

**Case #7:
Management of Endocrine-
Responsive Metastatic Breast
Cancer**

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Patient Profile

- **Symptomatic** bone (PS 1) and skin relapse in a 70-year-old gardener 2 years after early breast cancer
- Initial tumor: IDC pT1, N0, LVI[-], G II
 - ER/PgR >70%
 - HER2[-]
- Adjuvant therapy: Tamoxifen (progression on)
- Skin biopsy: M1 adenoc. ER/PgR[+], HER2[-]
- Visceral involvement **NO**
- Concomitant therapy with CYP2D6 inhibitors **?**

Clinical Decision

- **Radiation therapy**
- **Systemic therapy**
 - **Endocrine therapy**
 - **Chemotherapy**
- **Other measures**

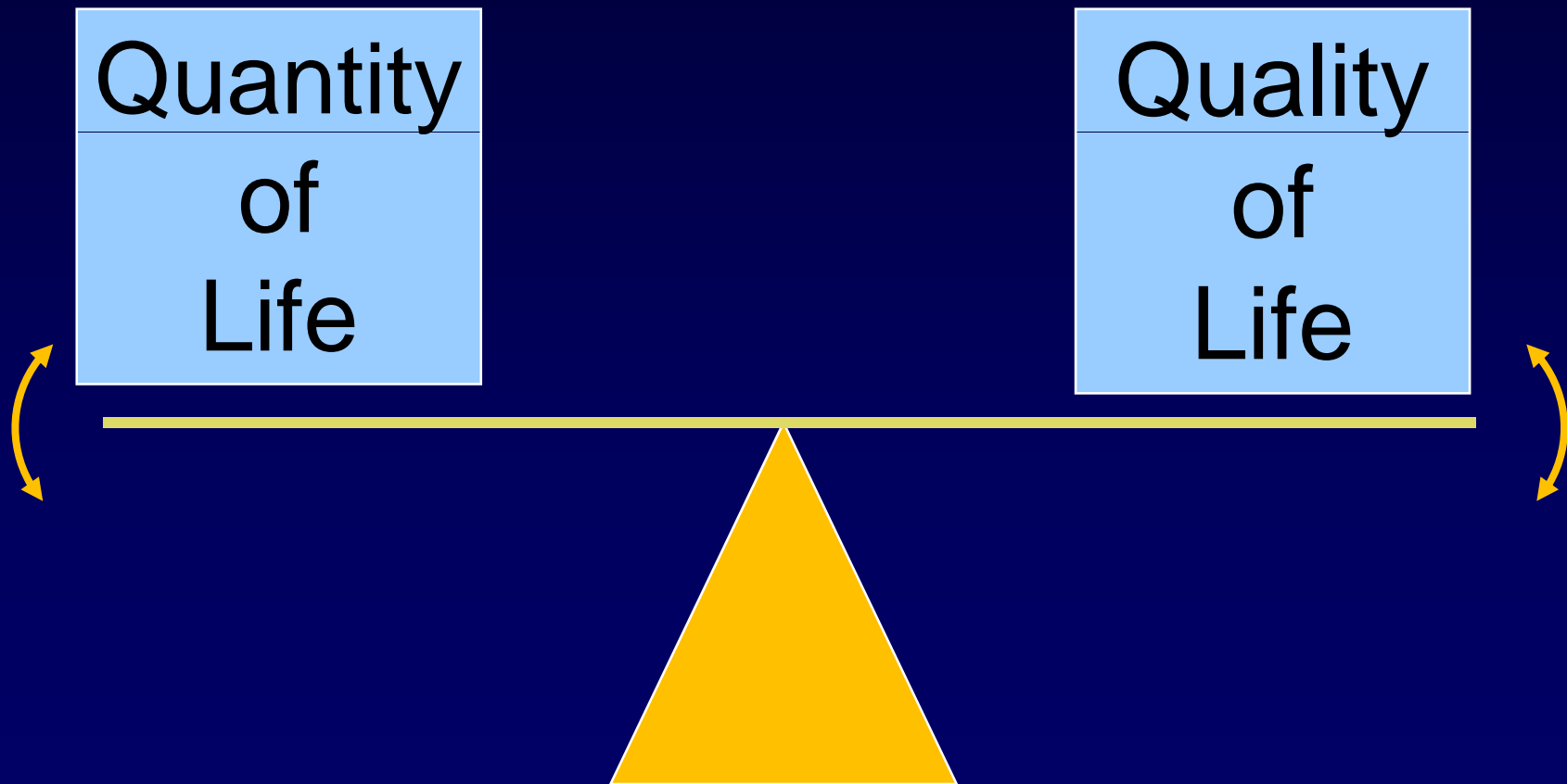
Clinical Decision

- **Radiation therapy** **YES**
- **Systemic therapy**
 - **Endocrine therapy or ?**
 - **Chemotherapy**
- **Other measures** **YES**
 - **Bisphosphonates**

Goals in the Treatment of Advanced Breast Cancer

- Control and regression of disease symptoms
- Prolongation of life
- Improvement in quality of life
- ??Cure

Balancing Treatment Efficacy and Toxicity Is a Major Objective



Choices in the Treatment of Advanced Breast Cancer

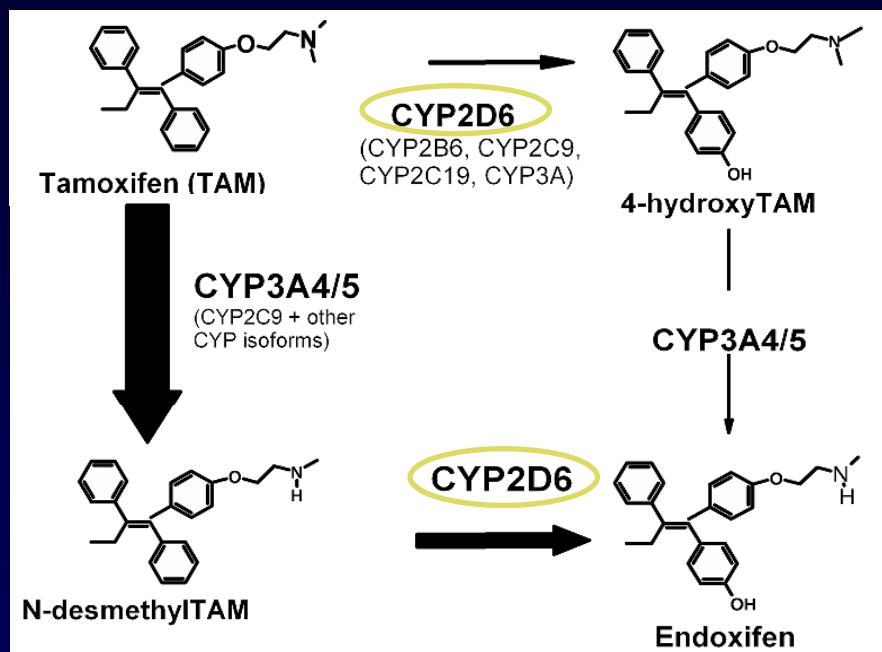
Choice of treatment based on:

- Age, menopausal status, general health, and PS
- Tumor ER status, HER2 status
- Previous treatments
 - Time since diagnosis or previous treatment
 - Response to previous treatment
- Extent and sites of disease
 - Presence of life-threatening disease
- Patient preference

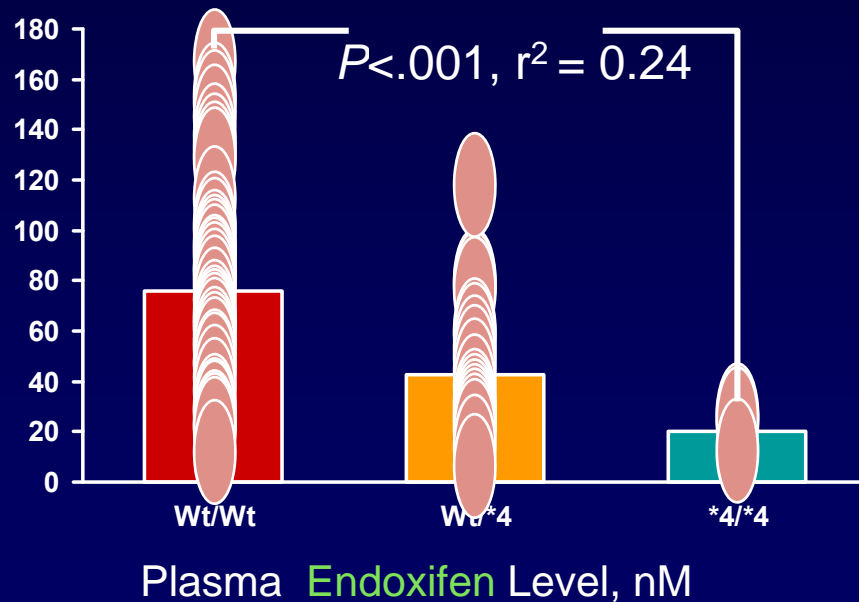
Questions About Tamoxifen in This Patient

- **Patient with an apparently good prognostic tumor (pT1, N0, ER+)**
- **Relapse on tamoxifen after just 2 years**
- **Is it a tamoxifen resistance or just some kind of tamoxifen inefficiency?**

CYP2D6 and Tamoxifen Metabolism

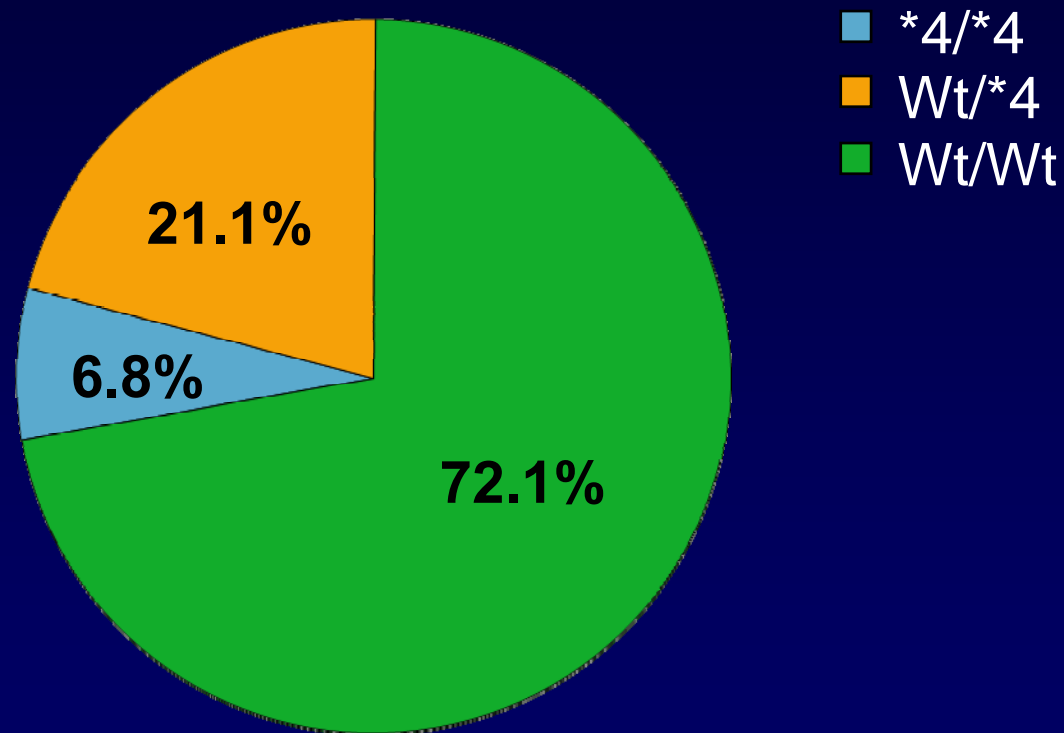


CYP2D6*4: an inherited genetic variant associated with a CYP2D6 poor metabolizer state

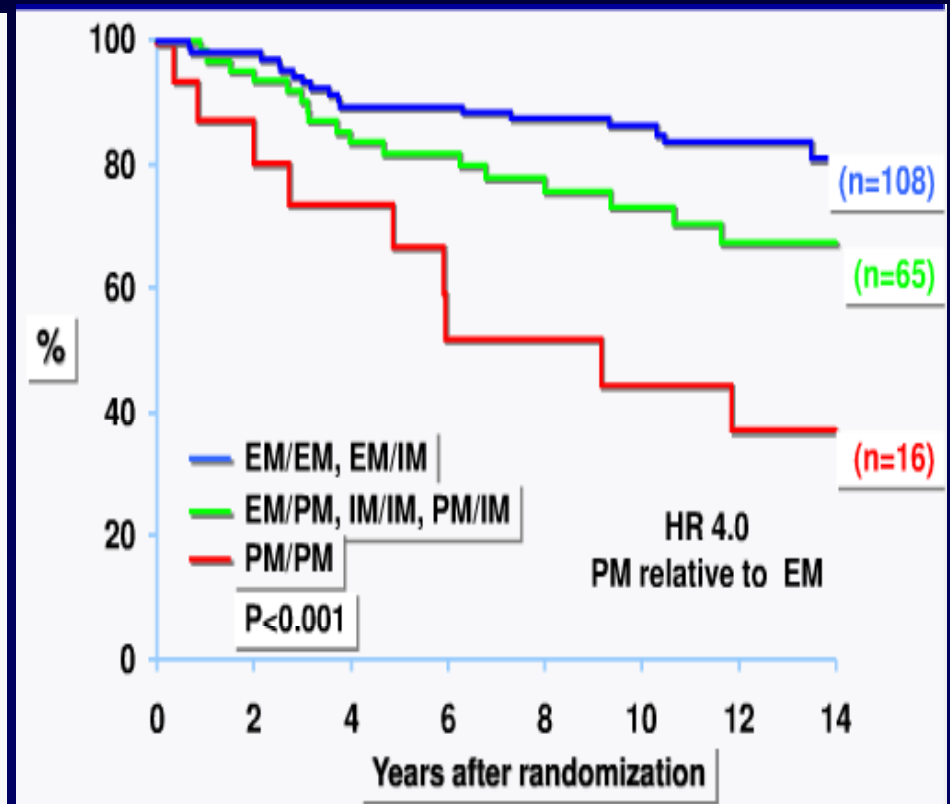
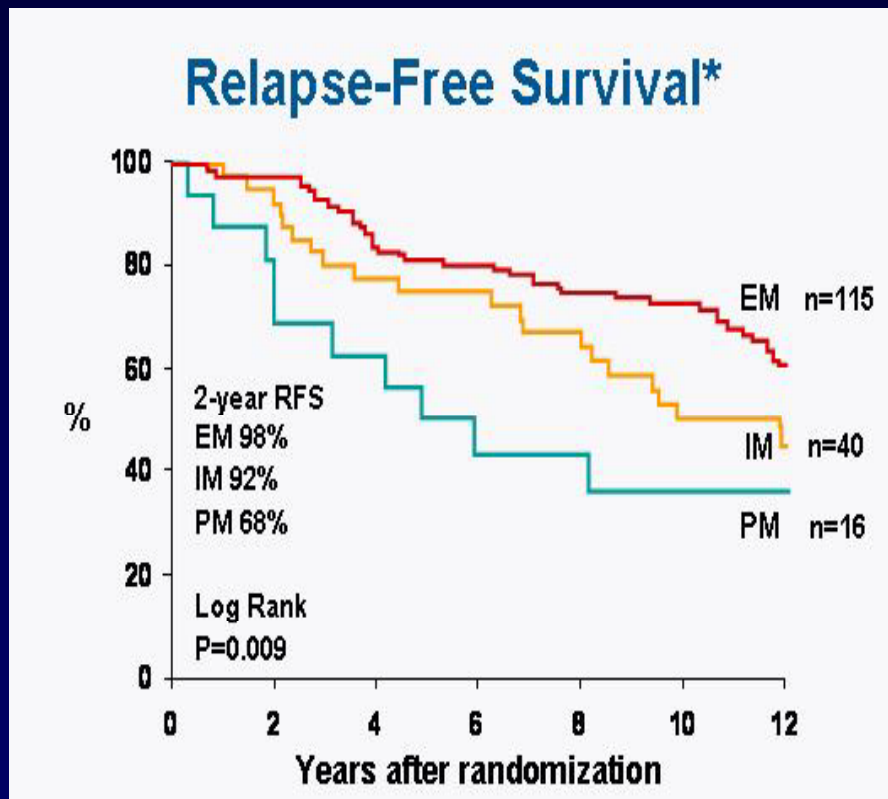


- 4-OH-tamoxifen and endoxifen are active metabolites of tamoxifen
- CYP2D6 enzyme involved in their metabolism

CYP2D6 Variant Genotype Frequencies



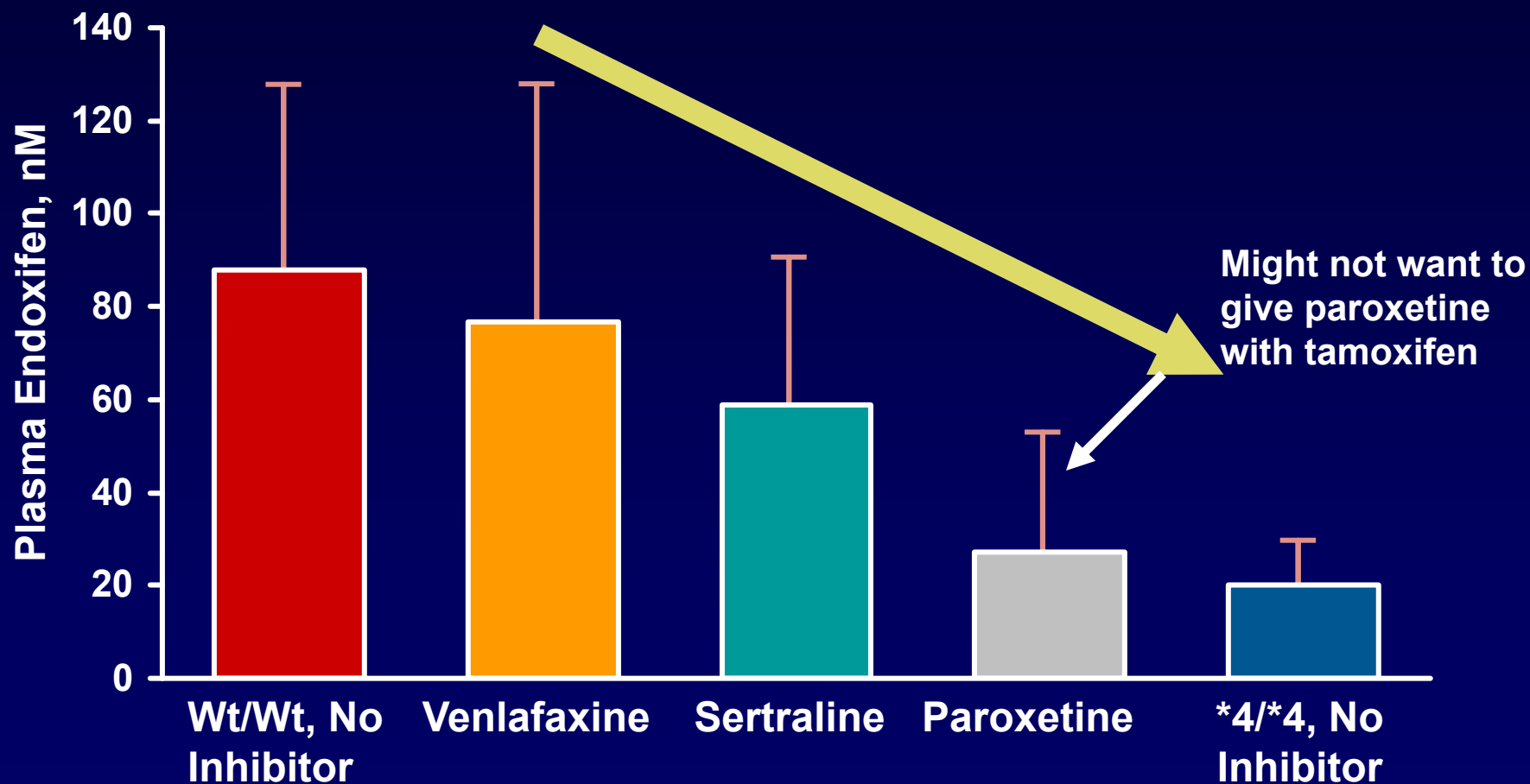
Tamoxifen, CYP2D6 Status, and Breast Cancer Relapse



*Breast cancer recurrence or death

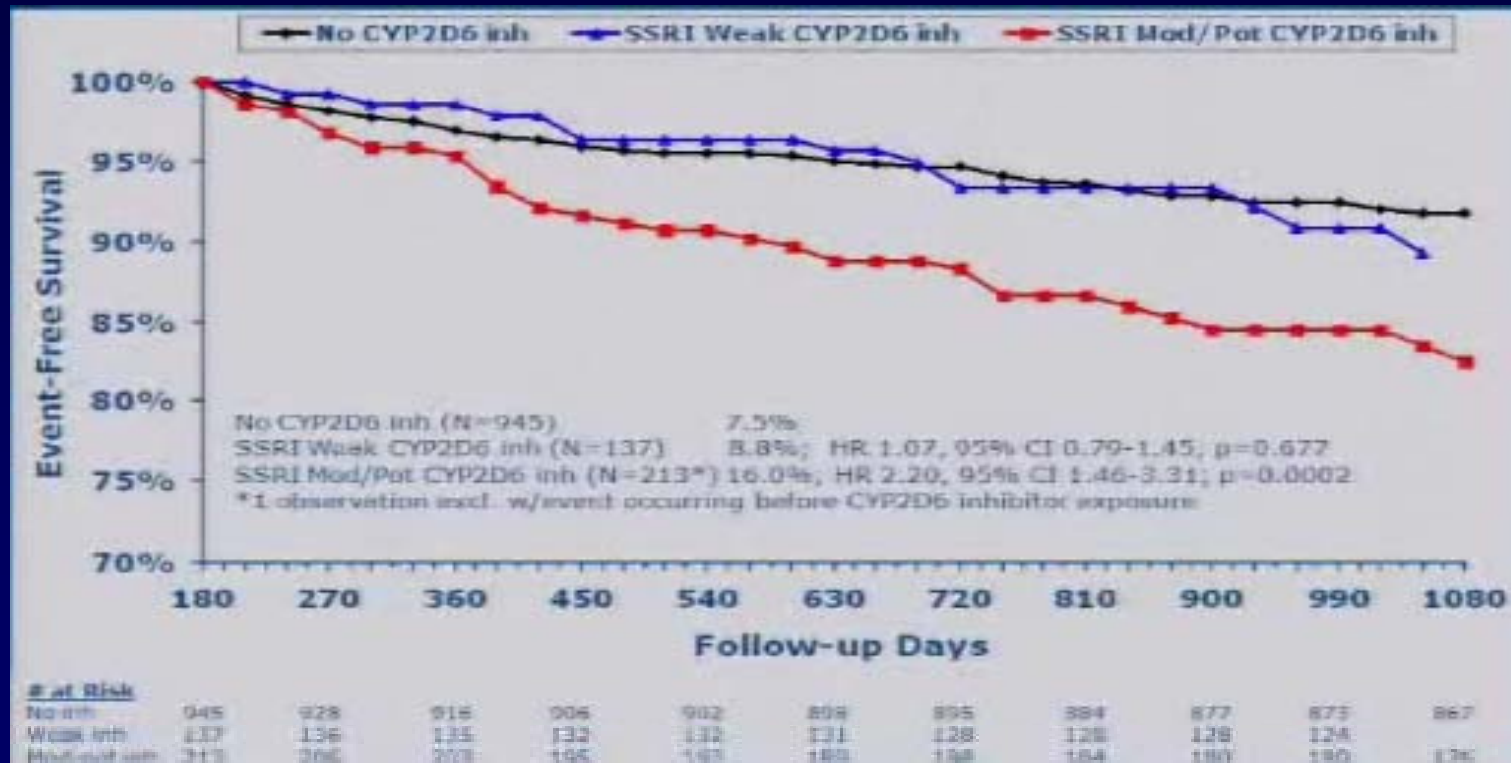
CYP2D6

Is a Key Metabolizer of Some Antidepressants



Risk of Cancer Recurrence in Women on Tamoxifen and CYP Inhibitors

SSRI moderate/potent CYP2D6 inhibitors, but not SSRI weak inhibitors are associated with increased risk of breast cancer recurrence



Optimal First-Line Endocrine Therapy for MBC

- **CYP2D6 status and potential inhibitors not relevant**
- **Even in these situations, there are best options**
- **Particular decision: Starting with an aromatase inhibitor (AI) or fulvestrant**

Randomized Phase III Trials of AIs vs Tamoxifen as First-line Treatment of MBC

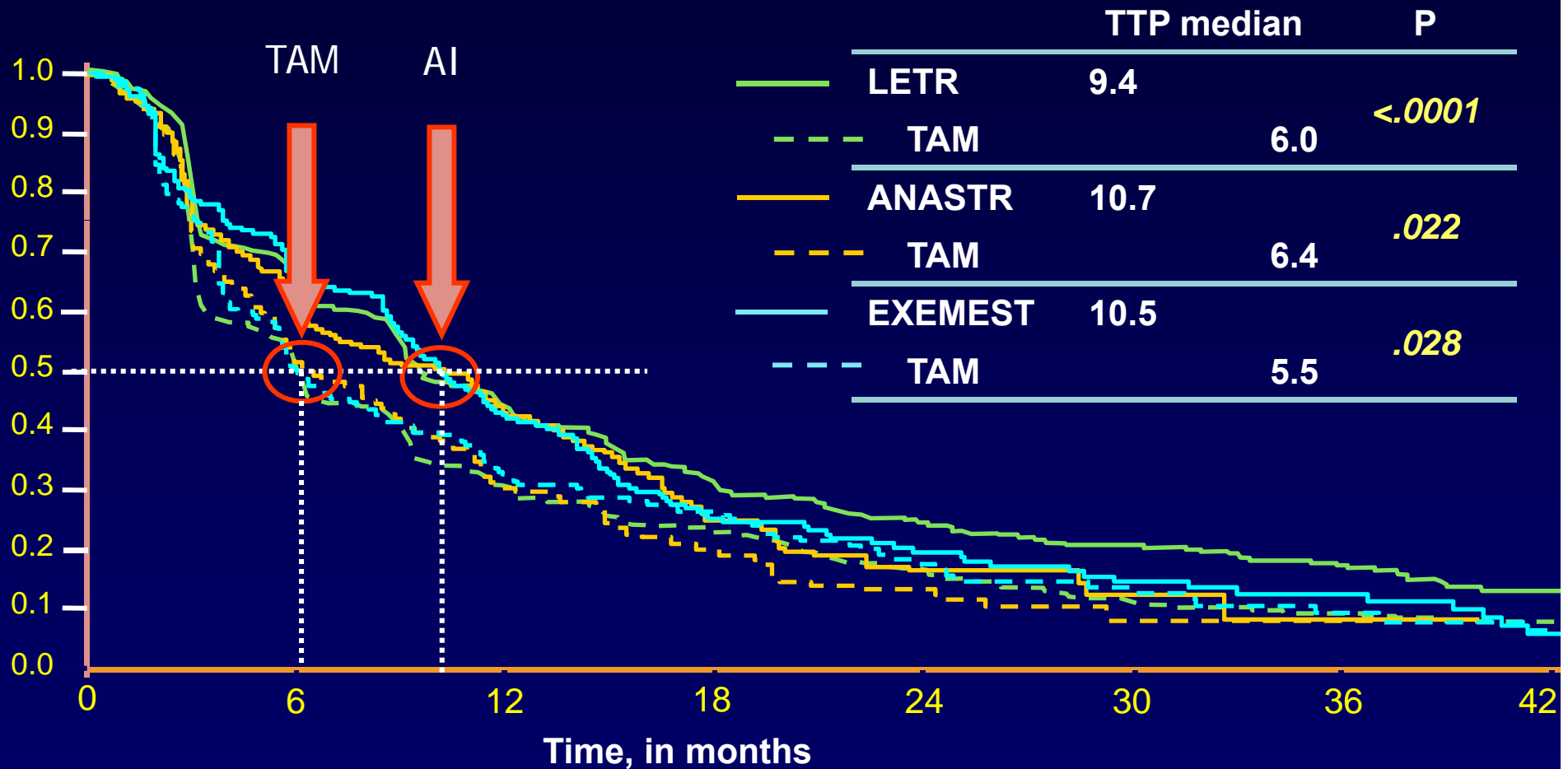
	Anastrozole ¹	Anastrozole ²	Letrozole ³	Exemestane ⁴
No. patients	170 vs 182	340 vs 328	453 vs 454	182 vs 189
ORR, %	21 vs 17	33 vs 33	32 vs 21*	46 vs 31*
CBR, %	59 vs 46*	56 vs 56	50 vs 38*	66 vs 49*
TTP or PFS, months	11 vs 6*	8 vs 8	9 vs 6*	10 vs 6*
ER status unknown, %	11 vs 11	56 vs 54	34 vs 33	15 vs 11

ORR = overall response rate; CBR = clinical benefit rate; TTP = time to progression; PFS = progression free survival; ER = estrogen receptor

***Statistically significant difference**

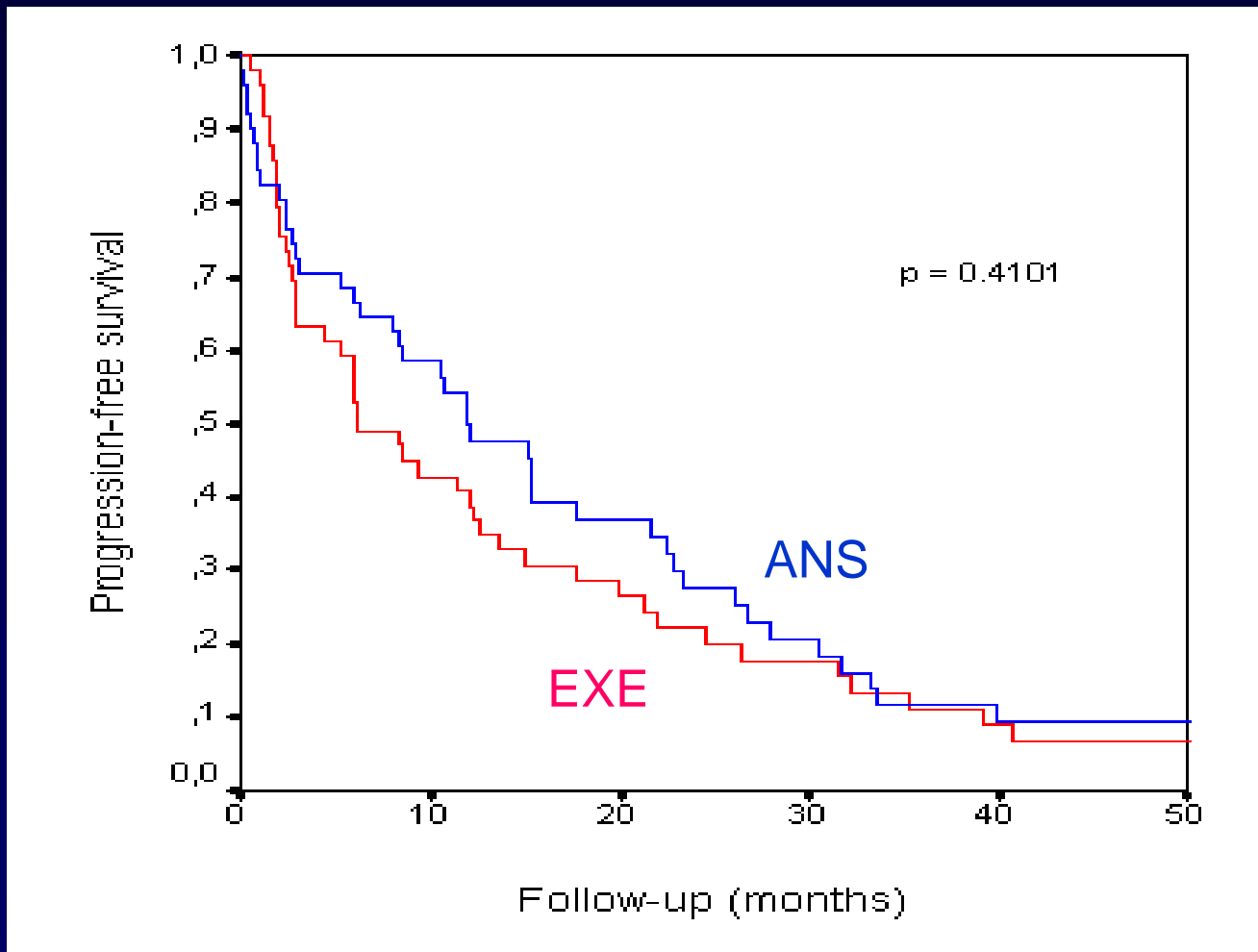
1. Nabholz JM, et al. *J Clin Oncol.* 2000;18(22):3758-3767. 2. Bonneterre J, et al. *J Clin Oncol.* 2000;18(22):3748-3757. 3. Mouridsen H, et al. *J Clin Oncol.* 2003;21(11):2101-2109. 4. Paridaens R, et al. *J Clin Oncol.* 2008;26(30):4883-4890.

Als vs TAM First-Line MBC Disease-Free Survival in ER[+] Population



1. Nabholz JM, et al. *J Clin Oncol.* 2000;18(22):3758-3767. 2. Bonneterre J, et al. *J Clin Oncol.* 2000;18(22):3748-3757. 3. Mouridsen H, et al. *J Clin Oncol.* 2003;21(11):2101-2109. 4. Paridaens R, et al. *J Clin Oncol.* 2008;26(30):4883-4890.

Exemestane vs Anastrozole First-Line MBC GEICAM 2001/03 Study



Fulvestrant vs AI as First-Line Endocrine Therapy for MBC

Trial 0020: International, randomized 1:1, open, parallel-group

Trial 0021: North American, randomized 1:1, DB-DD, parallel-group



Trials 0020 and 0021: Recruitment between May 1997 and August 1999



Postmenopausal women with advanced breast cancer receiving prior endocrine treatment for advanced breast cancer



Fulvestrant 250 mg IM once monthly
Trial 0020: 1 x 5 mL (n = 222)
Trial 0021: 2 x 2.5 mL (n = 206)



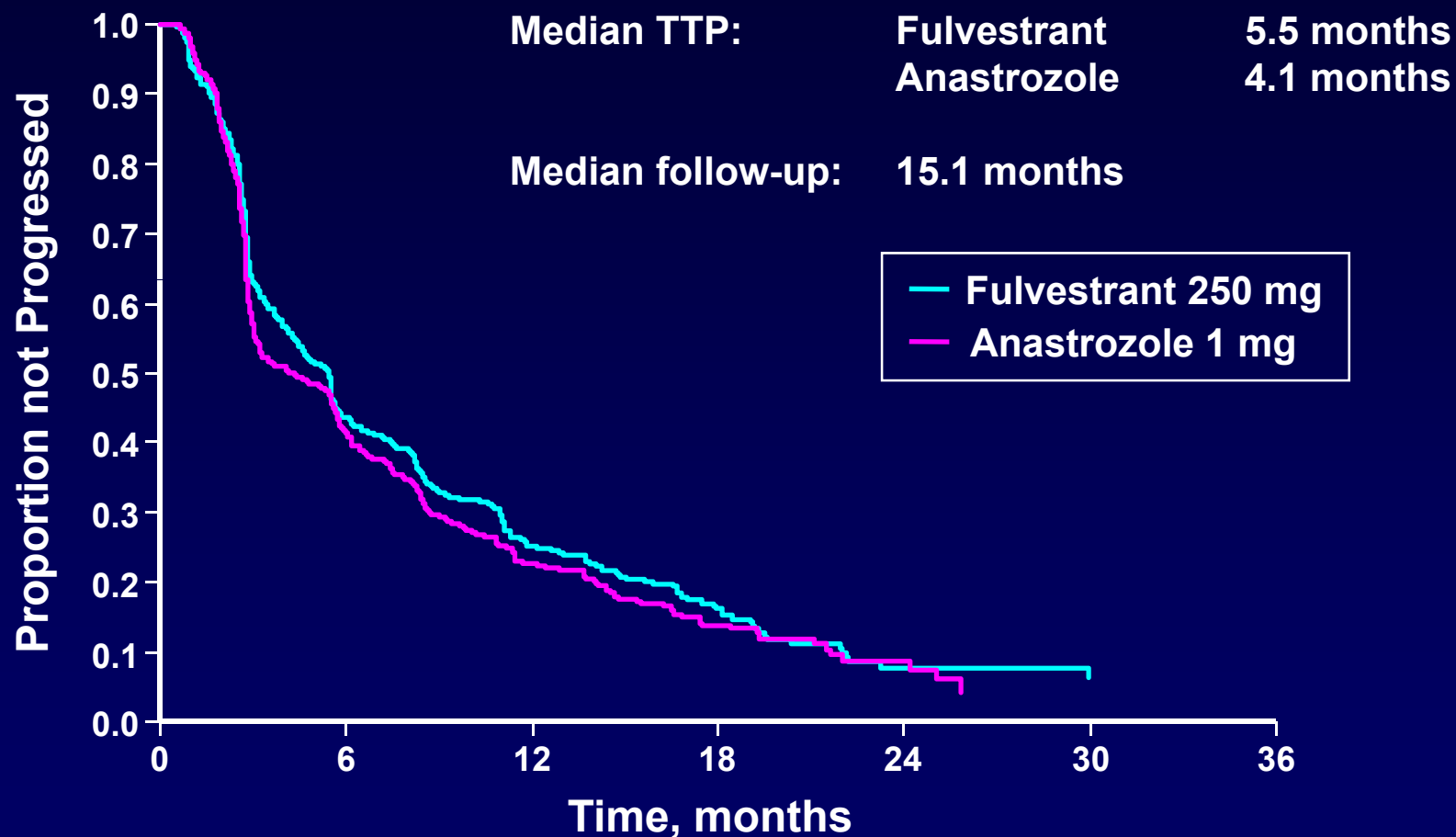
Anastrozole 1 mg daily, orally
Trial 0020: (n = 229)
Trial 0021: (n = 194)



Analysis after 340 events
(progression or death prior to progression)

Fulvestrant vs Anastrozole

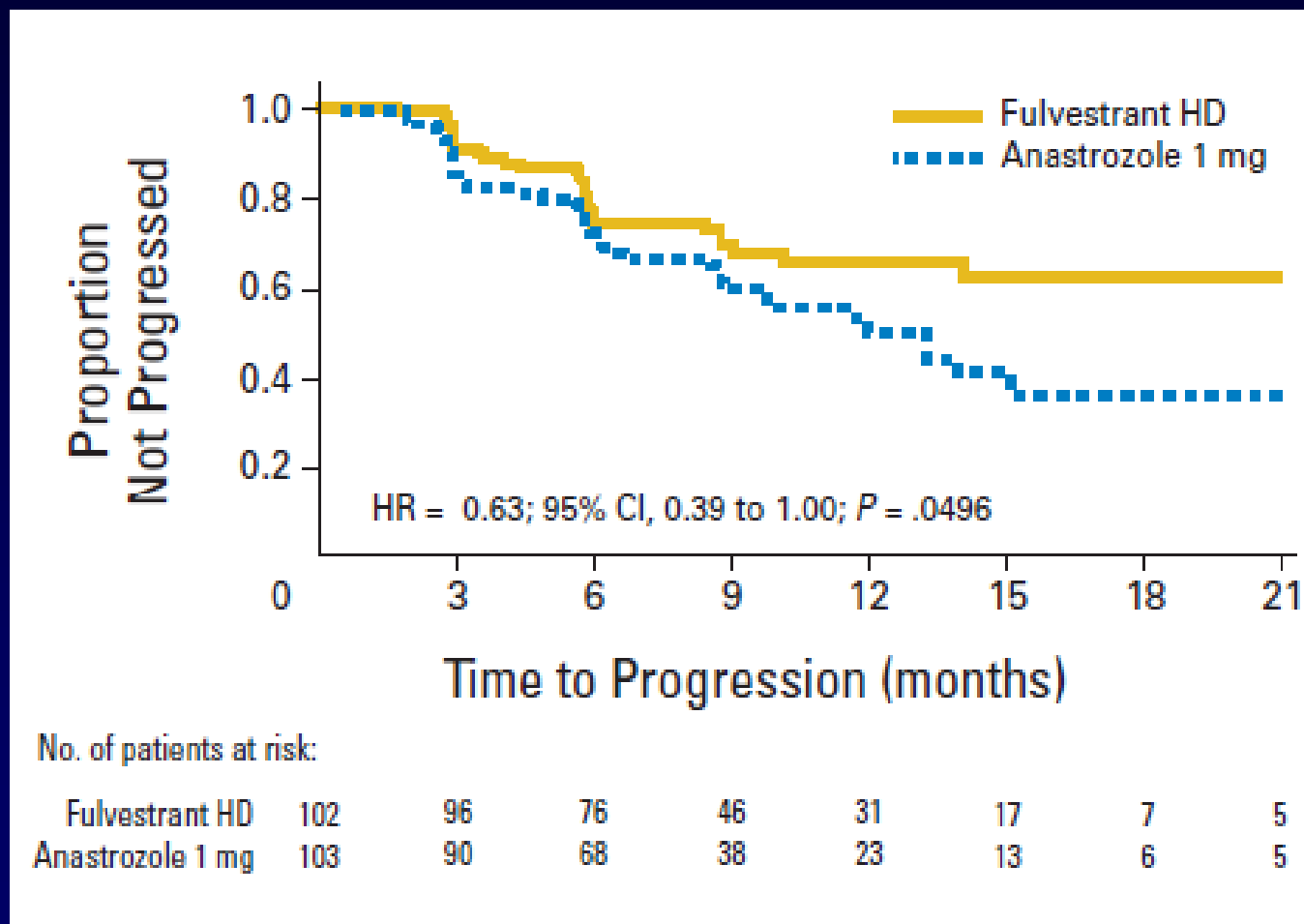
Phase III—Study 20 and 21—Combined Progression Analysis



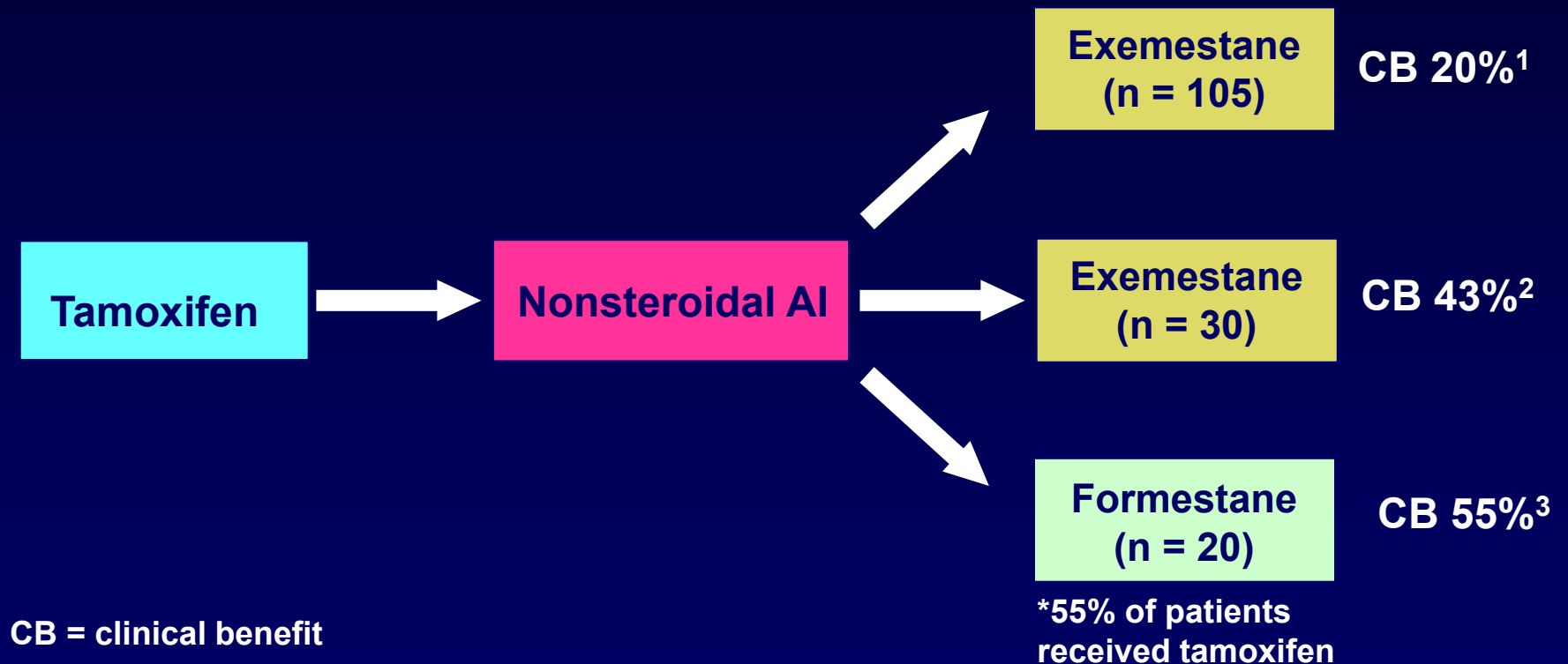
Hazard ratio (95.14% CI):
0.95 (0.82–1.10); $P = .48$

Robertson JF, et al. *Cancer*. 2003;98(2):229-238.

Fulvestrant High-Dose vs Anastrozole First-Line MBC (FIRST Study)

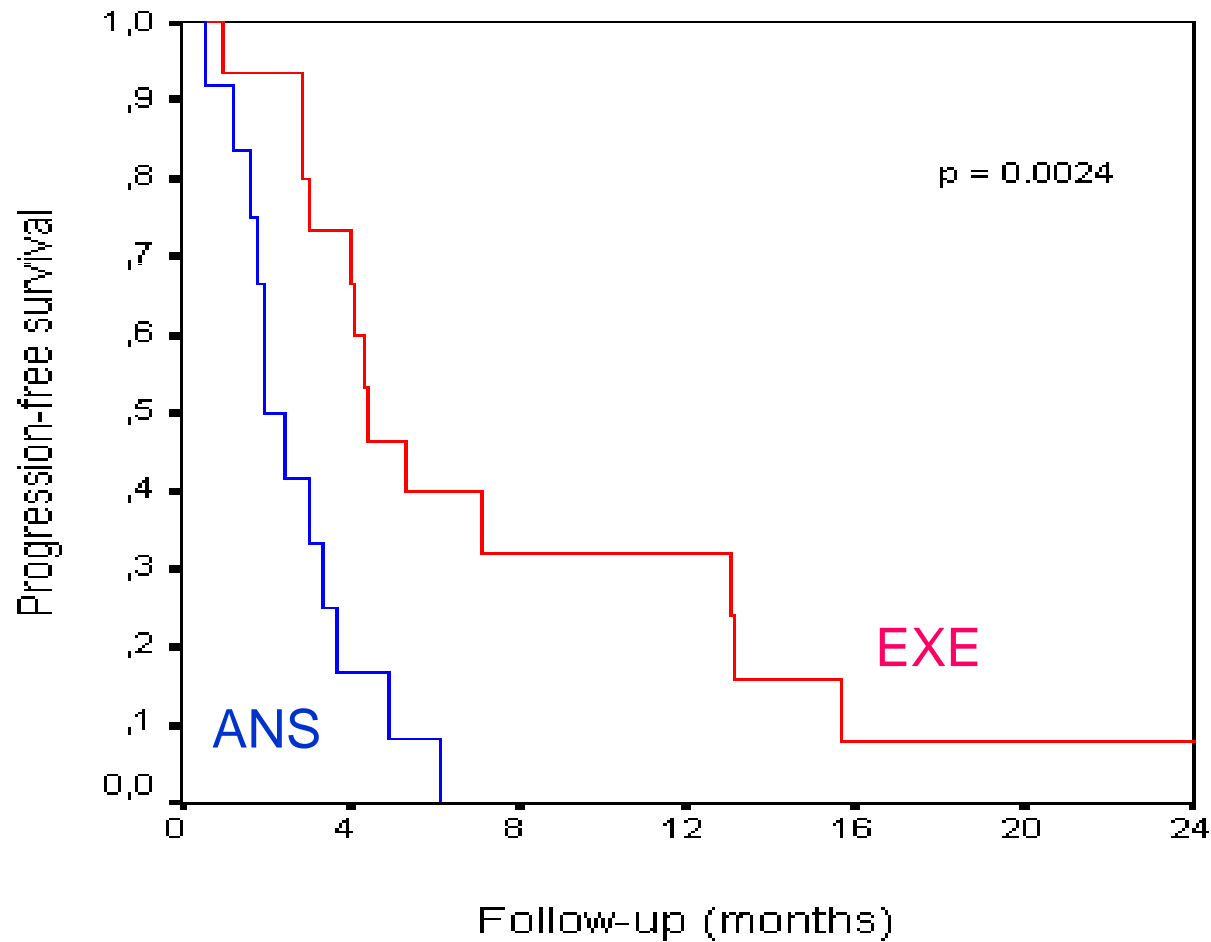


Steroidal AI Agents After Progression on Tamoxifen and a Nonsteroidal AI



1. Lønning PE, et al. *J Clin Oncol.* 2000;18(11): 2234-2244. 2. Carlini P, et al. *Ann Oncol.* 2002;13 (Suppl 5): Abstract 171P. 3. Carlini P, et al. *Ann Oncol.* 2001;12(11): 1539-1543.

Exemestane vs Anastrozole Second-Line (Cross-Over) GEICAM 2001/03



Sequences of Aromatase Inhibitors

- **Clinical benefit with exemestane in 43.5% and median TTP of 5.1 months in patients progressing on nonsteroidal AIs**
- **Clinical benefit with nonsteroidal AI in 55.6% and median TTP of 9.3 months in patients progressing on exemestane**

EFFECT: Evaluation of Fulvestrant and Exemestane Clinical Trial

500 mg Day 1,
250 mg Day 14
& 28, and
monthly

Prior nonsteroidal AI failure

Fulvestrant loading dose +
placebo for exemestane
(n = 330)

Exemestane 25 mg orally
daily + placebo for
fulvestrant (n = 330)

Progression

Progression

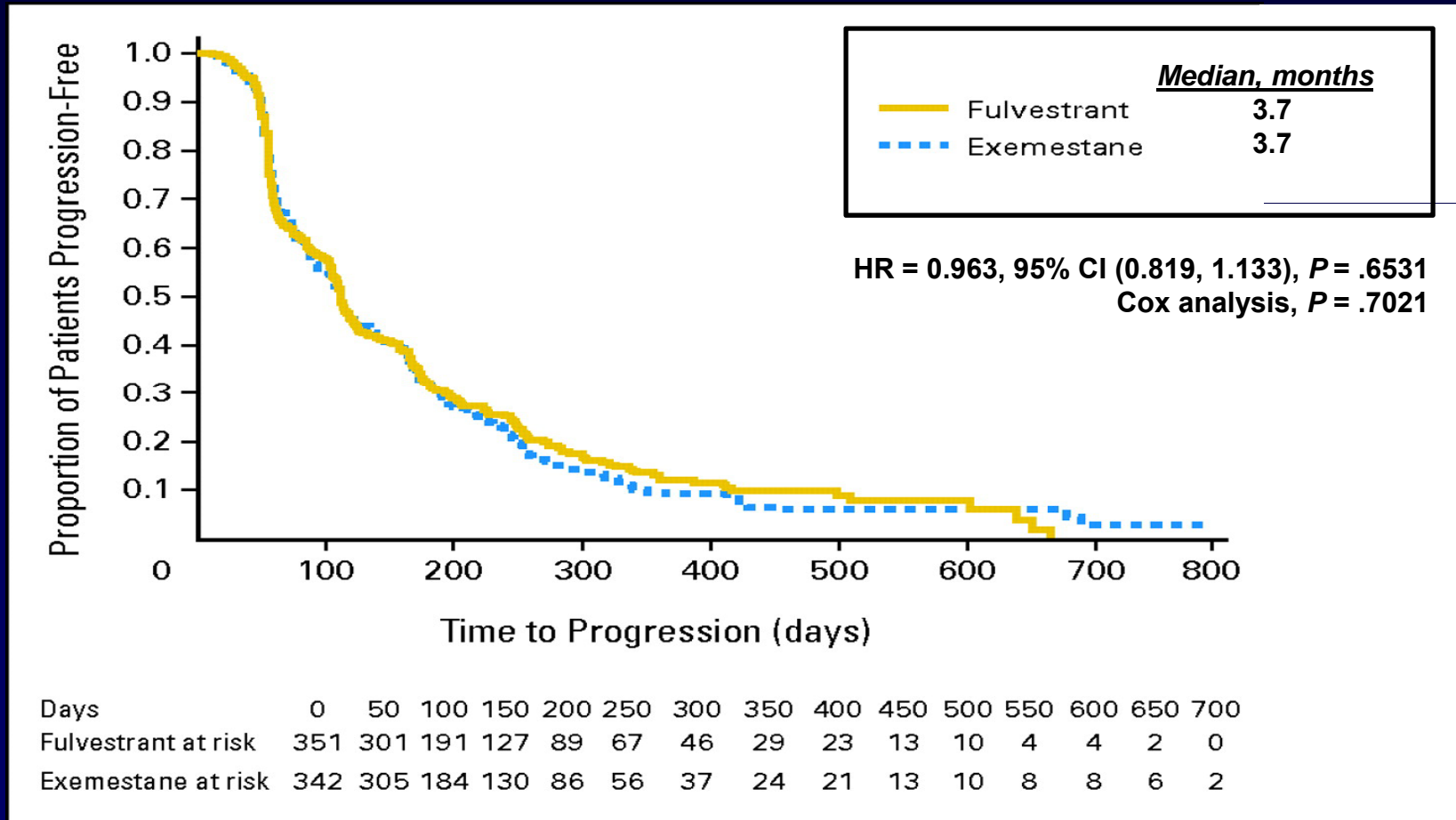
Survival

Survival

Analysis after 580 events
(progression or death)

EFFECT: Fulvestrant vs Exemestane After Progression on Nonsteroidal AI

Time to Progression



EFFECT: Objective Response and Clinical Benefit Rate

Evaluable for Response Population

	Fulvestrant	Exemestane	Odds Ratio* (95% CI)	P Value
OR rate	7.4%	6.7%	1.120	.7364
(CR+PR)	(20/270)	(18/270)	(0.578, 2.186)	
CB rate	32.2%	31.5%	1.035	.8534
(OR + SD \geq 24 weeks)	(87/270)	(85/270)	(0.720, 1.487)	

* Analyses are not adjusted for baseline covariates

My Personal Decision About This Patient

70-years-old ER[+] metastatic breast cancer relapse

I. Chemotherapy not indicated (as yet)

II. CYP2D6 status irrelevant (now)

III. Optimal endocrine therapy sequence unclear

IV. Two sequential options

