



Treatment for Advanced Breast Cancer Case Presentation



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ASCO-SEMCO 2007

Case Presentation

- A 60 year old postmenopausal woman presents with a palpable breast lesion. Biopsy demonstrates ER ++, PR+, HER2 FISH+ Infiltrative Duct Carcinoma.
- Bone scan positive for metastasis
- Imaging suggests liver metastasis (2 deposits) and biopsy from liver confirms disease.

Case Presentation

- The most appropriate first-line therapy is:
 1. Aromatase Inhibitor
 2. Tamoxifen
 3. Taxane (monotherapy or combination)
 4. Capecitabine
 5. Trastuzumab
 6. Trastuzumab + hormonal therapy
 7. Trastuzumab + Chemotherapy
 8. Other

Case Presentation

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Management Goals of Metastatic Breast Cancer

Tumor Control

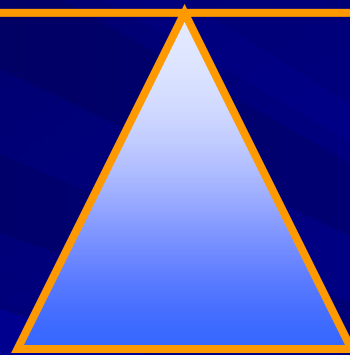
Why Do We Use Systemic Therapy For MBC ?

Cure?

Prolongation of survival

Palliation?

- Reducing tumor burden?
- Minimizing treatment toxicity?

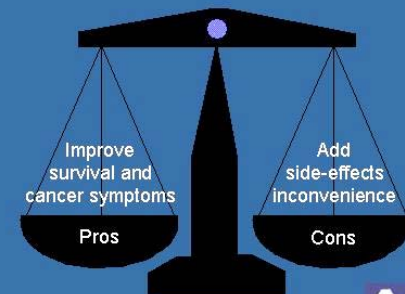


**Toxicity
QOL**

Outcome for MBC

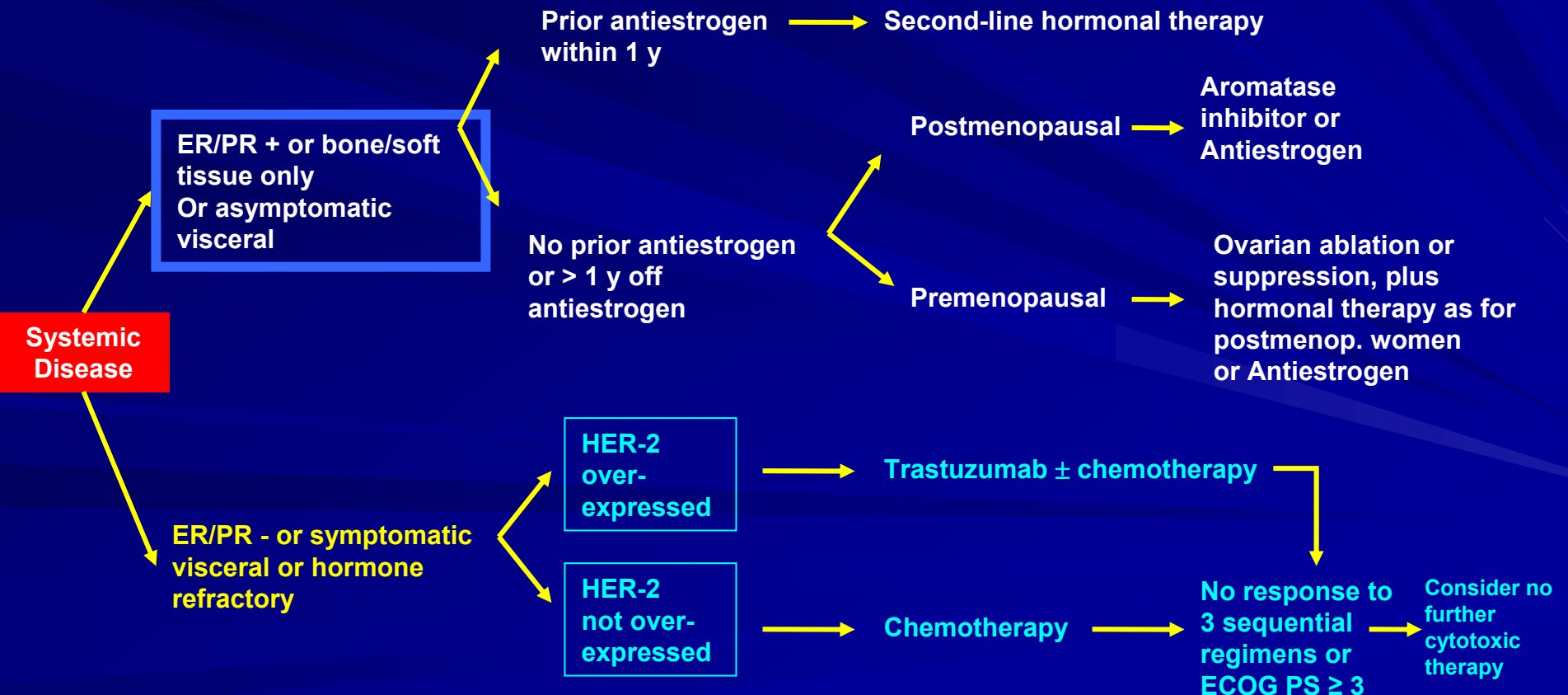
Median Survival 18-24 months

Effects of chemotherapy in advanced breast cancer



ASCO

Invasive Breast Cancer 2007 NCCN Practice Guidelines



Therapy for Metastatic Breast Cancer

- Hormonal therapy
- Chemotherapy
- Biologic therapy

Hormonal Therapy for MBC

Endocrine Agents for Postmenopausal Breast Cancer

■ Antiestrogens

- Tamoxifen
- Toremifene
- Fulvestrant

■ Aromatase inhibitors

- Anastrozole
- Letrozole
- Exemestane

■ Progestins

- Megestrol acetate
- Medroxyprogesterone acetate

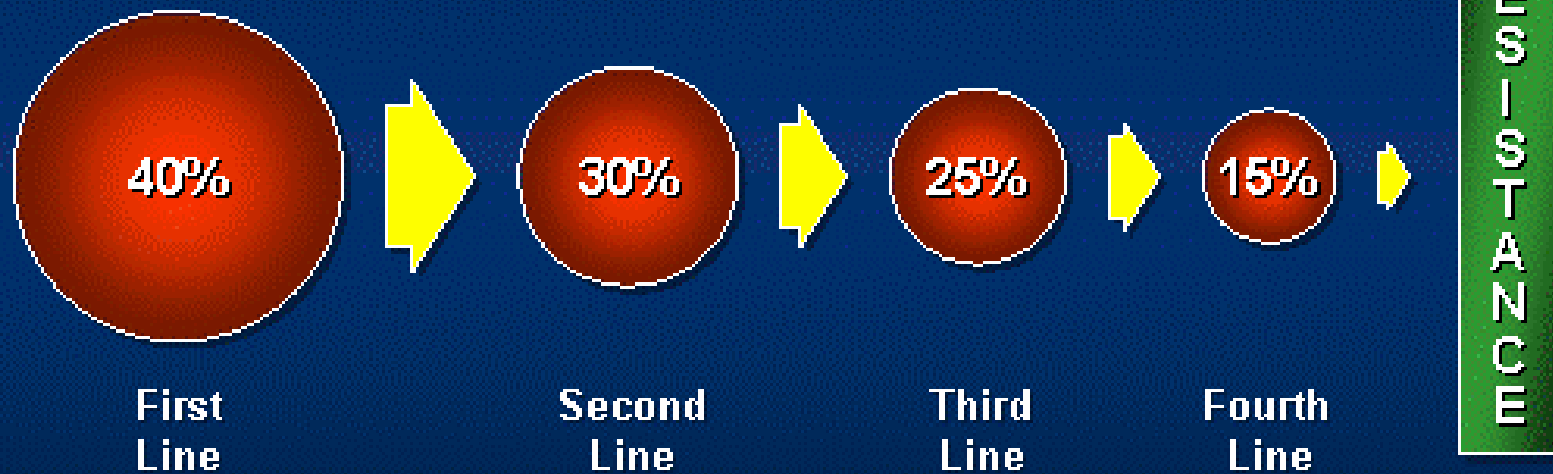
■ Estrogens

- Estradiol
- DES

■ Androgens

- Fluoxymesterone

Sequential Response to Hormonal Therapy



Rationale for Use of Aromatase Inhibitors in the First-line Setting

■ Benefits over tamoxifen:

- Proven superiority vs. tamoxifen in terms of median TTP
- Reduction in the incidence of thromboembolic events
- May be more effective in HER2 positive patients
- Unlikely to exert a proliferative effect on the endometrium

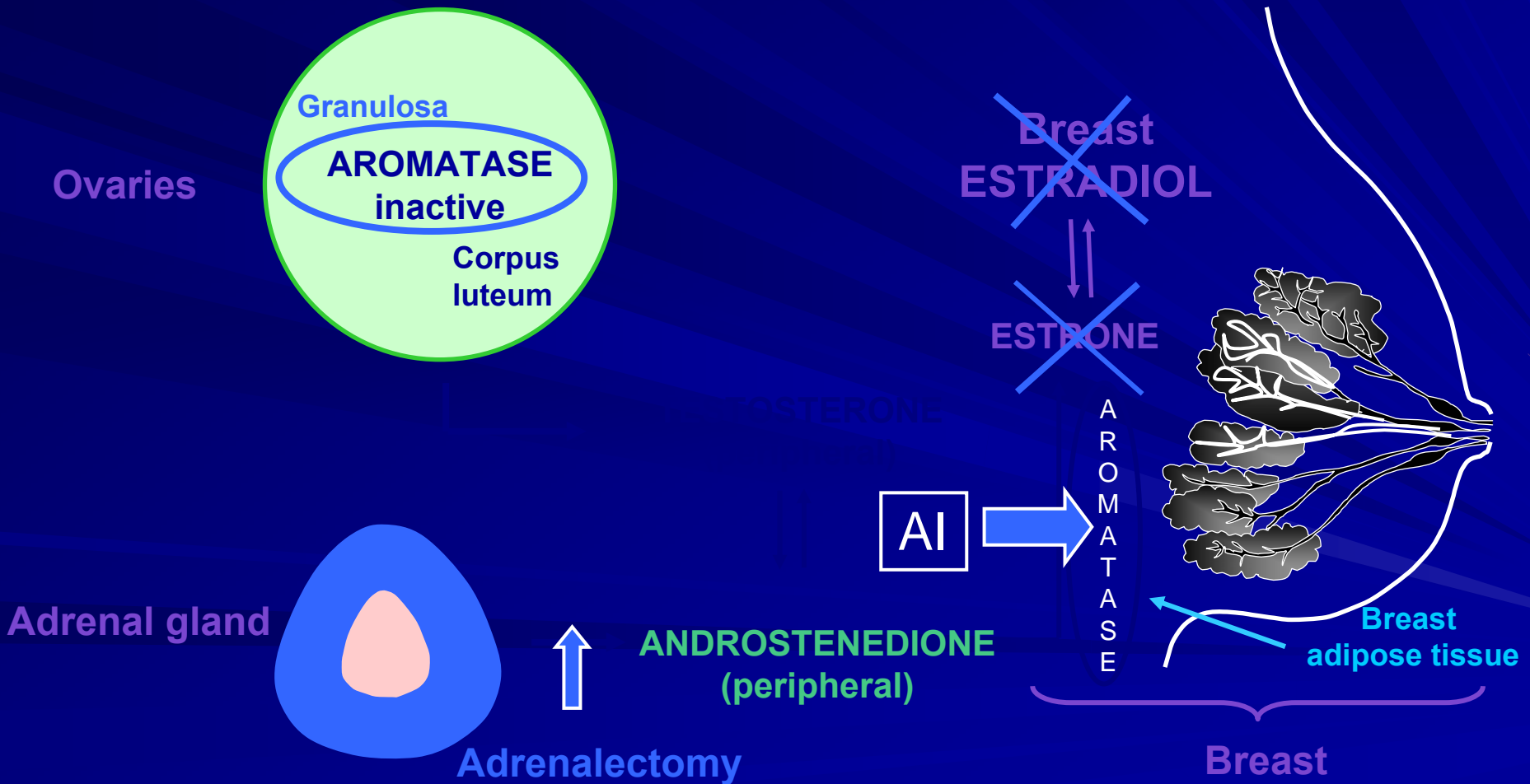
■ Proven efficacy in second-line treatment

■ Well tolerated; convenient, once-daily dosing

HER2 transfection renders MCF7 cells TAM-resistant

- **Agonist effects of TAM**
 - Non- ER pathway
 - Increase in cell proliferation (MAP kinase) with a lesser effect on apoptotic pathways (PI3 kinase)
- **Retained Antagonist Effect**
 - Able to reduce levels of ER-regulated genes
 - IGFR1
 - PgR
 - Bcl-2
 - p27

Estrogen Deprivation in Postmenopausal Women



Development of Anti-aromatase Agents

Toxicity

Specificity

Potency

First generation

Aminoglutethimide

Second generation

Fadrozole

4-OH A

Third generation

Anastrozole

Letrozole

Exemestane

**Rash,
etc.**

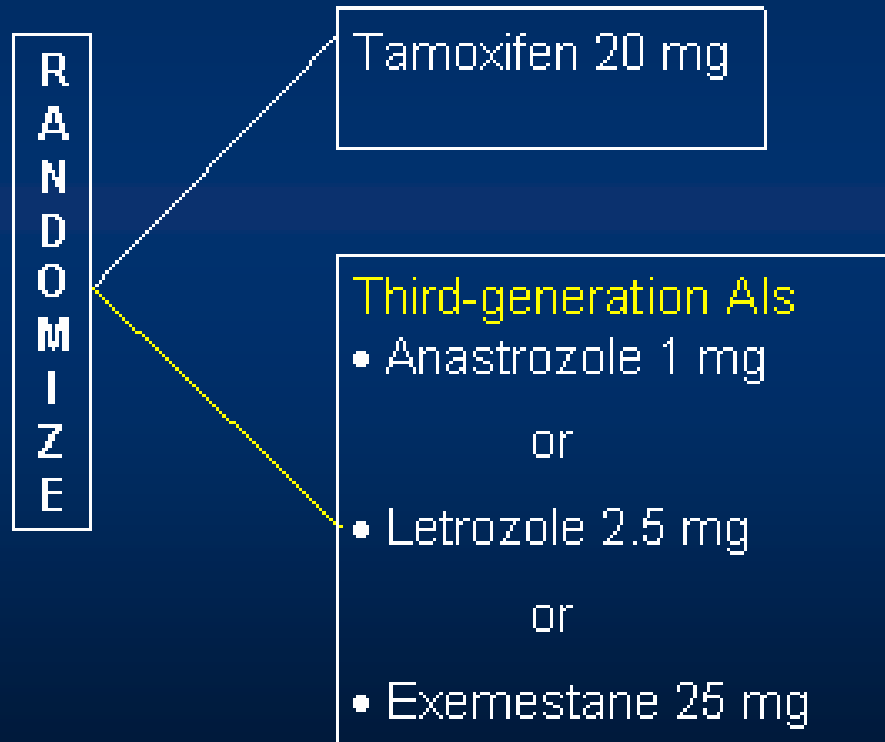
**No adrenal
insufficiency,
etc.**

1

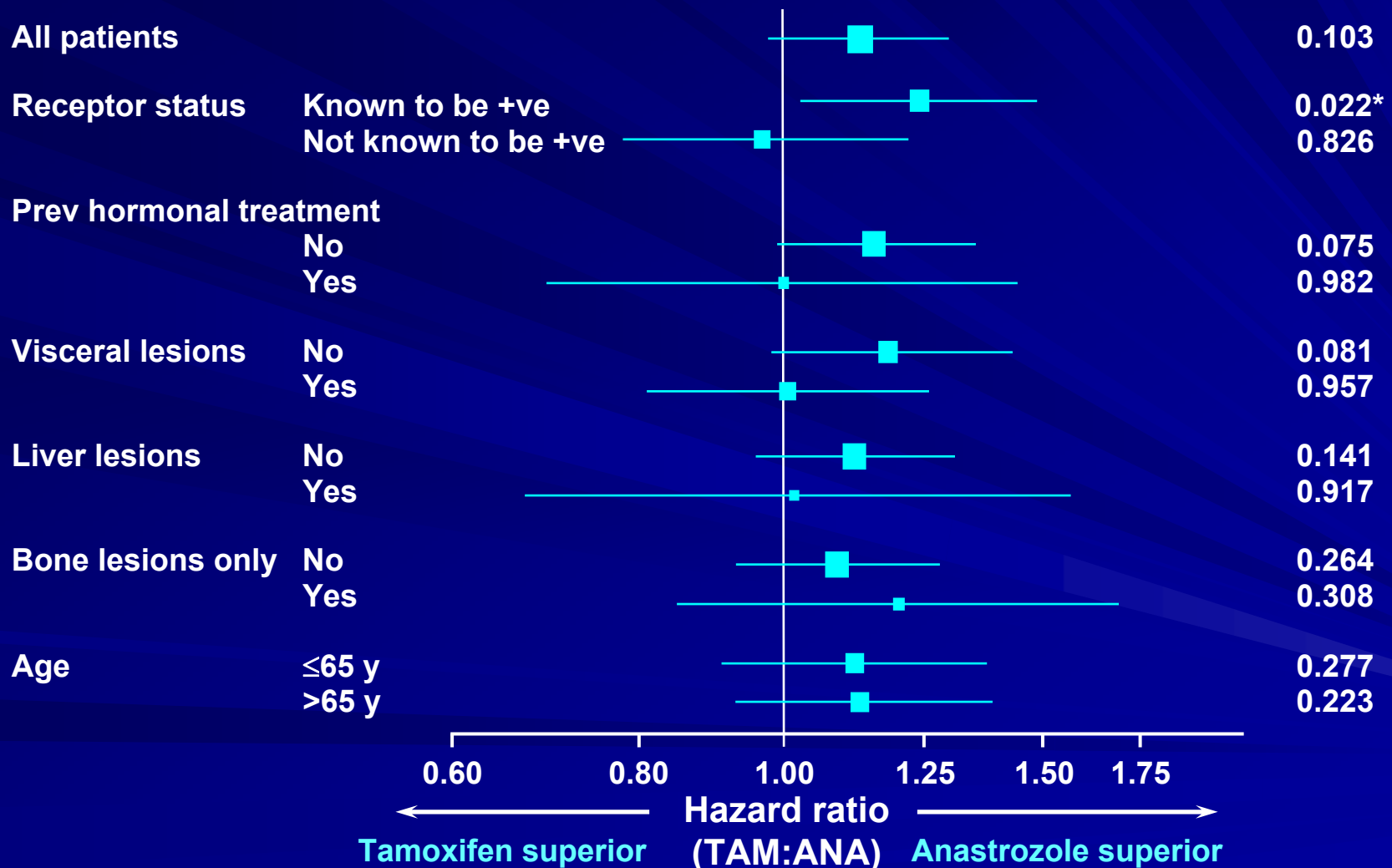
100

**1,000
to
10,000**

Third-Generation AIs in First-Line Studies

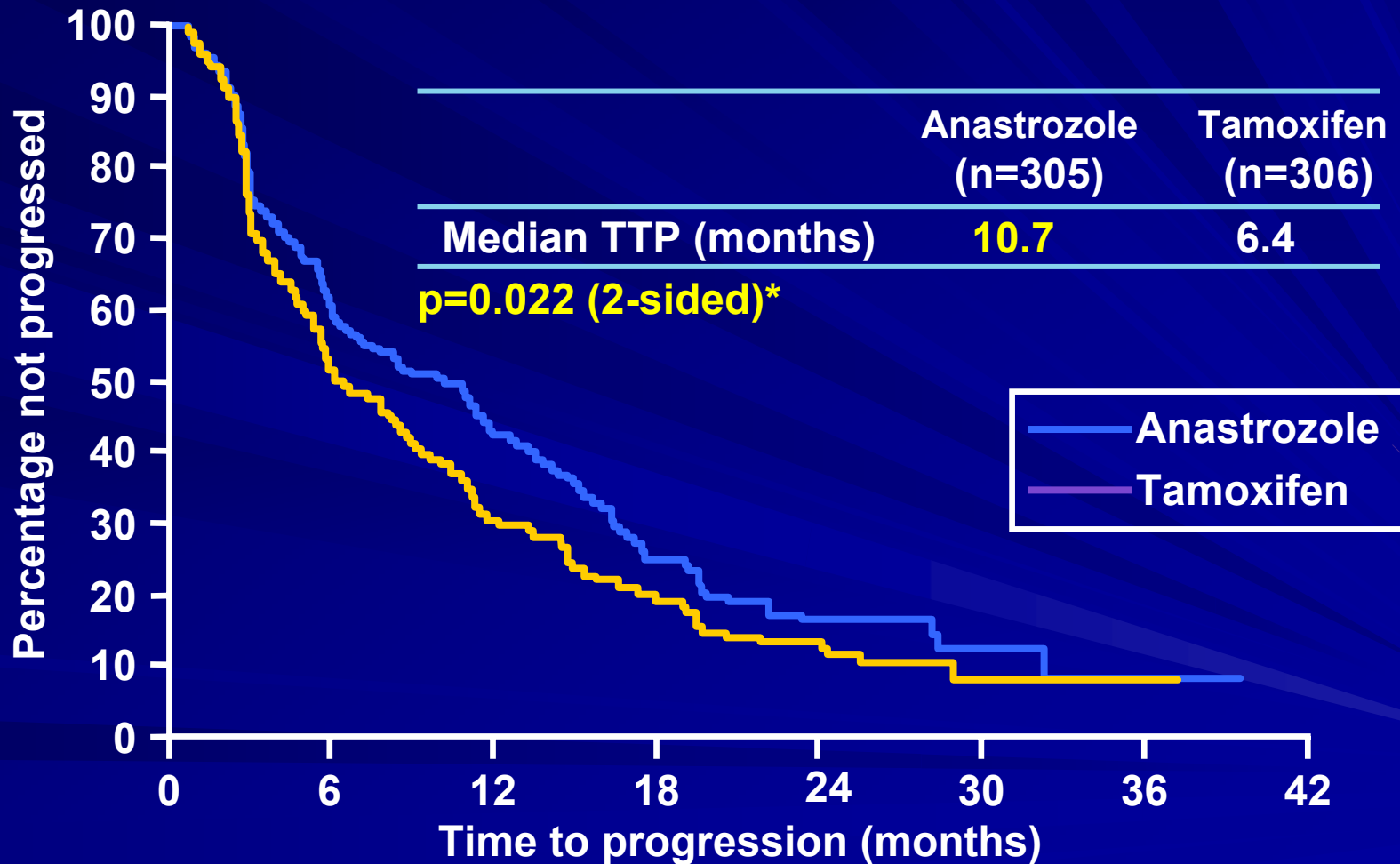


Anastrozole vs Tamoxifen Trials 0030 and 0027 Combined: Subgroup Analyses of TTP



Anastrozole vs Tamoxifen

Combined analysis of patients with receptor-positive tumours
Kaplan-Meier probability of TTP



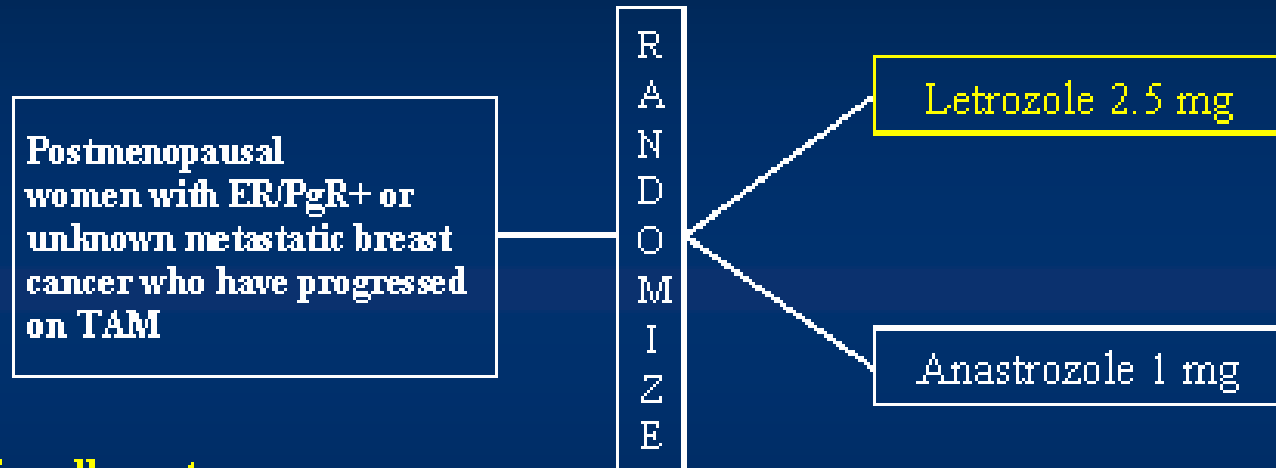
*Based on exploratory subgroup analysis

Bonneterre et al 2001

Letrozole vs Anastrozole

HT-18

Letrozole vs Anastrozole in Second-Line Treatment of MBC: FEM-INT-01



Enrollment

- Recruited from 105 centers in 19 countries
- 713 patients entered the trial

Anastrozole n=357

Letrozole n=356

End Points

TTP

ORR

Response Duration

Survival

Data collection stopped at visit 12 (30 months)

Letrozole vs Anastrozole

HT-19

Letrozole vs Anastrozole: Time Events

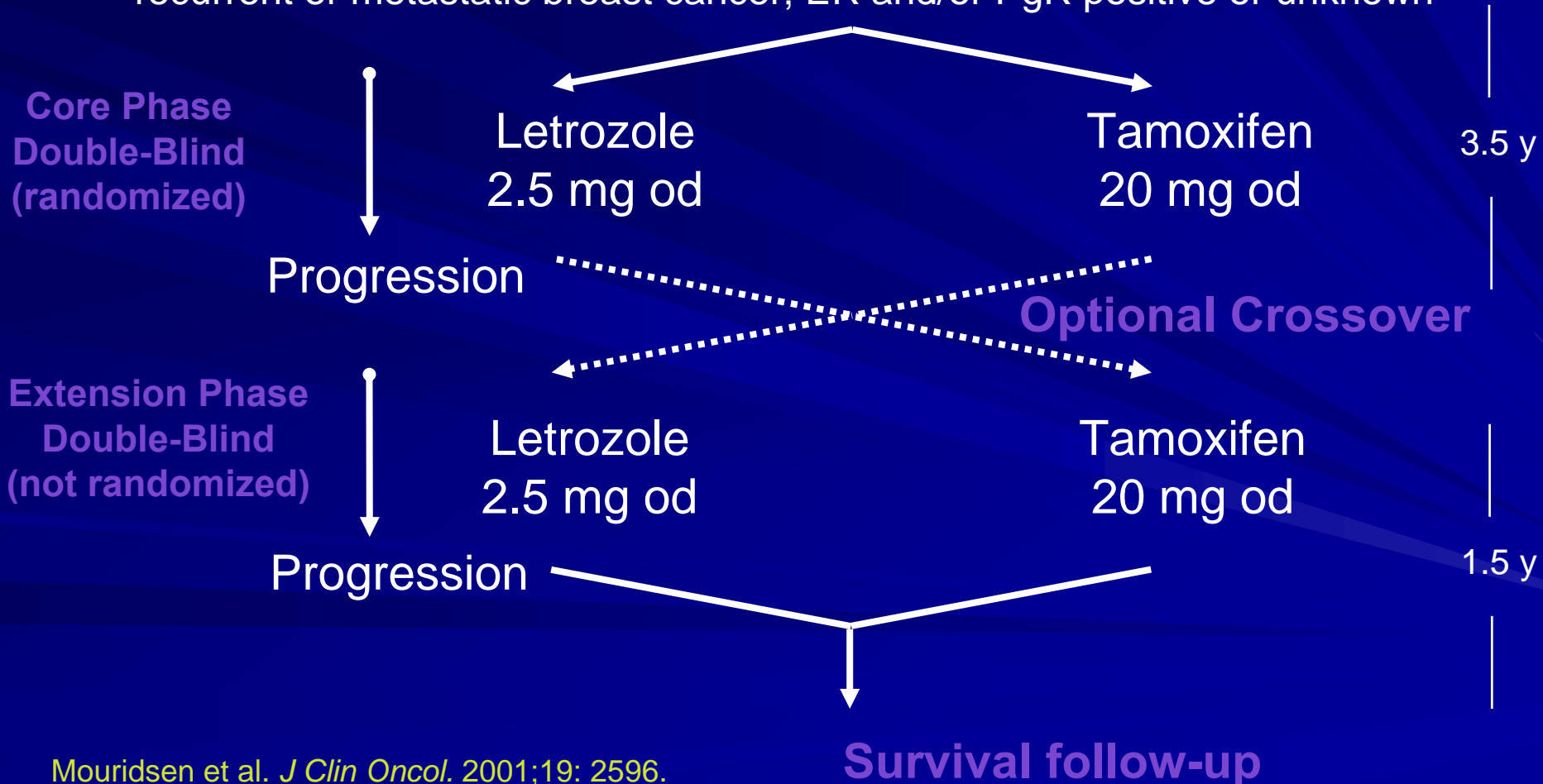
	ITT Population		<i>P</i> value
	Letrozole (n=356)	Anastrozole (n=357)	
Median TTP (mo) 90% CI	5.7 5.1-6.0	5.7 4.6-6.1	0.920
Median TTF (mo) 90% CI	5.6 4.4-5.8	5.6 4.0-6.0	0.761
Median OS (mo) 90% CI	22.0 19.6-24.6	20.3 18.0-23.1	0.624

FEM-INT-01: summary of adverse events

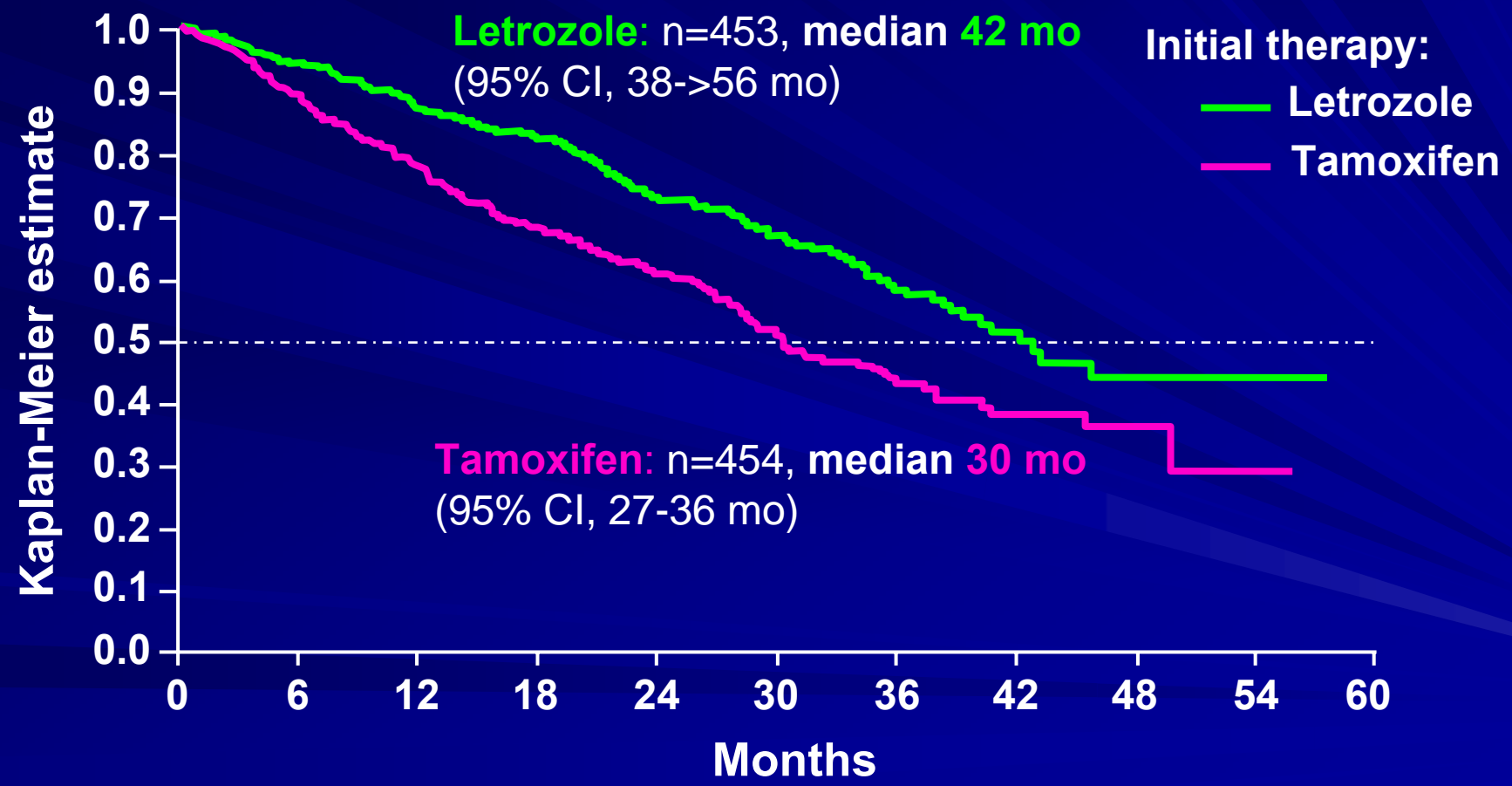
	Anastrozole (n=357)	Letrozole (n=356)
Adverse event >2%		
bone pain	47 (13)	53 (15)
dyspnoea	40 (11)	37 (10)
nausea	39 (11)	28 (8)
vomiting	19 (5)	23 (7)
abdominal pain	20 (6)	15 (4)
Any serious adverse event	63 (18)	68 (19)
Discontinuations due to adverse event	28 (8)	28 (8)

Protocol 025 Study Design: Letrozole vs. Tamoxifen as First-Line Therapy

Study population: Postmenopausal; locally advanced or locoregionally recurrent or metastatic breast cancer; ER and/or PgR positive or unknown



Exploratory Analysis: First-Line Survival (Data Censored at Crossover) **Letrozole** vs Tamoxifen



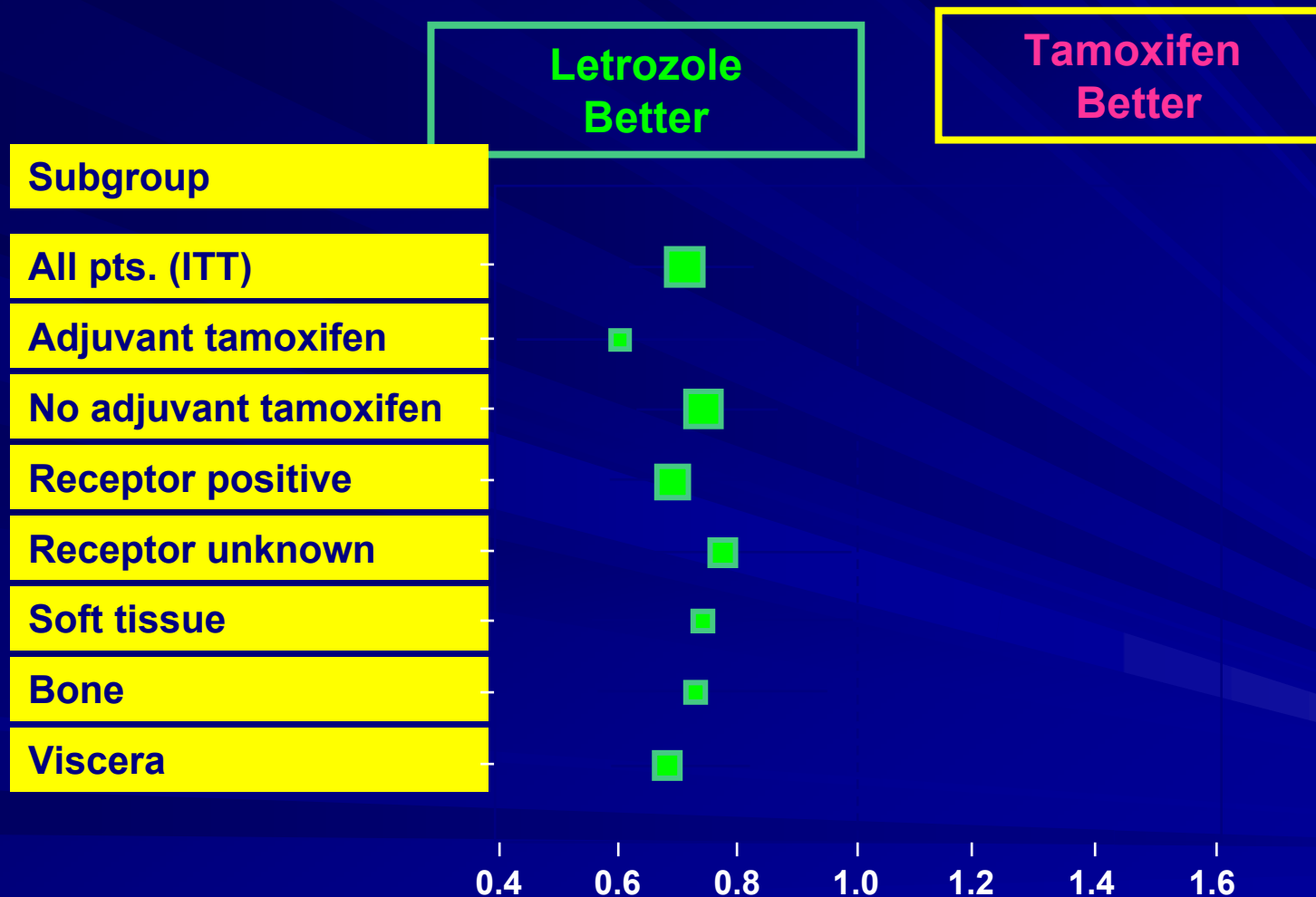
Update of Letrozole vs. Tamoxifen Trial P025

	At 1 year	At 2year
Efficacy endpoints		
■ TTP	Yes	Yes
■ TTF	Yes	Yes
■ ORR	Yes	Yes
■ CB	Yes	Yes
■ Survival	NO	Yes*
Safety/tolerability	Yes	Yes

Mouridsen et al. J Clin Onco. 2001 ; 19 : 2596l

* p=0.02

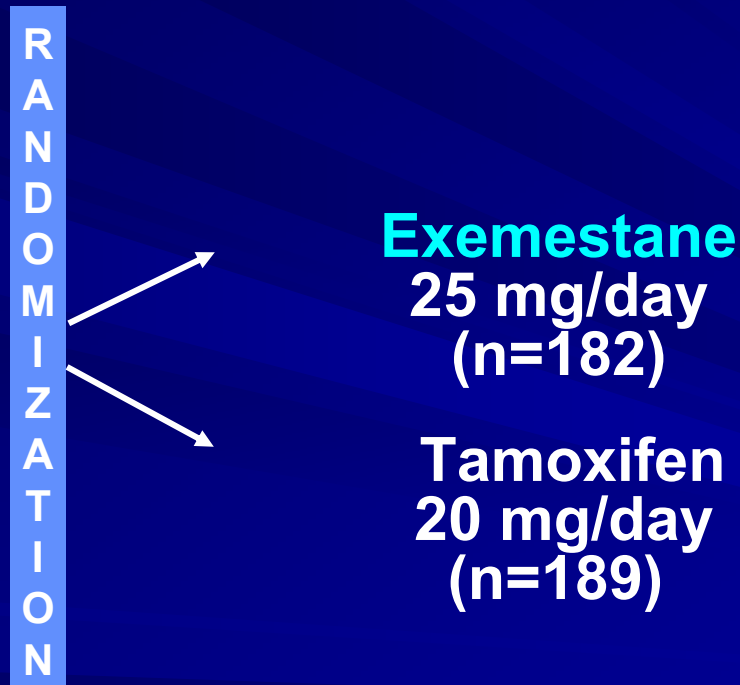
Letrozole vs. Tamoxifen: TTP by Baseline Covariates



Hazard Ratios and 95% Confidence Intervals

Exemestane as Initial Therapy for MBC: Randomized EORTC Phase II/III Trial (Postmenopausal)

EORTC 10951



EORTC 10951

Outcomes	EXE (n=182)	TAM (n=189)
Events to date, no (%)	158 (87)	161 (85)
Median PFS, months	9.9	5.8
Proportion with 12 month PFS,%	42	31

Overall survival was improved significantly with exemestane $p=0.02$

Invasive Breast Cancer

Clinical Practice Guidelines in Oncology 2007

Follow up Therapy for Hormone Treatment of Recurrence/Stage IV Disease

Continue hormonal therapy Until progression or Unacceptable toxicity

Progression

No clinical benefit after 3 consecutive hormonal therapy regimens Or symptomatic visceral disease

Yes

Chemotherapy

No

Trial of new hormonal therapy

No response

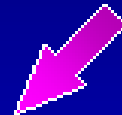
Chemotherapy

Fulvestrant: trial designs

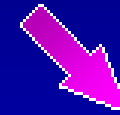
Postmenopausal women with advanced breast cancer receiving prior endocrine treatment for early or advanced breast cancer



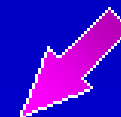
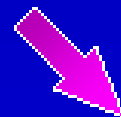
Trials 0020 and 0021



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

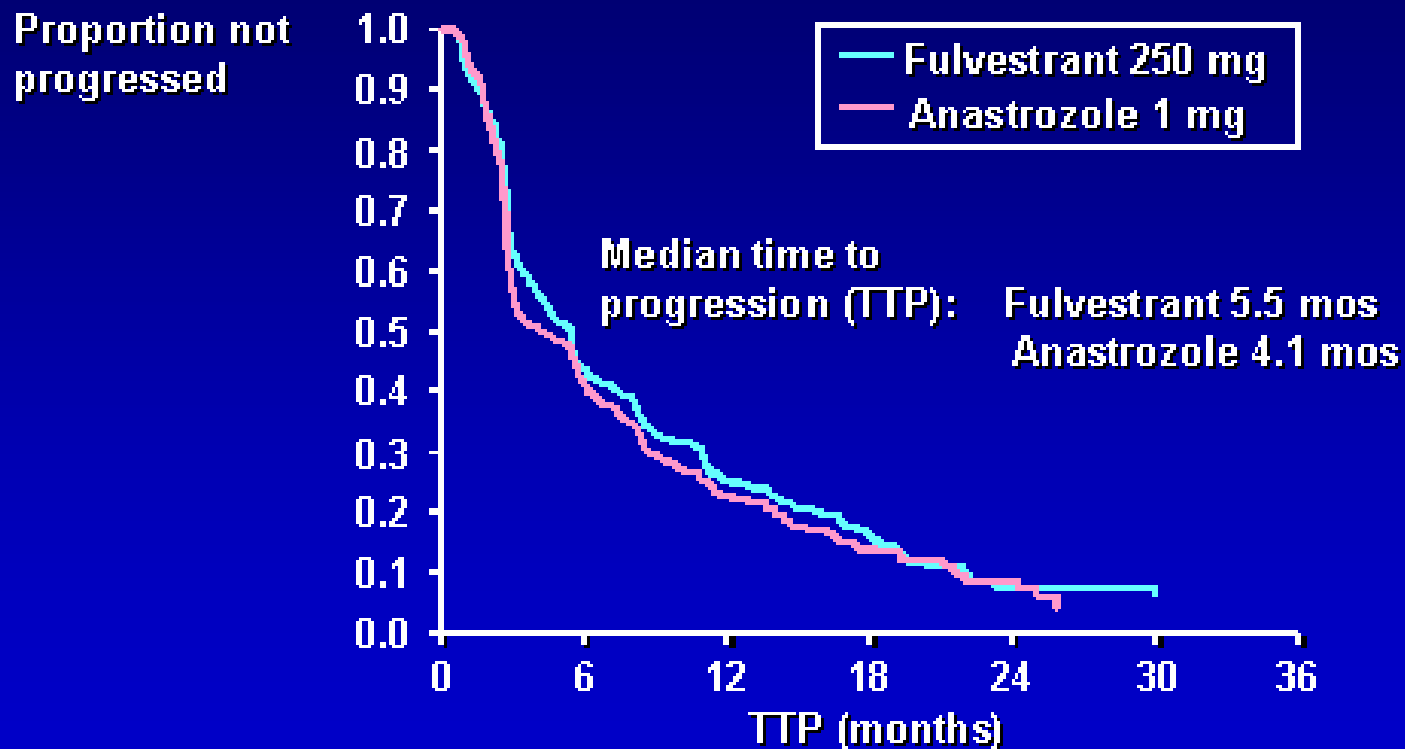


Anastrozole 1 mg daily orally
Trial 0020: (n=229)
Trial 0021: (n=194)



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

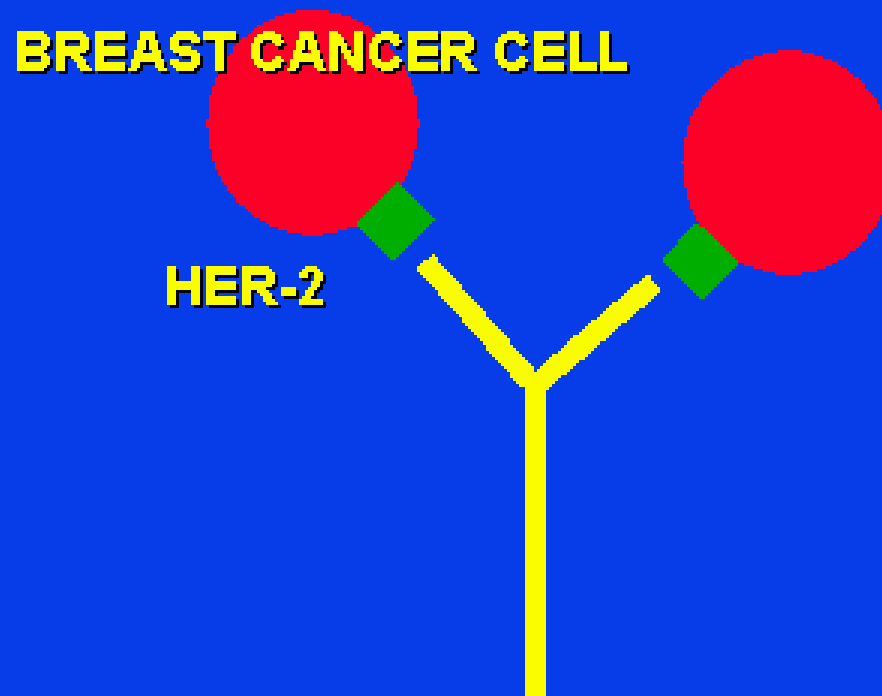
Fulvestrant: prospective combined analysis (time to progression)



HR 0.95;
95.14% CI 0.82, 1.10; p=0.48

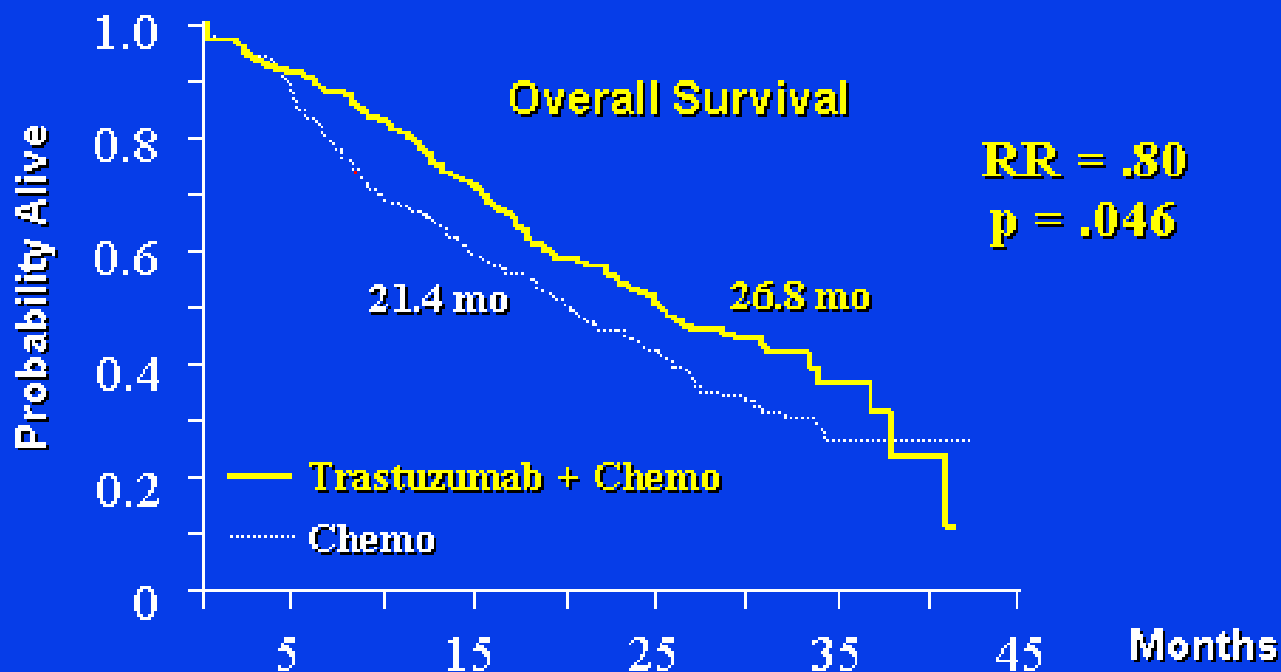
Howell et al, Eur J Cancer 2001; 37(suppl 5): 9(0-24)

Addition of Biologics to Chemotherapy: Trastuzumab (Herceptin) Anti-HER-2 Antibody



Chemotherapy +/- Trastuzumab (Herceptin) in Metastatic Breast Cancer

Slamon D et al, N Eng J Med 2001



65 % of CT group crossed over to trastuzumab at progression

Trastuzumab and Chemotherapy: Combination Index (CI) Scores for in Vitro Activity Against HER2+ Breast Cancer Cell Lines

Synergistic (CI <1)		Additive (CI = 1)		Less than Additive (CI >1)	
Vinorelbine	0.34	Doxorubicin	0.82–1.16	Methotrexate	1.36
Docetaxel/carboplatin	0.34	Paclitaxel	0.91	Gemcitabine	1.25–5.34
Docetaxel	0.41	Epirubicin	0.99	Fluorouracil	2.87
Etoposide	0.54	Vinblastine	1.09		
Cyclophosphamide	0.57				
Paclitaxel/carboplatin	0.64				
Thiotepa	0.67				
Cisplatin	0.67				
Liposomal doxorubicin	0.7				

Pegram M, Hsu S, Lewis G, et al. *Oncogene*. 1999;18:2241–2251.

Pietras RJ, Pegram MD, Finn RS, Maneval DA, Slamon DJ. *Oncogene*. 1998;17:2235–2249.

www.nci.cu.edu.eg



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Thank you