI: 0.58, 0.91; P = 0.004*]
- $RR_{L0.5:M} = 1.03$ [95% CI: 0.83, 1.27; P = 0.78*]

*unadjusted

AR/BC2:
Median Survival by Treatment Arm

- Letrozole 2.5 mg 740 days (642, +)
- Megestrol 659 days (515, 775)
- Letrozole 0.5 mg 645 days (544, 734)
- $RR_{L0.5;L2.5} = 1.26$ [95% CI: 0.93, 1.72; P = 0.13]
- $RR_{L2.5:M} = 0.78$ [95% CI: 0.67, 1.06; P = 0.11]
- $RR_{L0.5:M} = 0.99$ [95% CI: 0.74, 1.33; P = 0.96]

(unadjusted p values)

AR/BC2:
Secondary Endpoints

- Performance Status
- Pain Severity
- Quality of Life Data
- Pharmacokinetic Data
- Estrogen Suppression

AR/BC2: Performance Status

- Baseline performance status was better in completers than in dropouts in all arms
- In the letrozole arms in completers the performance status was stable regardless of response
- In the megestrol arm in completers the performance status declines with more decline in the nonresponder

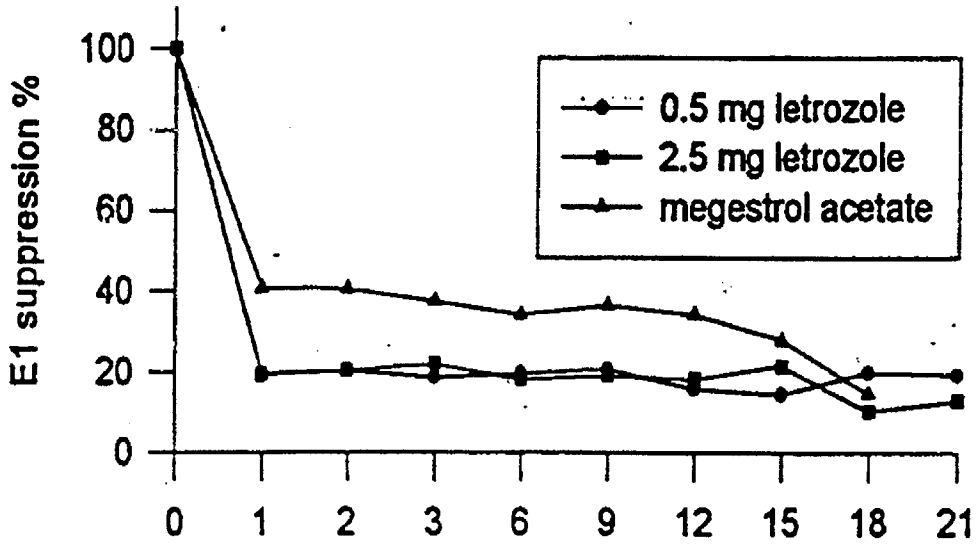
AR/BC2:
Pain Severity

- 40% - 50% of patients had no pain
- Baseline pain scoring on EORTC was lower for completers than dropouts
- On the letrozole arms for completers the pain scores were constant over the nine months of followup regardless of therapeutic response
- Dropouts-Improvement in pain scores over time in all arms

AR/BC2:
Pain Severity

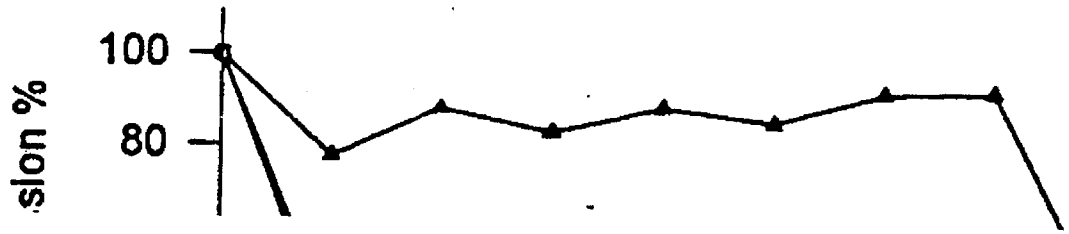
- Megestrol: Significant improvement in pain scores in responders and nonresponders
- The pain scores improved over time on all three arms for the dropouts

AR/BC2:
Estrone Suppression by Arm



- Time in months
- Not detected in ~ 40% after one month on study

AR/BC2:
Estradiol Suppression



- Time in months
- Not detectable in 15% after one month on study

Pharmacokinetic Data AR/BC2

- Letrozole 0.5 mg
  - Mean Plasma Trough Concentration$_{\text{steady state}}$: 45 nmol/L
- Letrozole 2.5 mg
  - Mean Plasma Trough Concentration$_{\text{steady state}}$: 360 nmol/L

AR/BC2: Safety Review

- One death on the megestrol arm due to PTE
- Serious Adverse Events
  - More SAEs on the megestrol arm; more treatment related SAEs
  - More study discontinuation due to treatment related AE on the megestrol arm
  - More SAEs on the letrozole 0.5 mg arm than on the letrozole 2.5 mg arm

AR/BC2: Safety Review

- Significantly increased incidence of thromboembolic events on the megestrol arm ($p = 0.045$)
- Significantly increased incidence of vaginal bleeding related to study drug ($p = 0.03$)
- Increased Grade III/IV nausea and vomiting on the letrozole arm (not significant)

AR/BC2:
Common Adverse Events by Study Arm

[redacted]	Letrozole 0.5 mg	Letrozole 2.5 mg	Megestrol
Nausea	11.2%	6.3%	4.2%
Vomiting	3.2%	2.9%	1.6%
Weight Increase	2.1%	2.1%	7.9%
Peripheral Edema	2.7%	6.3%	3.7%
Increased Appetite	0.0	1.1%	3.7%
Hot Flushes	4.3%	5.2%	3.7%
Fatigue	3.2%	5.2%	3.7%
Dyspnea	1.6%	0.6%	3.7%
Alopecia	2.1%	3.4%	1.1%
Constipation	3.2%	1.7%	2.1%
Headache	6.4%	6.3%	4.8%
Hypertension	3.2%	0.0	2.6%

AR/BC2: Safety Review

- Age: hot flushes, nausea, alopecia < age 70; none over age 70
- Serious cumulative toxicity: none
- Grade III/IV Gamma-GT Elevation:
  - Letrozole 0.5: 0.5%
  - Letrozole 2.5: 1.1%
  - Megestrol: 5.7%

AR/BC3: Trial Design

- Open label
- Protocol similar to AR/BC2
- Enrollment:
  - Letrozole 0.5 mg Arm: 192
  - Letrozole 2.5 mg Arm: 185
  - Aminoglutethimide: 178

AR/BC3:
Objective Response

- Letrozole 0.5 mg: 16.7%
- Letrozole 2.5 mg: 17.8%
- Aminoglutethimide: 11.2%
- Odds Ratio$_{L0.5:L2.5}$ = 0.92 [95% CI: 0.54, 1.57; P = 0.76*]
- Odds Ratio$_{L0.5:A}$ = 1.58 [95% CI: 0.87, 2.88; P = 0.14*]
- Odds Ratio$_{L2.5:A}$ = 1.72 [95% CI: 0.94, 3.12; P = 0.08*]

*Unadjusted

AR/BC3:
Duration of Response

- Letrozole 0.5 mg - 628 days
- Letrozole 2.5 mg - 707 days
- Aminoglutethemide - 427 days

- No significant differance between arms

AR/BC3:
Median Time To Progression

- Letrozole 0.5 mg - 104 days
- Letrozole 2.5 mg - 104 days
- Aminoglutethimide - 102 days
- $RR_{L0.5:L2.5} = 1.12$ [95% CI: 0.88, 1.42; P = 0.37*]
- $RR_{L0.5:A} = 0.86$ [95% CI: 0.68, 1.09; P = 0.20*]
- $RR_{L2.5:A} = 0.77$ [95% CI: 0.60, 0.98; P = 0.04*]

*unadjusted

AR/BC3:
Deaths; Median Time to Death

- Letrozole 2.5 mg
  - Deaths: 63/185 (34.0%)
  - Median Time to Death: 793 days
- Aminoglutethimide
  - Deaths: 76/178
  - Median Time to Death: 593 days
- Letrozole 0.5 mg
  - Deaths: 79/172 (41.1%)
  - Median Time to Death: 637 days

AR/BC3: Survival

- $RR_{L0.5:L2.5}$ = 1.28
  - [95% CI: 0.92, 1.79]
  - P = 0.14 *
- $RR_{L0.5:A}$ = 1.07
  - [95% CI: 0.78, 1.47]
  - P = 0.67*
- $RR_{L2.5:A}$ = 0.80
  - [95% CI: 0.57, 1.12]
  - P =0.10*

*unadjusted

AR/BC3:
Treatment Related AEs

	Letrozole 0.5	Letrozole 2.5 mg	Aminoglutethimide
Nausea	13.5%	15.7%	19.7%
Fatigue	5.0%	6.0%	2.8%
Rash	0.5%	3.2%	8.4%
Somnolence	2.6%	3.2%	7.3%

Summary:
Objective Responses

	AR/BC2		AR/BC3	
Objective Response				
Letrozole 0.5 mg	11.7%		16.7%	
Letrozole 2.5 mg	23.6%		17.8%	
Comparator	16.3%		11.2%	
Odds Ratios				
L0.5: L2.5	0.43	(p=0.004)	0.92	(p=0.76)
L0.5: Comparator	0.68	(p=0.191)	1.58	(p=0.14)
L2.5: Comparator	1.57	(p=0.089)	1.72	(p=0.08)

Summary:
Median Time to Progression

	AR/BC2	AR/BC3
Median Time to Progression		
Letrozole 0.5 mg	154 days	104 days
Letrozole 2.5 mg	170 days	104 days
Comparator	168 days	102 days
Relative Risk		
L0.5:L2.5	1.24 (p=0.09)	1.12 (p= 0.37)
L0.5: Comparator	0.97 (p=0.03)	0.86 (p= 0.20)
L2.5: Comparator	0.77 (p=0.77)	0.77 (p= 0.04)

Summary:
Median Time to Treatment Failure

	AR/BC2	AR/BC3
Median TTF		
Letrozole 0.5 mg	91 days	100 days
Letrozole 2.5 mg	102 days	127 days
Comparator	120 days	150 days
Relative Risk:		
L0.5: L2.5	1.41 (p=0.003)	1.1 (p=0.24)
L0.5: Comparator	0.72 (p=0.004)	0.84 (p=0.14)
L2.5: Comparator	1.30 (p=0.78)	0.73 (p=0.011)

Summary:
Survival Information

	AR/BC2	AR/BC3
Median Time to Death		
Letrozole 0.5 mg	633 days	637 days
Letrozole 2.5 mg	740 days	793 days
Comparator	659 days	593 days
Risk Ratio		
L0.5: L2.5	1.26 (p= 0.13)	1.28 (p=0.14)
L0.5: Comparator	0.78 (p=0.11)	1.07 (p=0.67)
L2.5: Comparator	0.99 (p=0.96)	1.12 (p=0.10)

Summary:
AE Profile: Letrozole 2.5 mg

	AR/BC2	AR/BC3
Nausea	6.3%	10.3%
Fatigue	5.2%	3.2%
Vomiting	2.9%	
Rash	2.9%	2.2%
Somnolence	0.6 %	3.2%
Headache	6.3%	
Peripheral edema	1.7%	
Alopecia	3.4%	

NDA 20-726
FEMARA™ (LETROZOLE)

- Proposed Indication: treatment of postmenopausal women with receptor positive or unknown advanced breast cancer which has progressed on / after antiestrogen therapy

AR/BC2:
Objective Response and Antiestrogen Withdrawal

	Not at Risk	At Risk
Letrozole 0.5	7/99 (7.1%)	15/89 (16.9%)
Letrozole 2.5	17/88 (19.5%)	24/86 (27.9%)
Megestrol	19/99 (19.2%)	12/91 (13.2%)