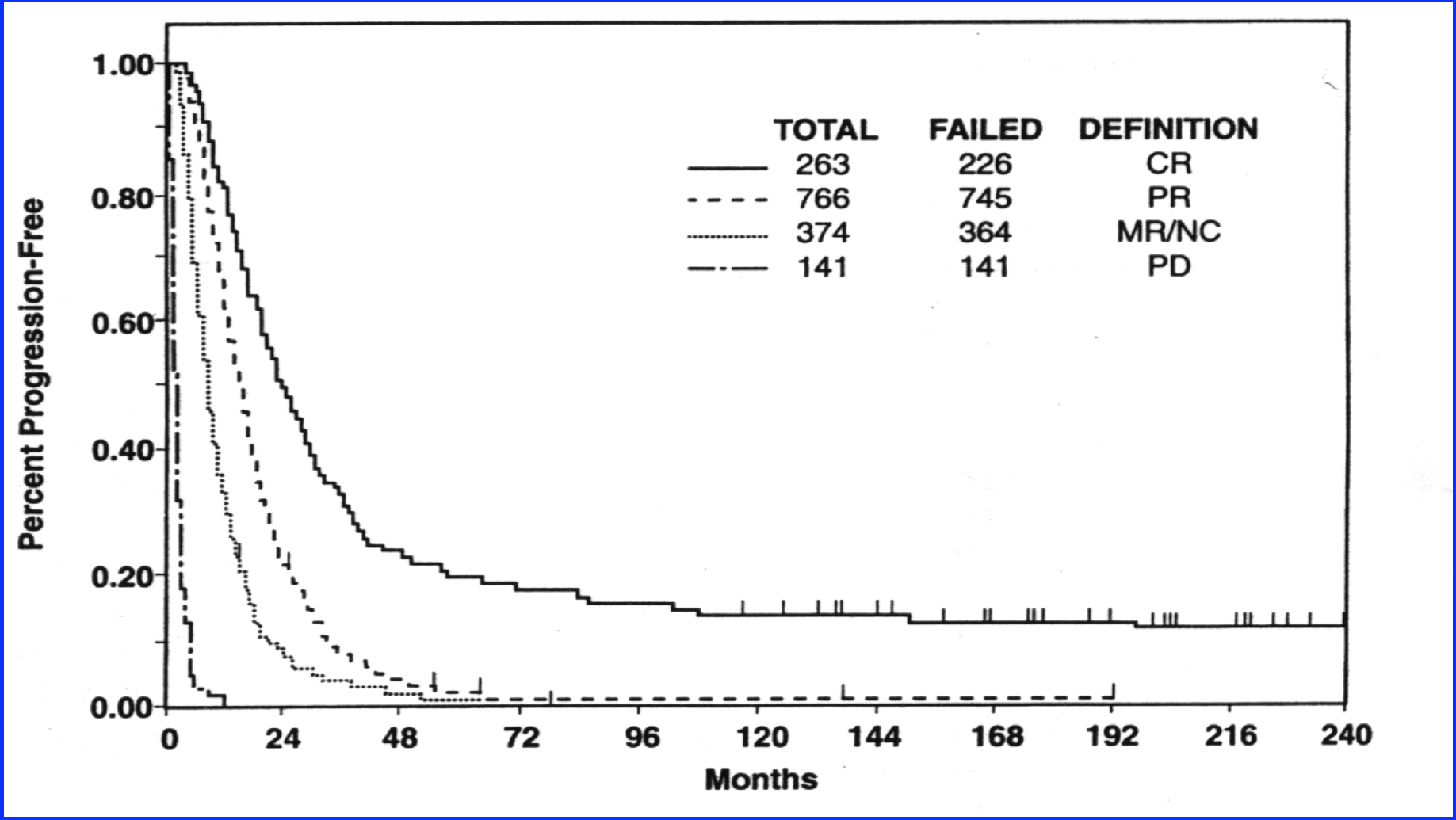
Treatment of Metastatic Breast Cancer: Endocrine Therapies

Robert W. Carlson, M.D.
Professor of Medicine
Stanford University

MDACC Experience with FAC in Chemotherapy-Naive MBC



Greenberg et al, J Clin Oncol 1996

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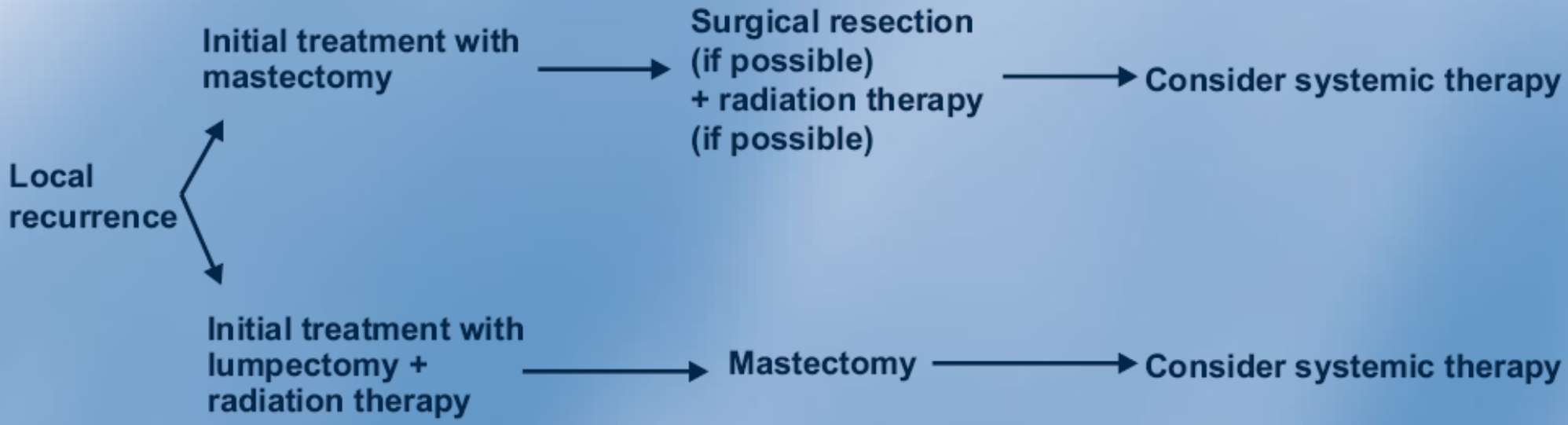
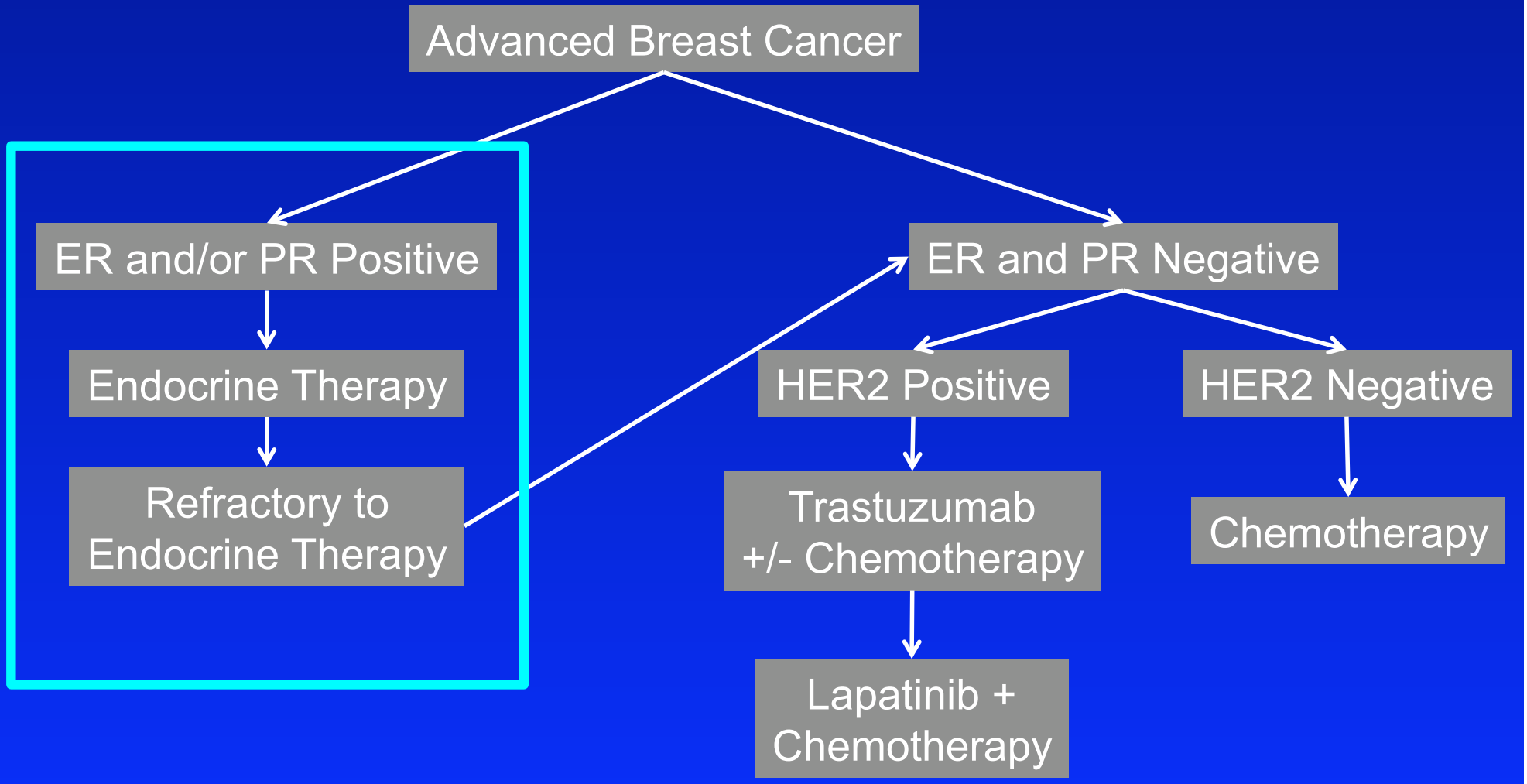
TREATMENT OF RECURRENCE/STAGE IV DISEASE



BINV-16

Biological Approach to Advanced Breast Cancer



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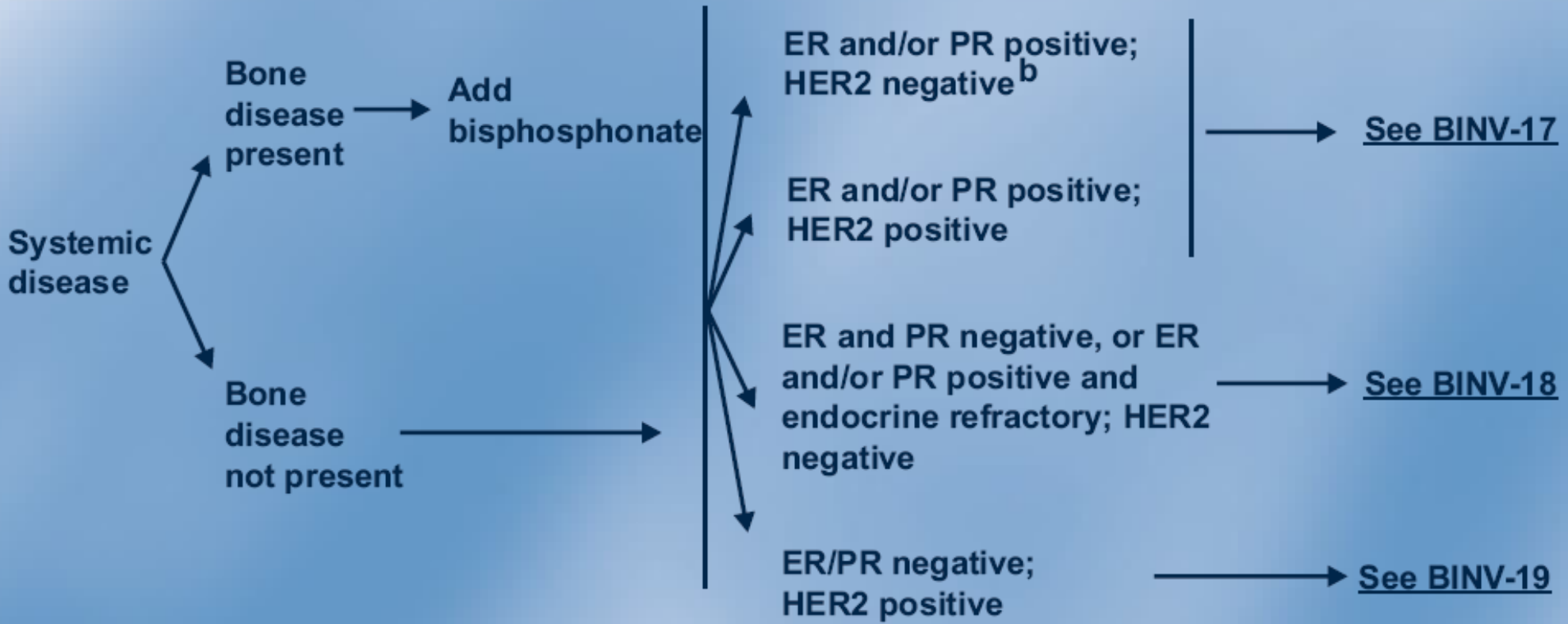

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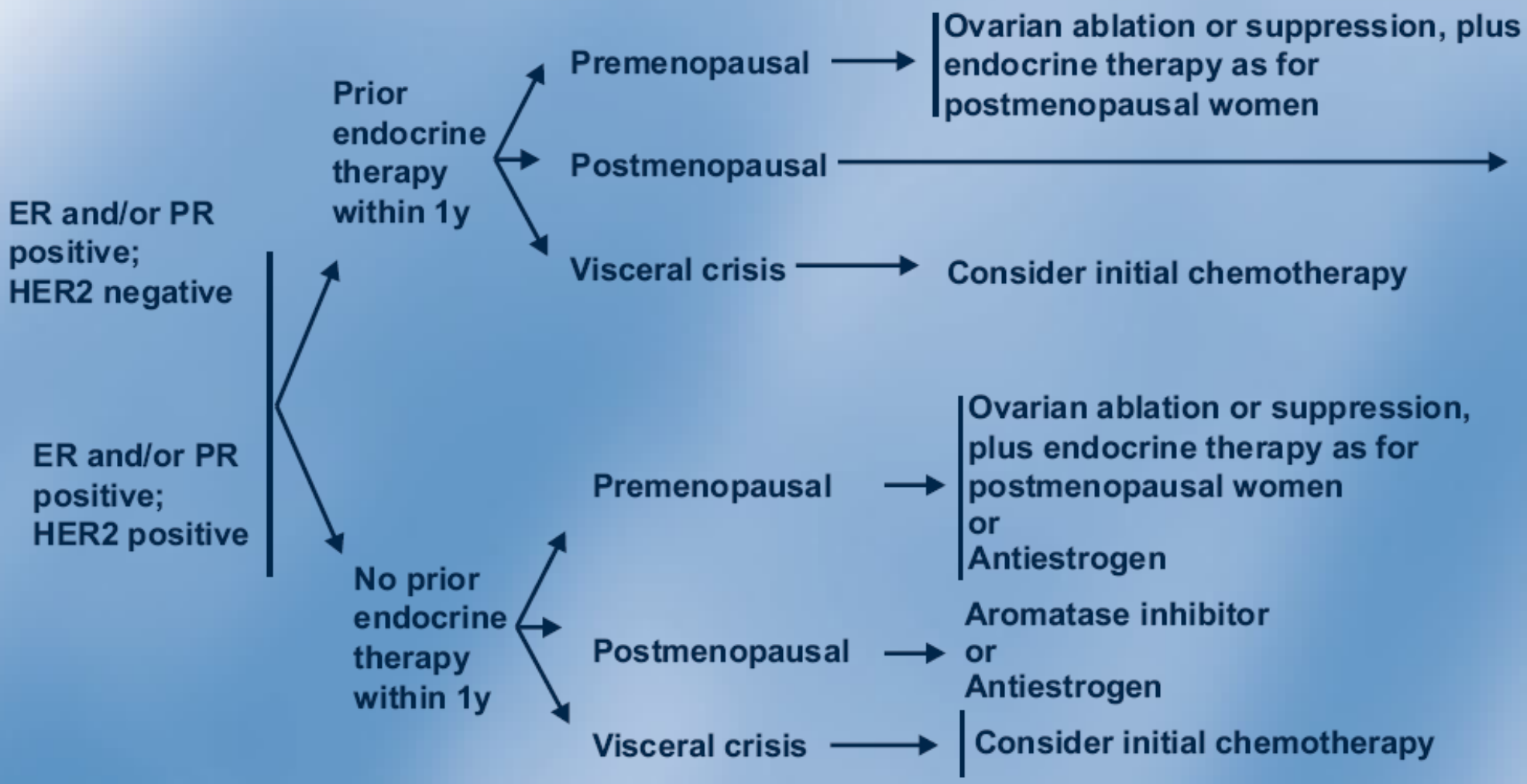
TREATMENT OF RECURRENCE/STAGE IV DISEASE

ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE



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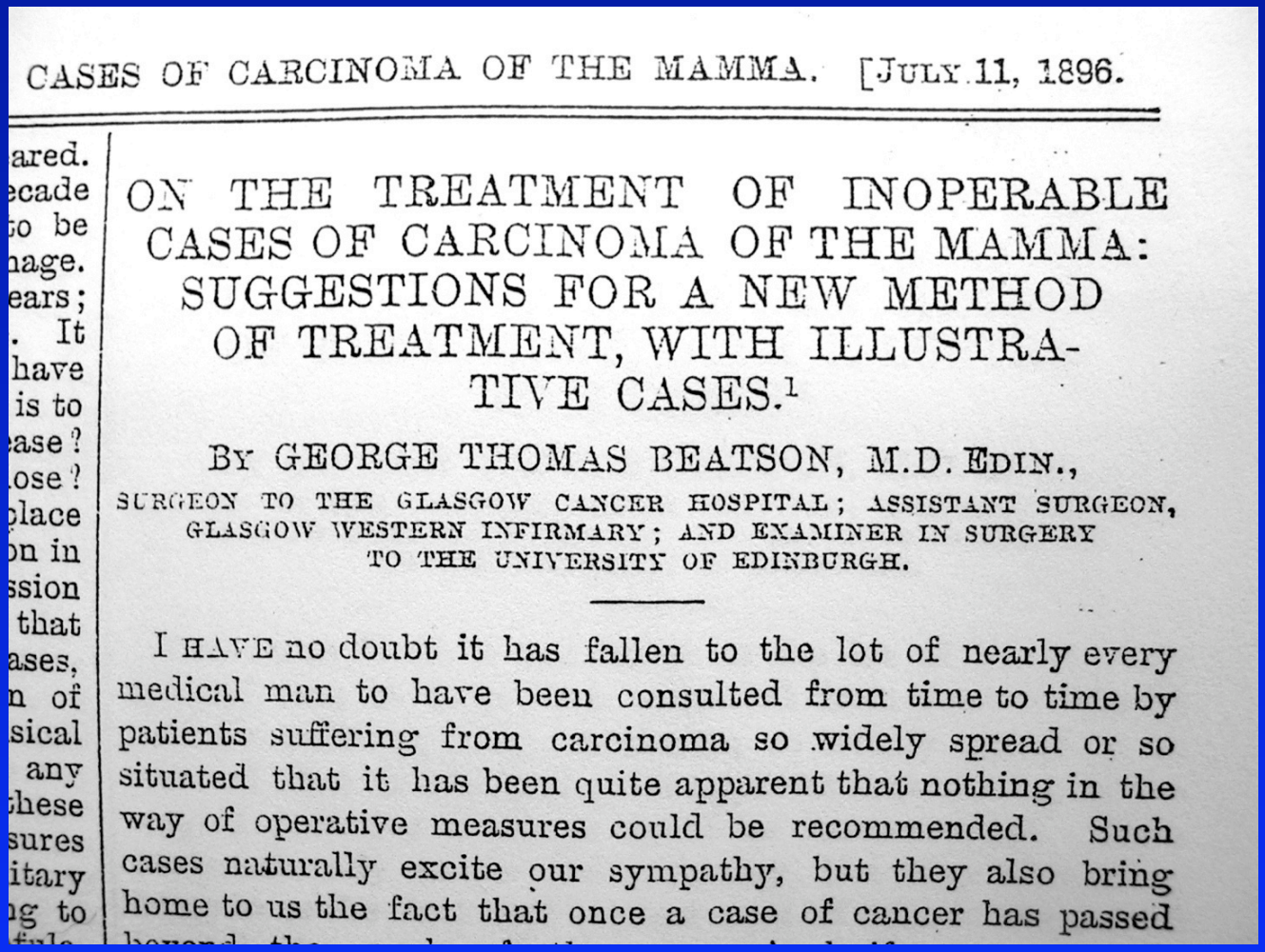
Endocrine Therapy of Breast Cancer



CASES OF CARCINOMA OF THE MAMMA. [JULY 11, 1896.

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ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.[1]

BY GEORGE THOMAS BEATSON, M.D. EDIN.,
SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.

I HAVE no doubt it has fallen to the lot of nearly every medical man to have been consulted from time to time by patients suffering from carcinoma so widely spread or so situated that it has been quite apparent that nothing in the way of operative measures could be recommended. Such cases naturally excite our sympathy, but they also bring home to us the fact that once a case of cancer has passed

Metastatic Breast Cancer Hormone Responsiveness

Receptor Status	Likelihood of Tumor Response
ER+, PR+	50-75%
ER+, PR-	20-30%
ER-, PR+	30-50%
ER-, PR-	<10%

ER = Estrogen receptor
PR = Progesterone receptor

Endocrine Therapies for Breast Cancer

Menopausal Status

	Pre	Post
Ovarian ablation	X	
LHRH agonists		X
Aromatase inhibitors/inactivators	X	
Progestins		
Androgens		
ER Down-regulators	?	

Others: antiprogestins, antiandrogens, somatostatins, glucocorticoids, estrogens.

X=Not Applicable

Meta-analysis if LH-RH Agonists +/- Tamoxifen in Metastatic Breast Cancer

- Four studies included
- Total of 506 premenopausal subjects
- Based on individual patient data

Kiljn,2001

Results
LHRH + T v LHRH

	LHRH + T	LHRH	P-value
Objective response	39%	30%	0.03
Duration of response	602 days	350 days	

Kiljn,2001

Results
LHRH + T v LHRH

	HR (95% CI)	P-value
Survival	0.78 (0.63-0.96)	0.02
Progression-free survival	0.70 (0.58-0.85)	0.0003

Kiljn,2001

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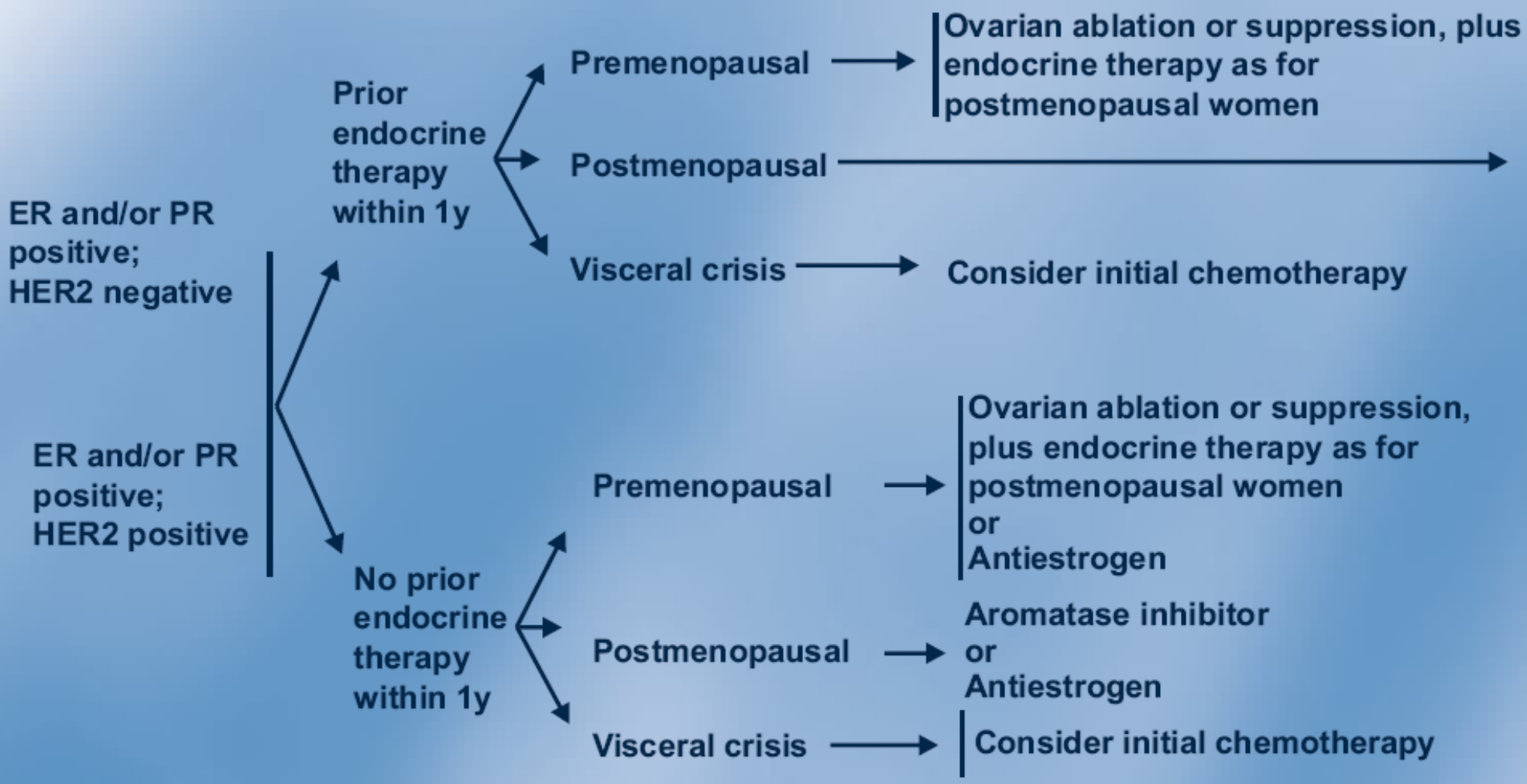

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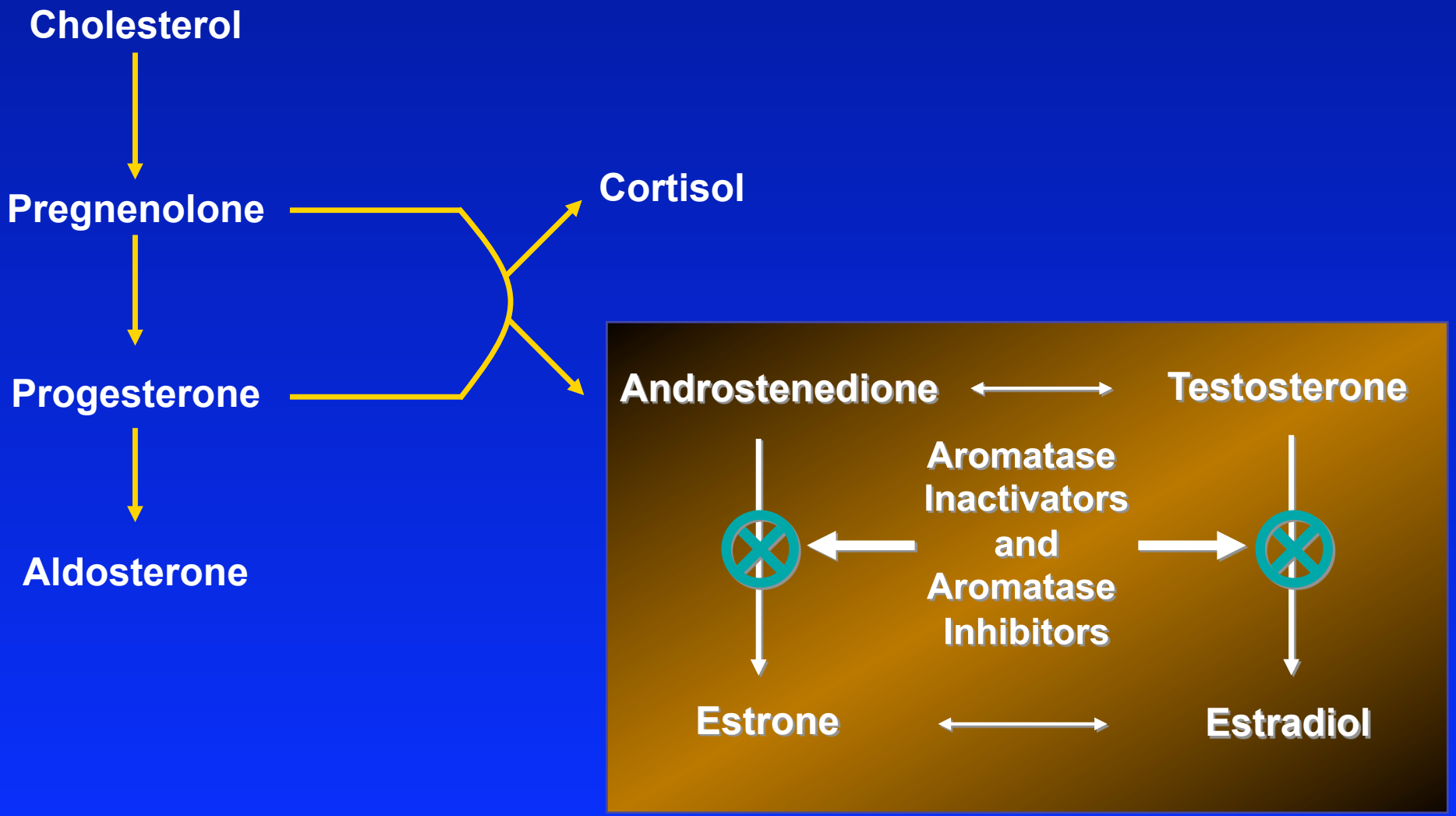
Aromatase Inhibitors: Mechanism of Action

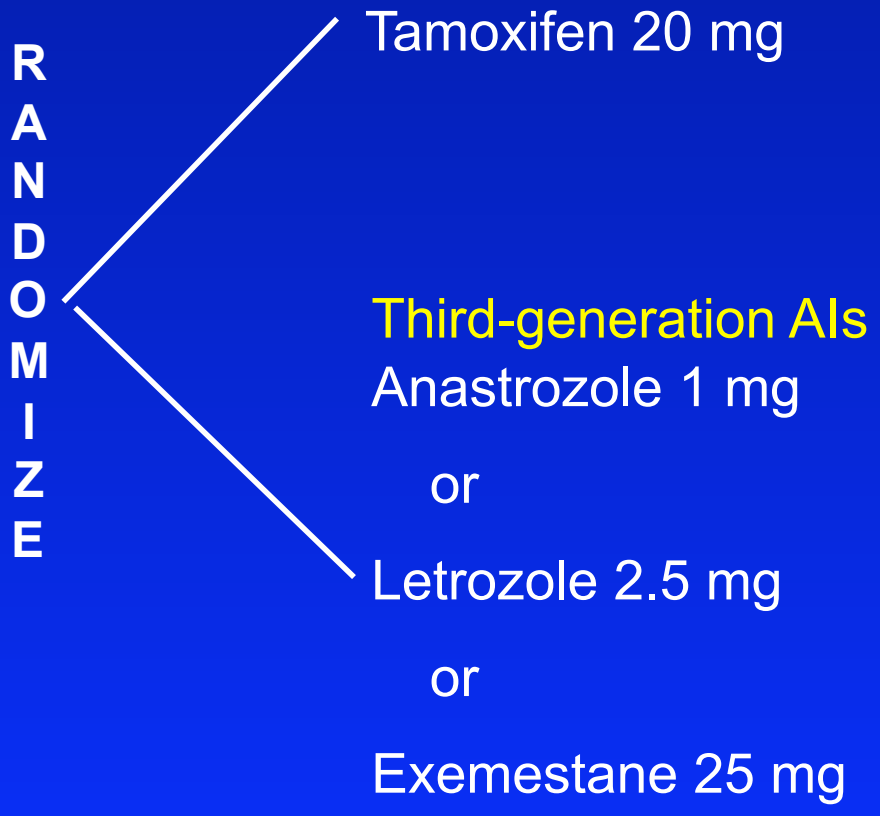


Aromatase Inhibitors*: Characteristics

Agent	Selective	Competitive	Steroidal
Aminoglutethimide (Cytadren®)	No	Yes	No
Anastrozole (Arimidex®)	Yes	Yes	No
Letrozole	Yes	Yes	No (Femara®)
Exemestane	Yes	No	Yes (Aromasin®)

*Available in the United States.

Third-Generation AIs in First-Line Studies



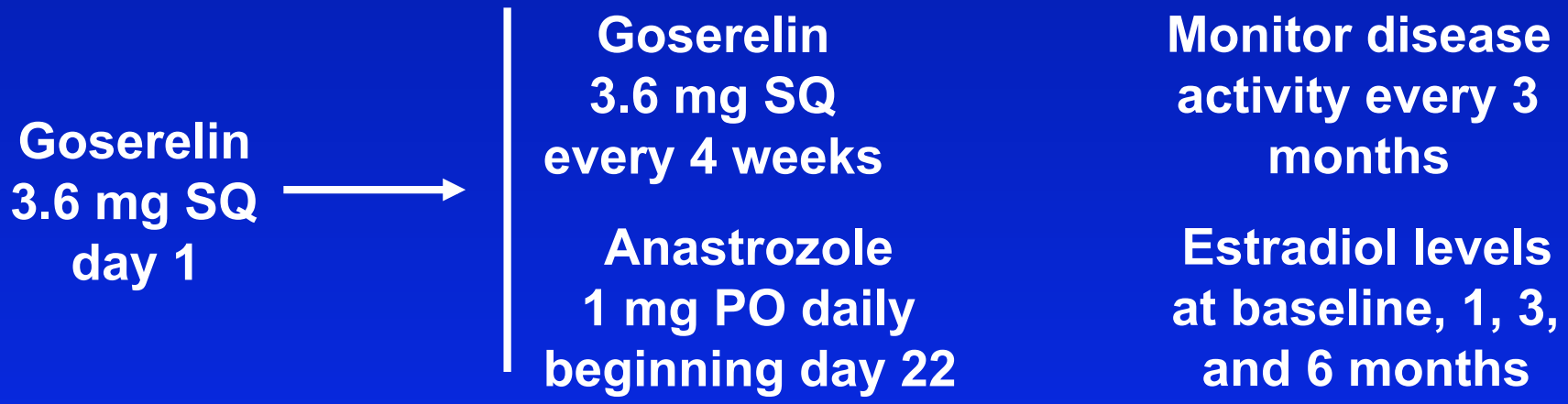
Randomized phase III studies of Aromatase Inhibitors vs Tamoxifen as Initial Therapy of Metastatic Breast Cancer

	Anastrozole	Anastrozole	Letrozole	Exemestane
Patients, N	170 vs 182	340 vs 328	453 vs 454	182 vs 189
OR, %	21 vs 17	33 vs 33	30 vs 20*	46 vs 31*
Clin. Benefit, %	59 vs 46*	56 vs 56	49 vs 38*	66 vs 49*
TTP/PFS, mo	11 vs 6*	8 vs 8	9 vs 6*	10 vs 6*
ER unknown, %	11 vs 11	56 vs 54	34 vs 33	15 vs 11

Aromatase Inhibitors

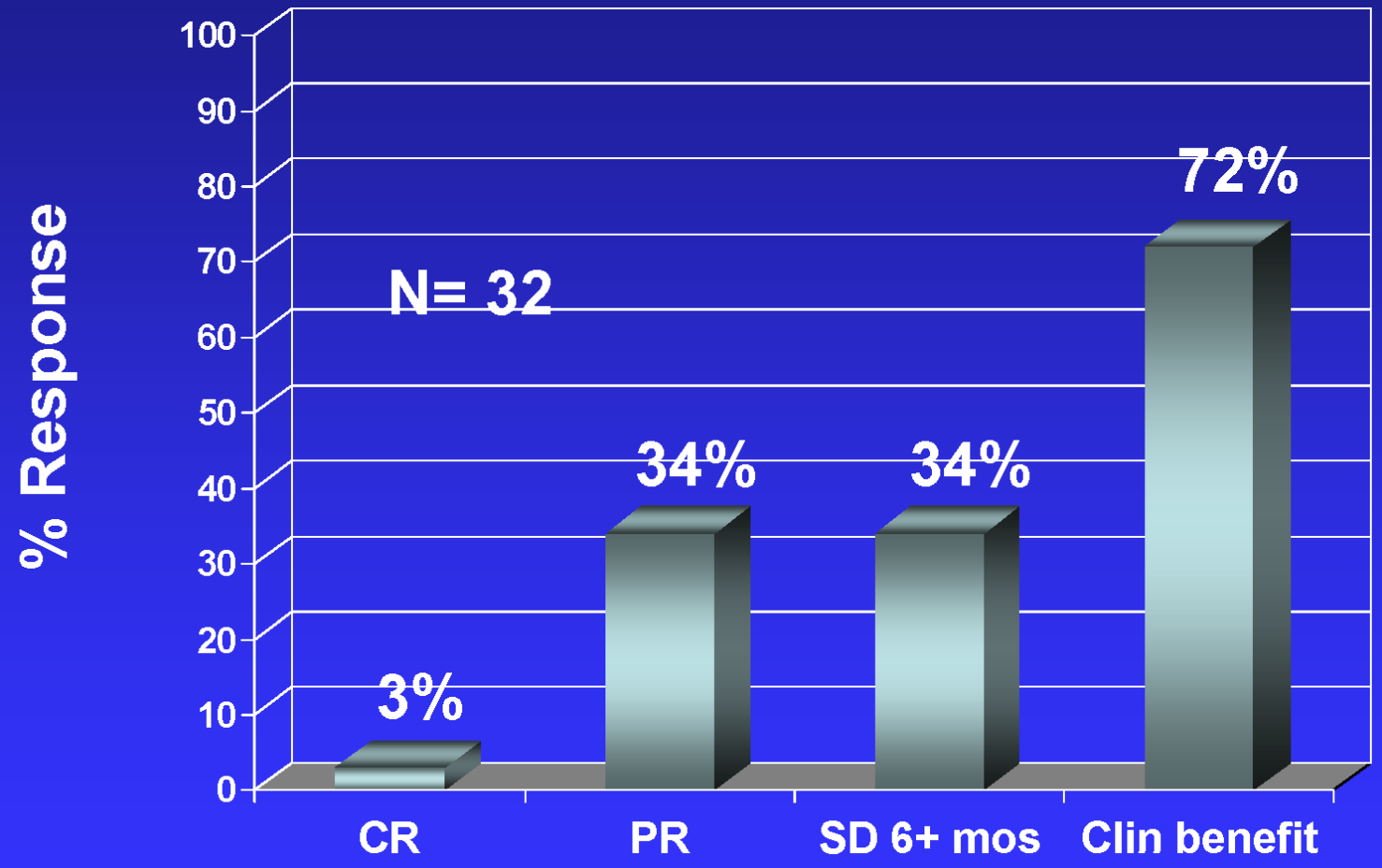
- Anastrozole, letrozole, exemestane superior to tamoxifen in 1st line therapy and megestrol acetate as 2nd line therapy.
- Limited toxicity (arthralgias/bone loss).
- Non cross-resistance (reversible and non-reversible).

Goserelin + Anastrozole Trial Schema



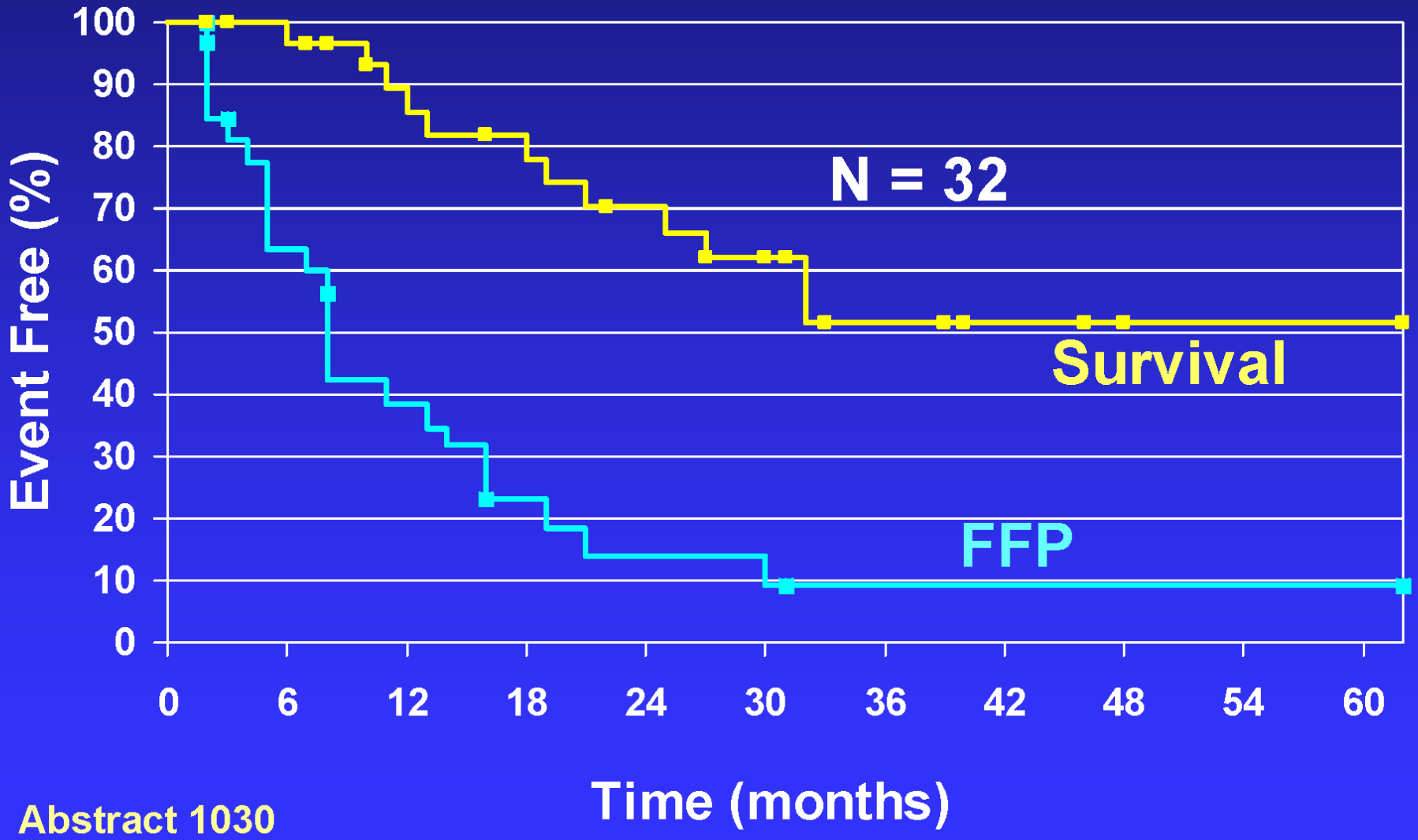
All subjects premenopausal with hormone receptor positive, metastatic breast cancer

Rates of Response



Abstract 1030

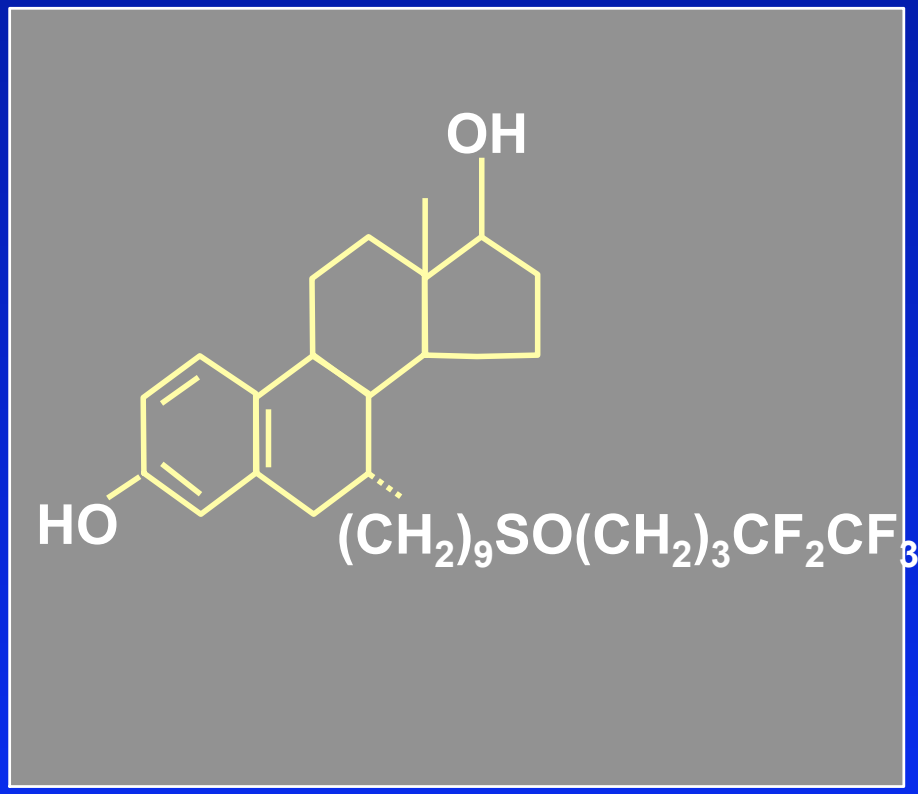
Freedom from Progression and Overall Survival



Abstract 1030

Fulvestrant (Fasolodex™, ICI 182,780)

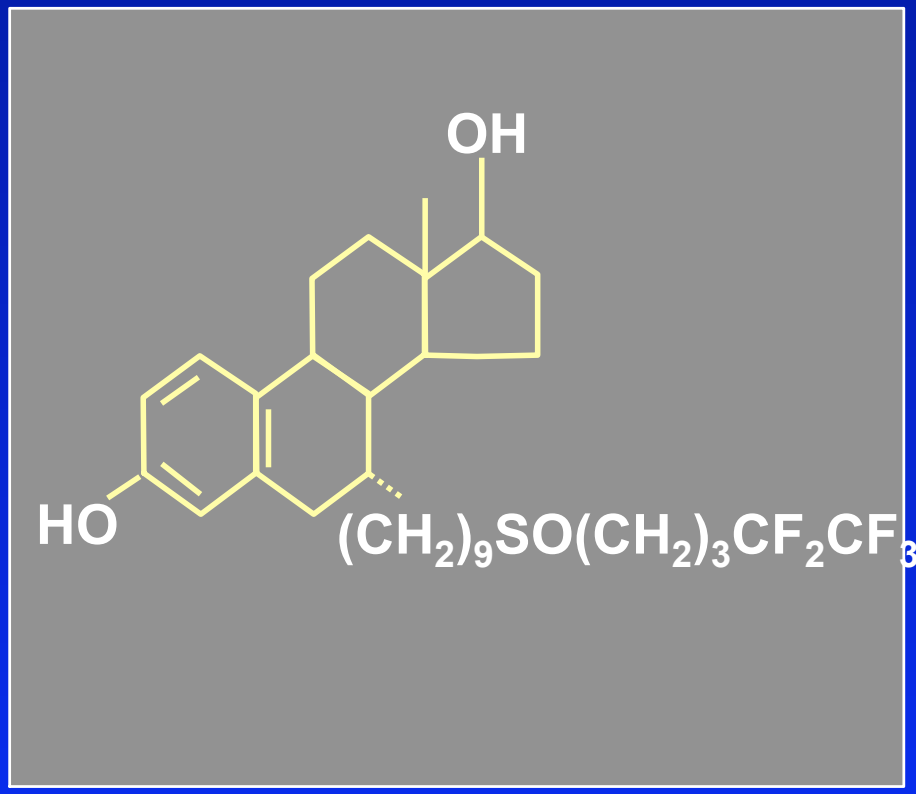
- Binds estrogen receptor with high affinity
- Causes estrogen receptor degradation and downregulation



Fulvestrant

Fulvestrant (Fasolodex™, ICI 182,780)

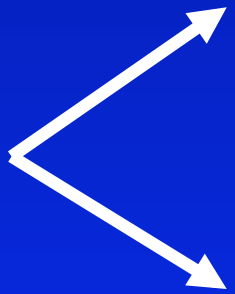
- A pure estrogen antagonist
- I.M. administration
- No endometrial stimulation



Fulvestrant

Trial 021
Study Design

Metastatic breast cancer
Postmenopausal
Prior tamoxifen therapy



Fulvestrant

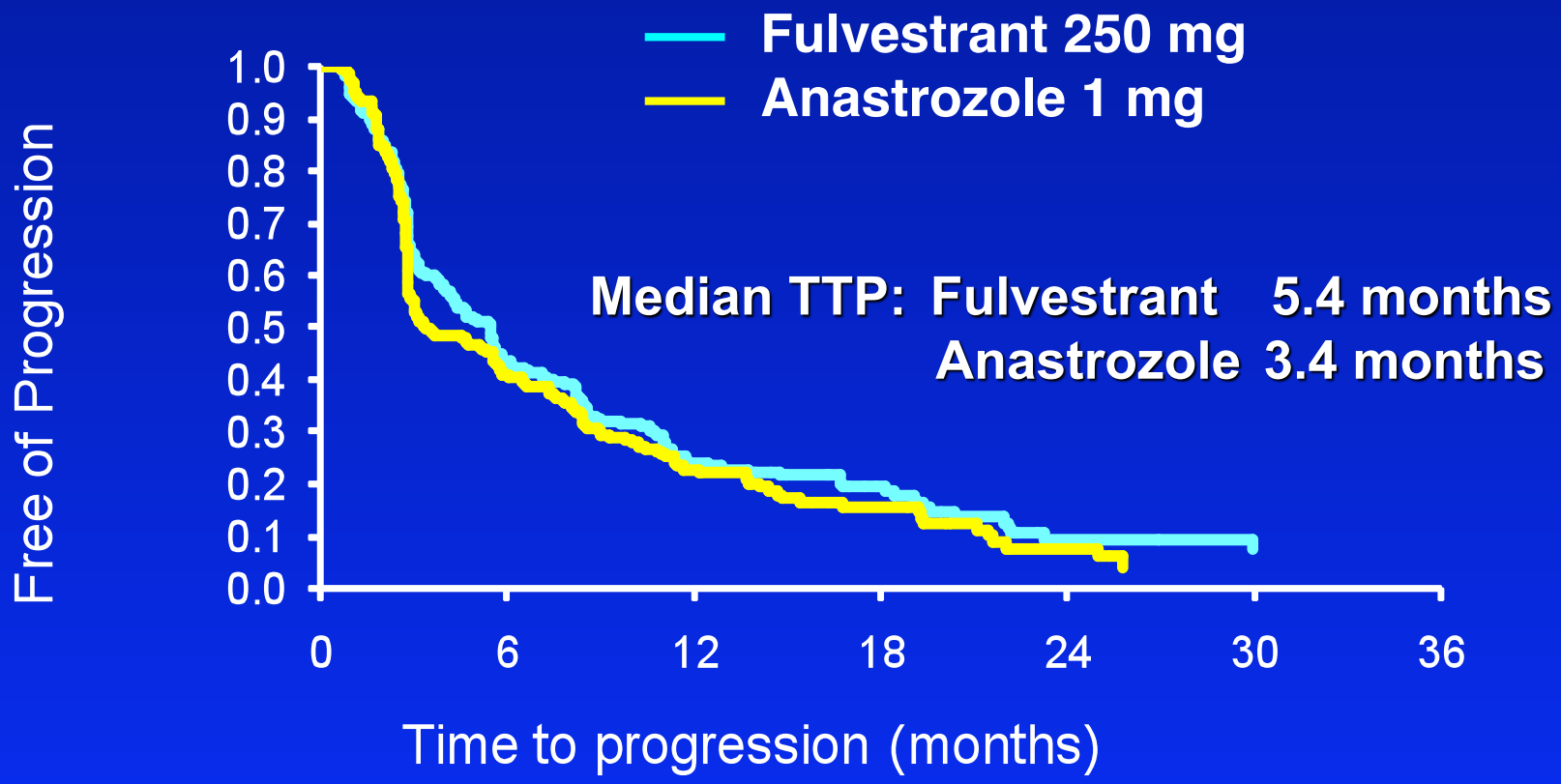
Anastrozole

Response to Treatment
Trial 021 (North American Trial)

	Number of patients (%)	
	Fulvestrant (*n*= 206)	**Anastrozole (*n*=194)**
Complete response (CR)	**10(4.9)**	**7(3.6)**
Partial response (PR)	**26(12.6)**	**27(13.9)**
Objective response (CR+PR)	**36(17.5)**	**34 (15.7)***
Stable disease ≥ 24 weeks	**51(24.8)**	**36 (18.6)**
Clinical Benefit (CR + PR + SD ≥ 24 weeks)	**87(42.2)**	**70 (36.1)**

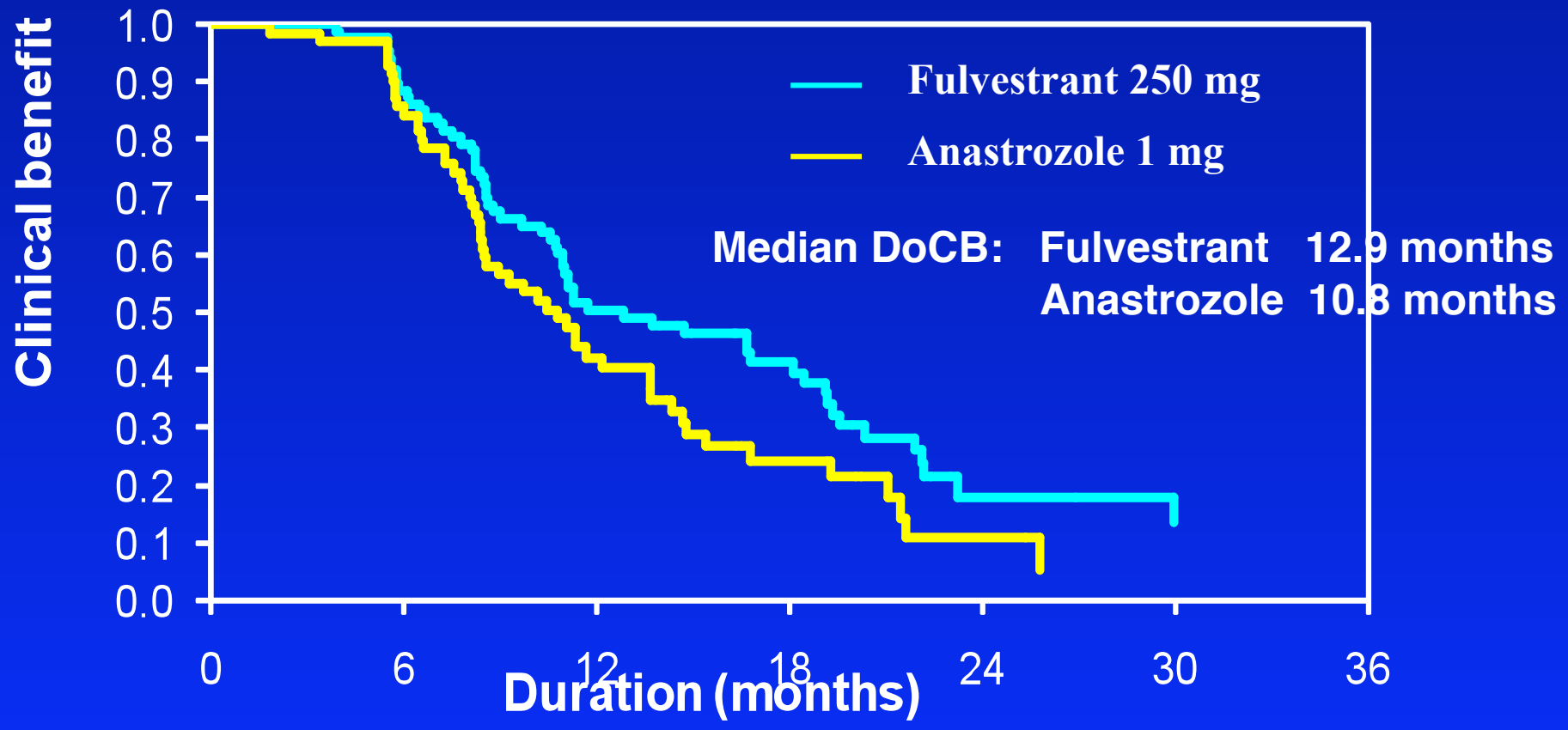
* Odds ratio (95.14 CI) 1.38 (0.84–2.29), *P*=0.20

Time to Progression (TTP)
Trial 021 (North American)



Hazard ratio (95.14% CI): 0.92 (0.74–1.14); *P*=0.43

Duration of Clinical Benefit (DoCB) Trial 021 (North American Trial)

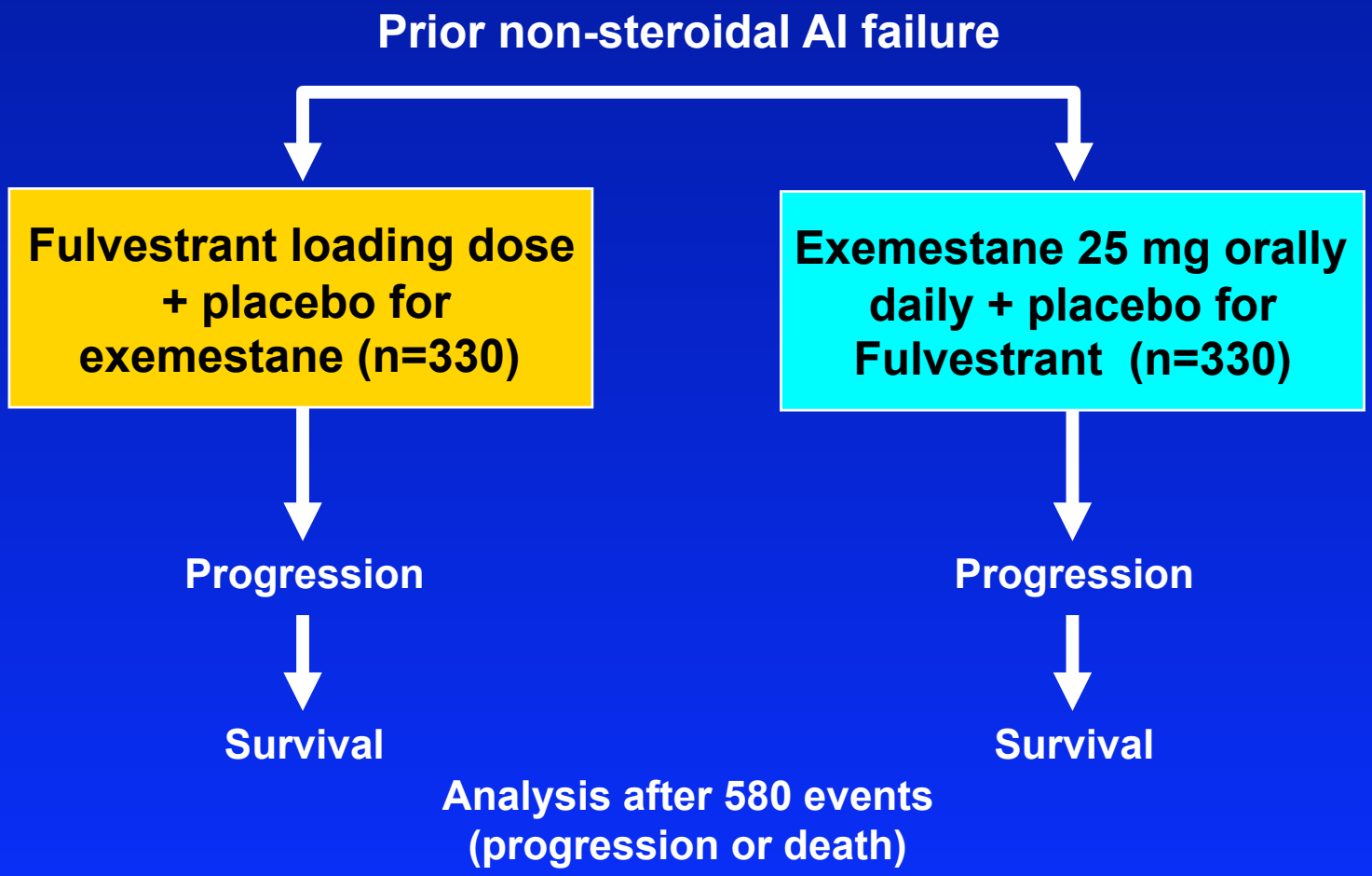


Fulvestrant and exemestane after progression on non-steroidal AIs

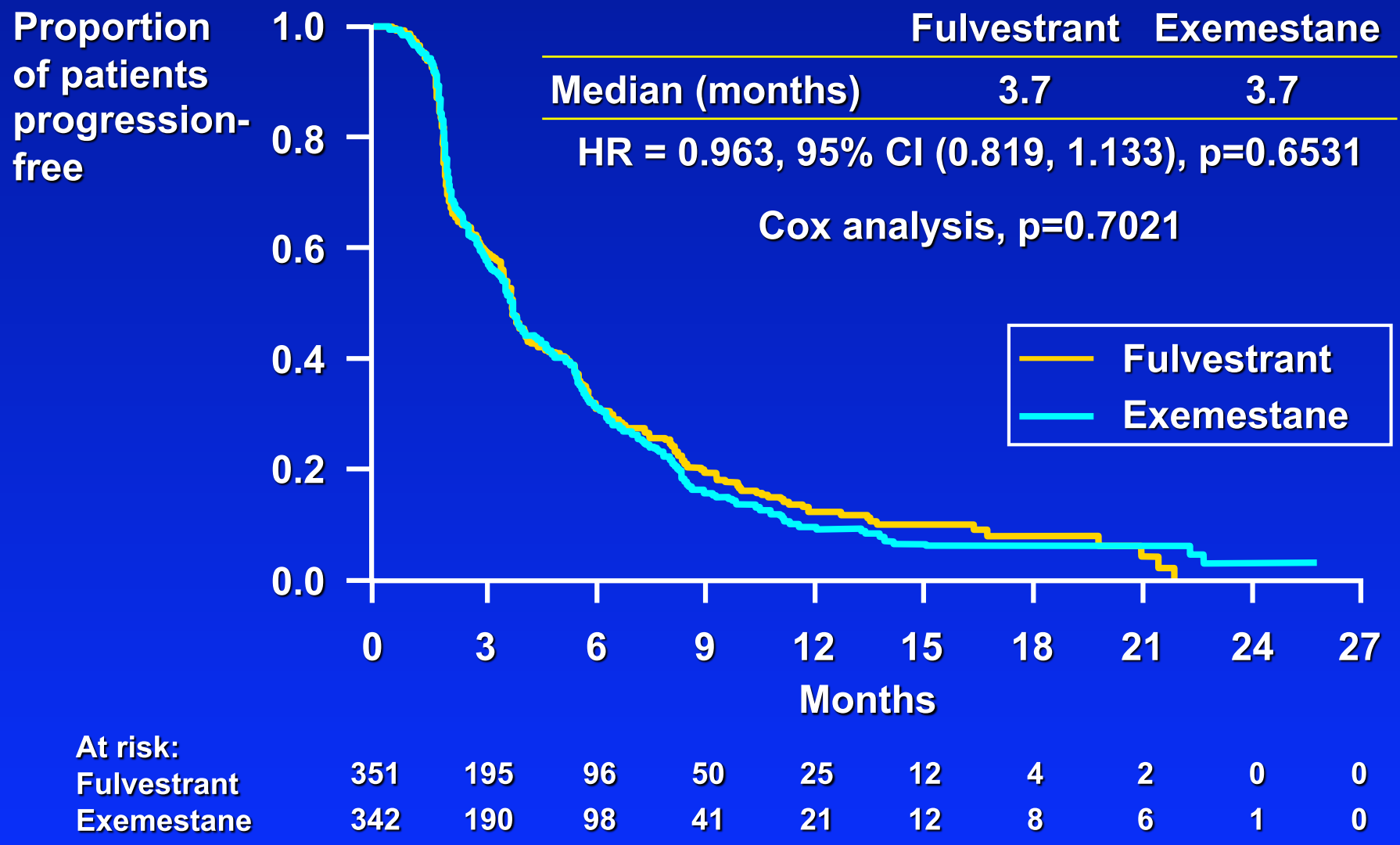
Endocrine agent	Reference	CBR (%)
Fulvestrant	Ingle et al 2006	35
	Perey et al 2006	30
Exemestane	Lønning et al 2000	20

Ingle et al. J Clin Oncol 2006; 24:1052–1056
Perey et al, Ann Oncol Advance Access published online on October 9, 2006
Lønning et al. Clin Oncol 2000; 18: 2234–44

Effect Trial



Time to progression (ITT)



Gradishar, SABCS 2006

Objective response and clinical benefit rate
(evaluable for response population)

	Fulvestrant	Exemestane	Odds ratio* (95% CI)	p-value
OR rate (CR + PR)	7.4% (20/270)	6.7% (18/270)	1.120 (0.578, 2.186)	0.7364
CB rate (OR + SD ≥24 wks)	32.2% (87/270)	31.5% (85/270)	1.035 (0.720, 1.487)	0.8534

* Analyses are not adjusted for baseline covariates

Gradishar, SABCS 2006

Fulvestrant Clinical Trials

1. Similar to aromatase inhibitors in tam-resistant patients.
2. Similar to tamoxifen as first-line therapy.
3. Active post AIs.
4. Minimal side effects.
5. Requires IM administration.
6. Optimal dose and schedule uncertain.

Postmenopausal ER+ Disease
Recurrent or Metastatic Disease

- Tamoxifen, steroidal AIs, non-steroidal AIs, fulvestrant all have similar activity
- Sequence of therapy minimally important
- Megesterol acetate seems inferior to above agents
- Recent data suggests lack of prior endocrine response does not predict lack of response to additional endocrine agent.

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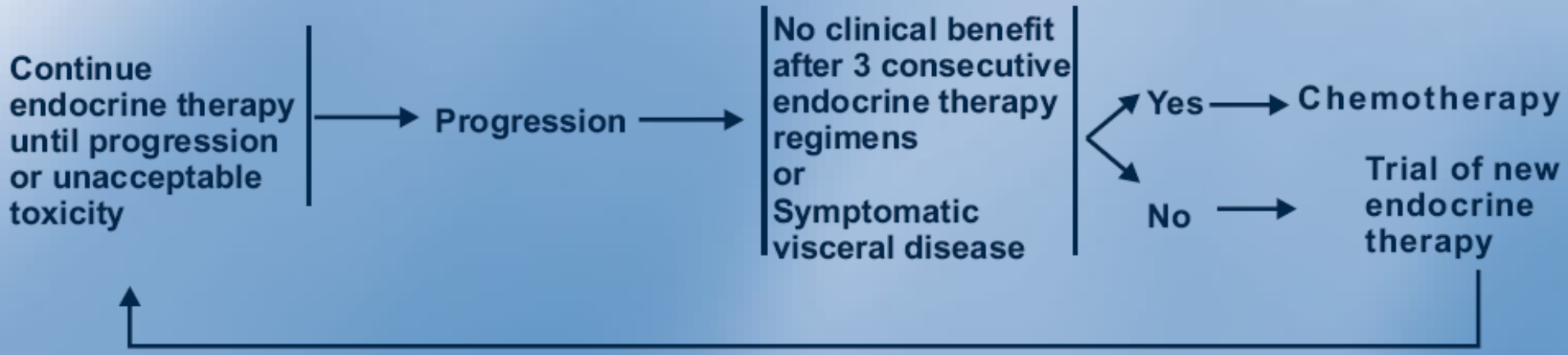
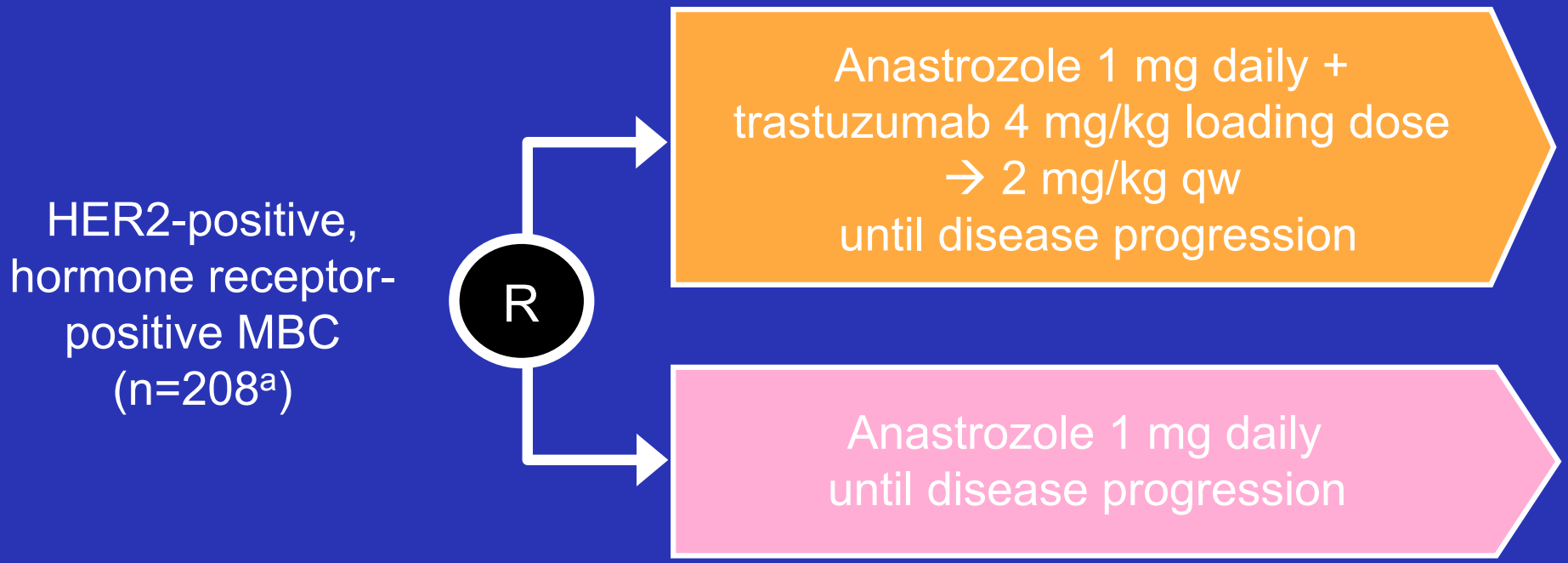
FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENCE/STAGE IV DISEASE



BINV-20

TAnDEM study design

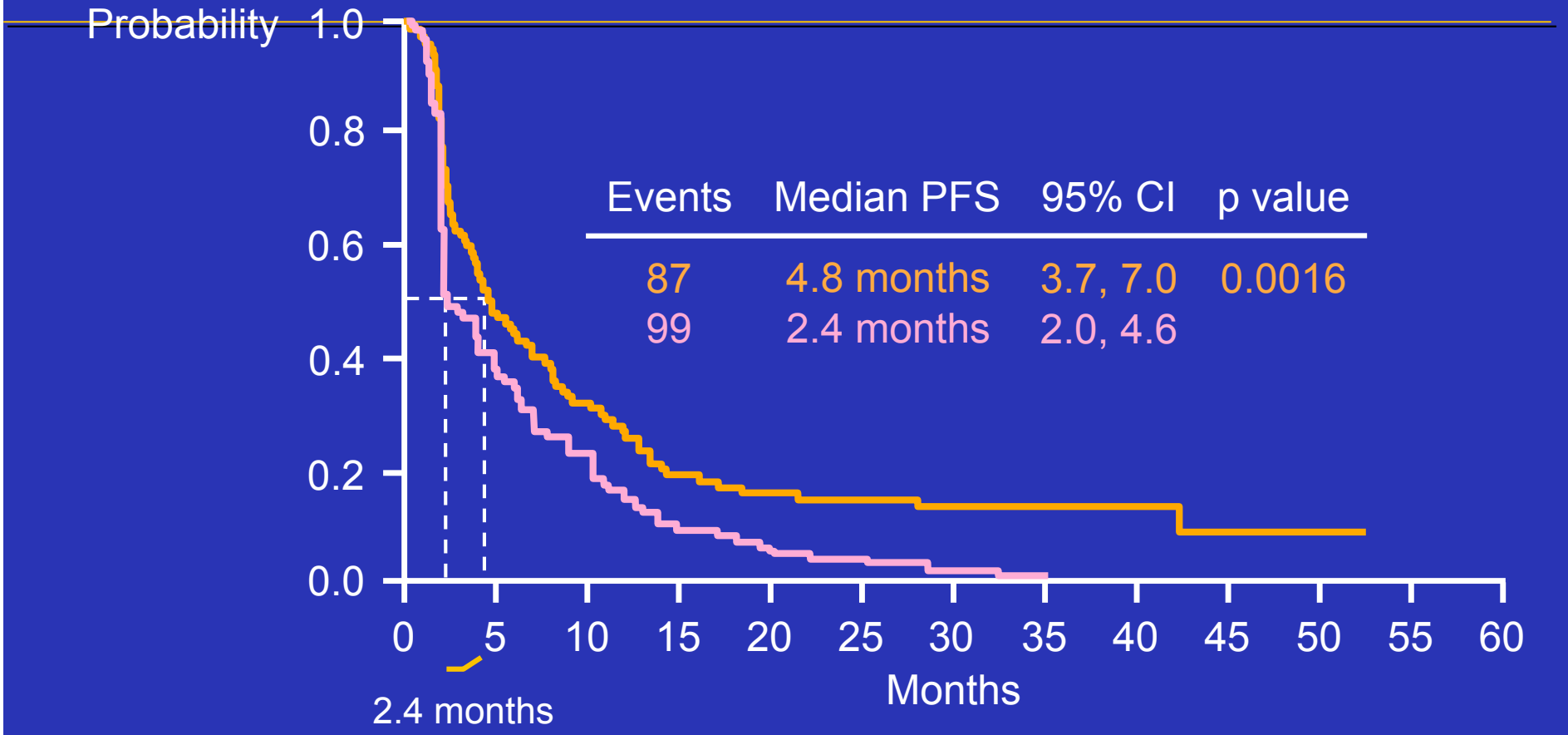


- **Crossover to receive trastuzumab was actively offered to all patients who progressed on anastrozole alone**

[a]One patient did not receive study drug and was excluded from analyses
MBC, metastatic breast cancer

McKay et al, SABCS 2006

Progression-free survival



Events	Median PFS	95% CI	p value
87	4.8 months	3.7, 7.0	0.0016
99	2.4 months	2.0, 4.6	

No. at risk

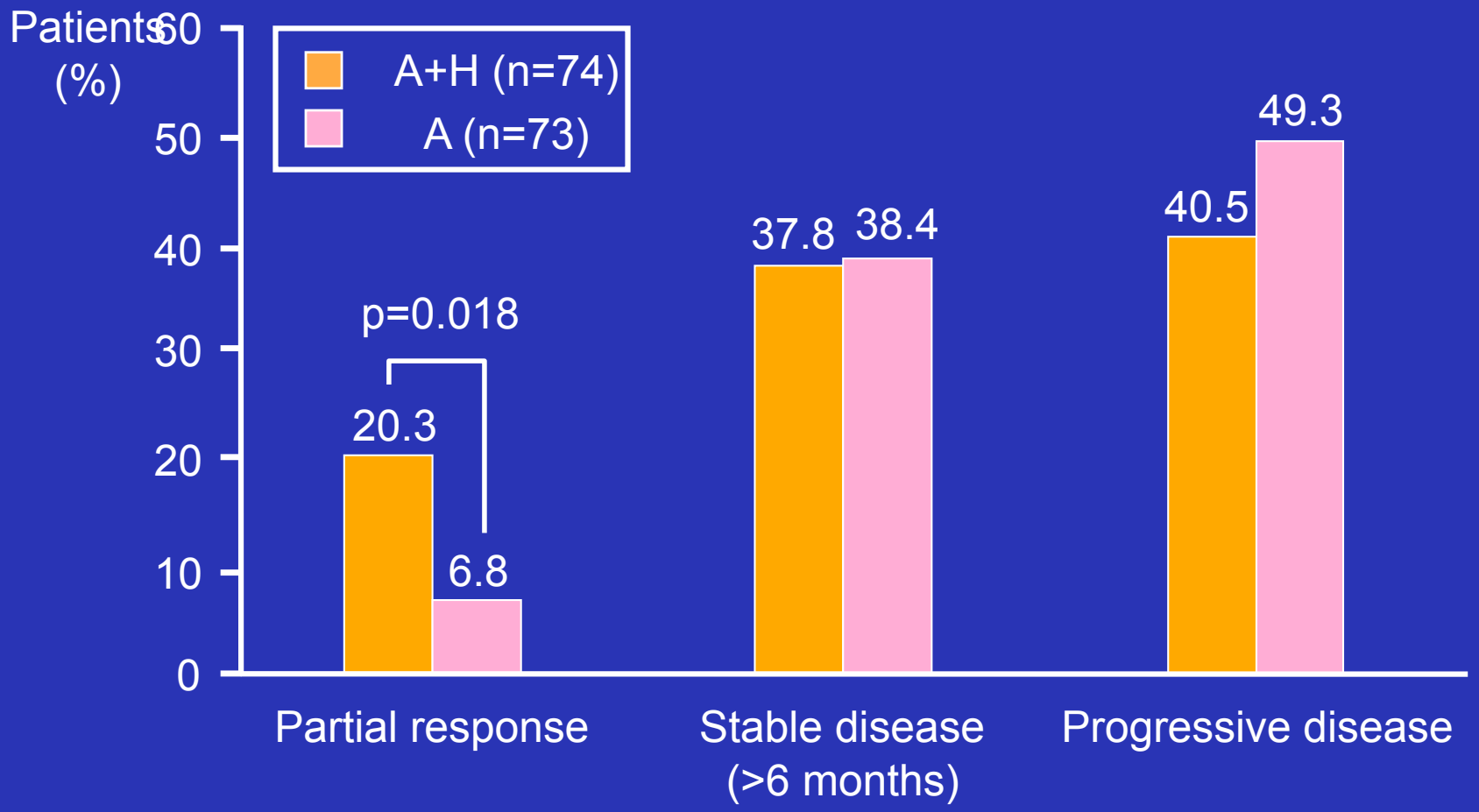
A+H	103	48	31	17	14	13	11	9	4	1	1	0	0
A	104	36	22	9	5	4	2	1	0	0	0	0	0

CI, confidence interval

PFS = time from randomisation to date of progressive disease or death

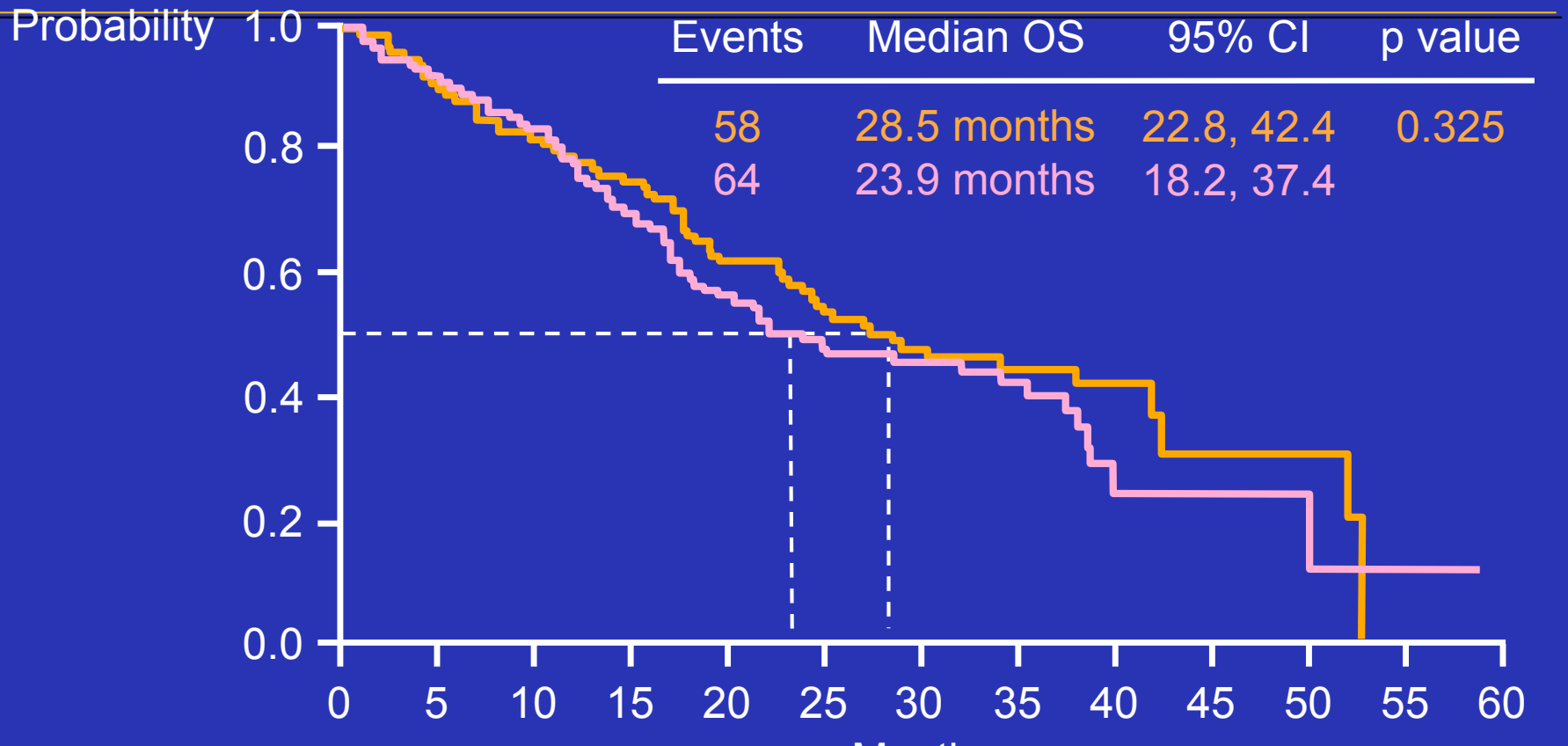
McKay et al, SABCS 2006

Patients with measurable disease evaluable for response



McKay et al, SABCS 2006

Overall survival



No. at risk

A+H	103	91	83	76	63	49	36	24	12	4	3	0	0
A	104	96	87	73	58	42	34	22	5	2	1	1	0

73 / 104 patients (70%) received H later during the course of disease

McKay et al, SABCS 2006

Hormonal Therapy of Metastatic Breast Cancer

- Effective only in those with ER and/or PR positive breast cancer
- High rates of response
- Sequential responses common
- Longer durations of response than with chemotherapy
- Less toxicity compared with cytotoxics
- Response rates across hormonal therapies similar
- Major criteria for preference is toxicity

SUBSEQUENT HORMONAL THERAPY FOR SYSTEMIC DISEASE
(For first-line hormonal therapy see BINV-16)

Premenopausal patients with ER-positive disease should have ovarian ablation/suppression and follow postmenopausal guideline

POSTMENOPAUSAL PATIENTS

- Non-steroidal aromatase inhibitor (anastrozole, letrozole) or steroidal aromatase inactivator (exemestane)
- Fulvestrant
- Tamoxifen or Toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

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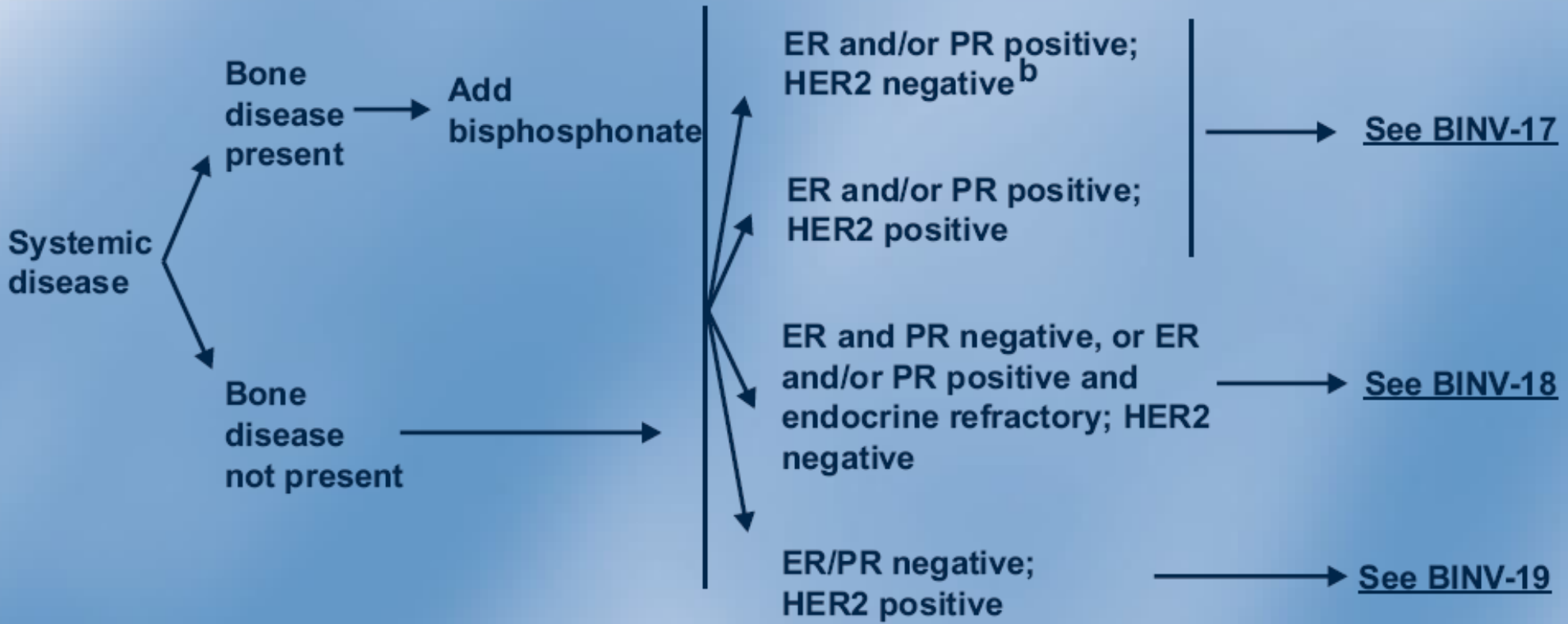

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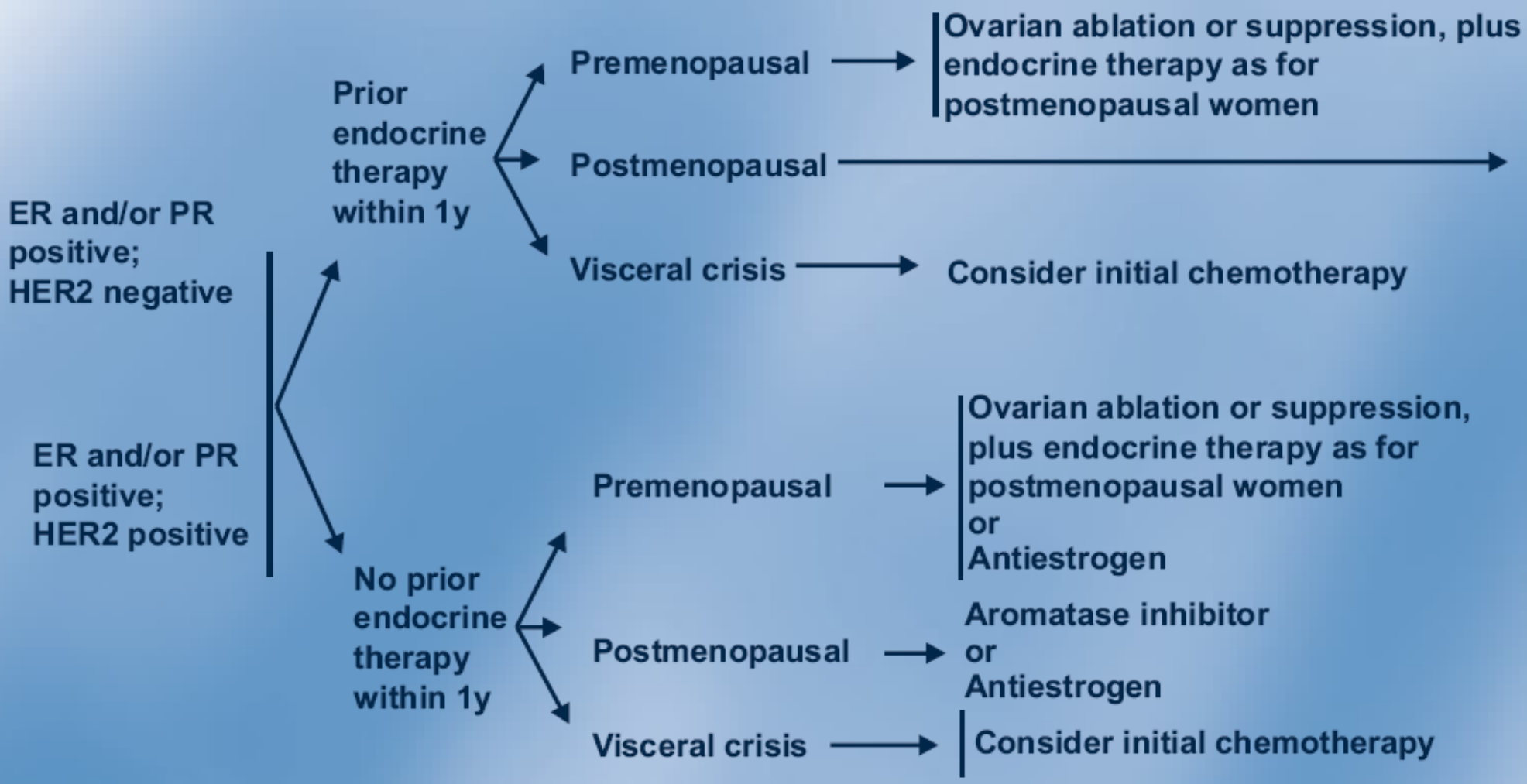

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