ATLAS OF MOLECULAR ONCOLOGY

BREAST CANCER PATHWAYS

Current Clinical and Future Developmental Paradigms Involving Molecular Pathways in Breast Cancer. Estrogen and Progesterone Receptor Pathways and Agents

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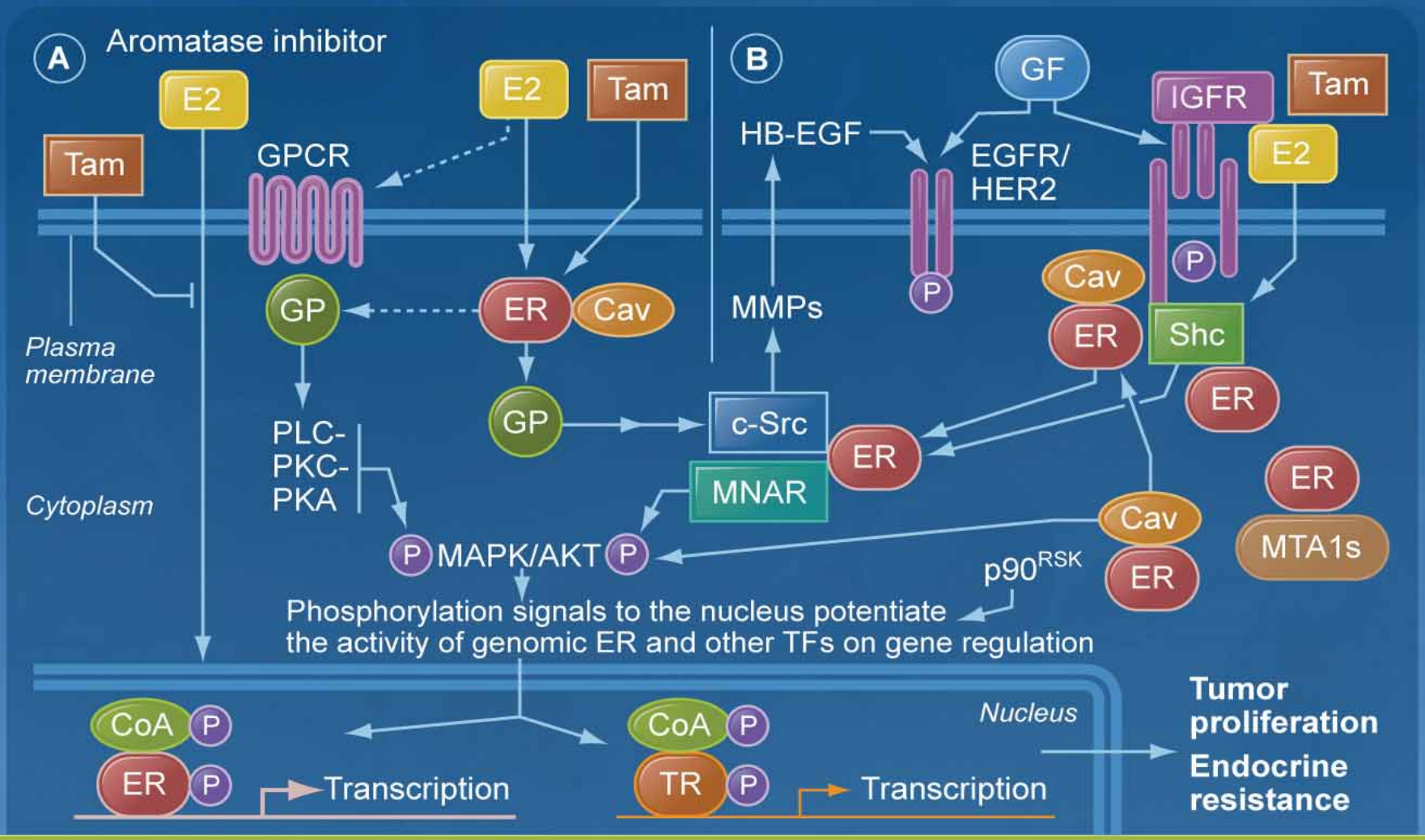
Disclosures for Paul E Goss, MD, PhD, FRCPC, FRCP (UK)

No real or apparent conflicts of interest to disclose

Road Map to Talk

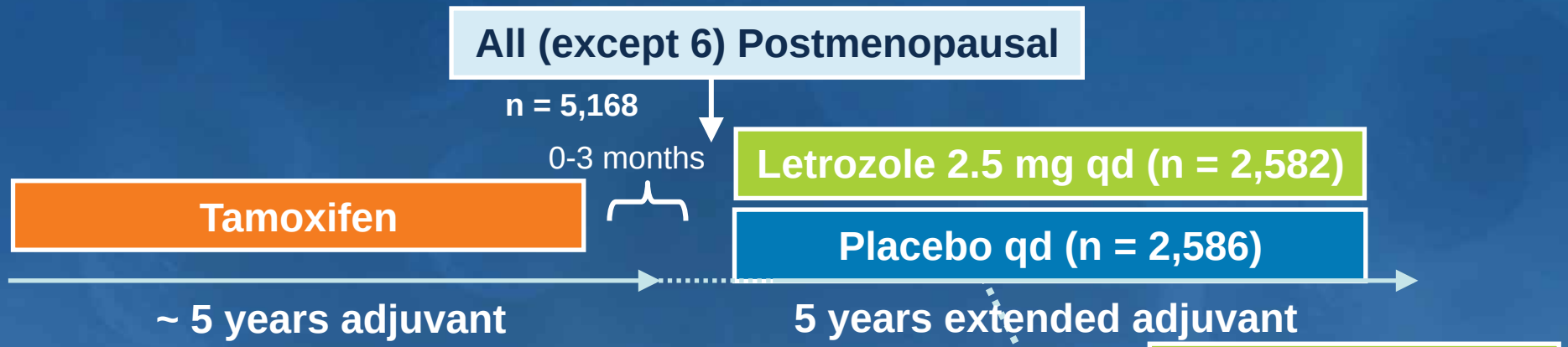
- Estrogen Receptor Pathways in Breast Cancer
  - Genomic and Non-genomic pathways
- Evolving Strategies in ER-Positive Early Breast Cancer
  - Optimal: duration, agent, combination, schedule
- Novel Endocrine + Targeted Therapy Combinations
  - Her2
  - IGF1R
  - Pi3Kinase/PTEN
  - Src/Abl
  - WT1 Antigen Specific Cancer Vaccine
  - Her1,3,4

Integration of Genomic and Non-genomic/Rapid ER Signaling and Its Crosstalk with Growth Factor Receptor and Cell Kinase Pathways in Endocrine Resistance: A Working Model



Arpino G et al. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: Molecular mechanism and clinical implications for endocrine therapy resistance. *Endocr Rev* 2008;29:217-233. Copyright 2008, the Endocrine Society.

Optimal Duration: 10 Years vs 5 Years Endocrine Therapy (MA.17)



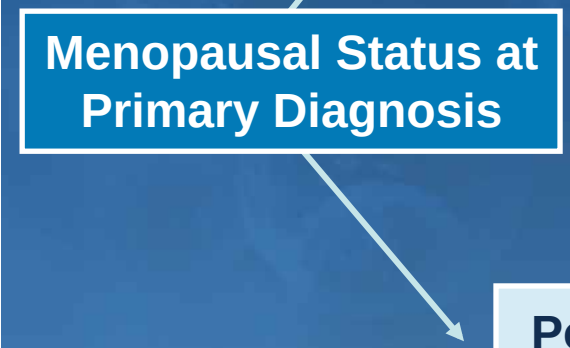
- **Immediate Letrozole improved[2,3]:**
  - DFS (HR 0.58; p < 0.001)
  - DDFS (HR 0.60; p = 0.002)
  - OS (HR 0.82; p = 0.3)

  → **Regulatory Approval**
- **Delayed (post-unblinding) letrozole improved[7]:**
  - DFS (HR 0.31; p < 0.0001)
  - DDFS (HR 0.28; p = 0.002)
  - OS (HR 0.58; p significant)

  → **Regulatory Approval Extended**

[2]Goss et al. *N Engl J Med.* 2003;349:1793 [3]Goss, P et al. J Natl Cancer Inst. 2005;97:1262; [7]Goss et al. *J Clin Oncol* 2008;26(12):1948-55.

MA.17: Premenopausal Status at Primary Diagnosis



Premenopausal n = 889

a) <50 years of age with menses but underwent subsequent bilateral oophorectomy when tamoxifen started **or**

b) <50 years of age with menses when tamoxifen started but became amenorrheic during adjuvant chemotherapy or on tamoxifen

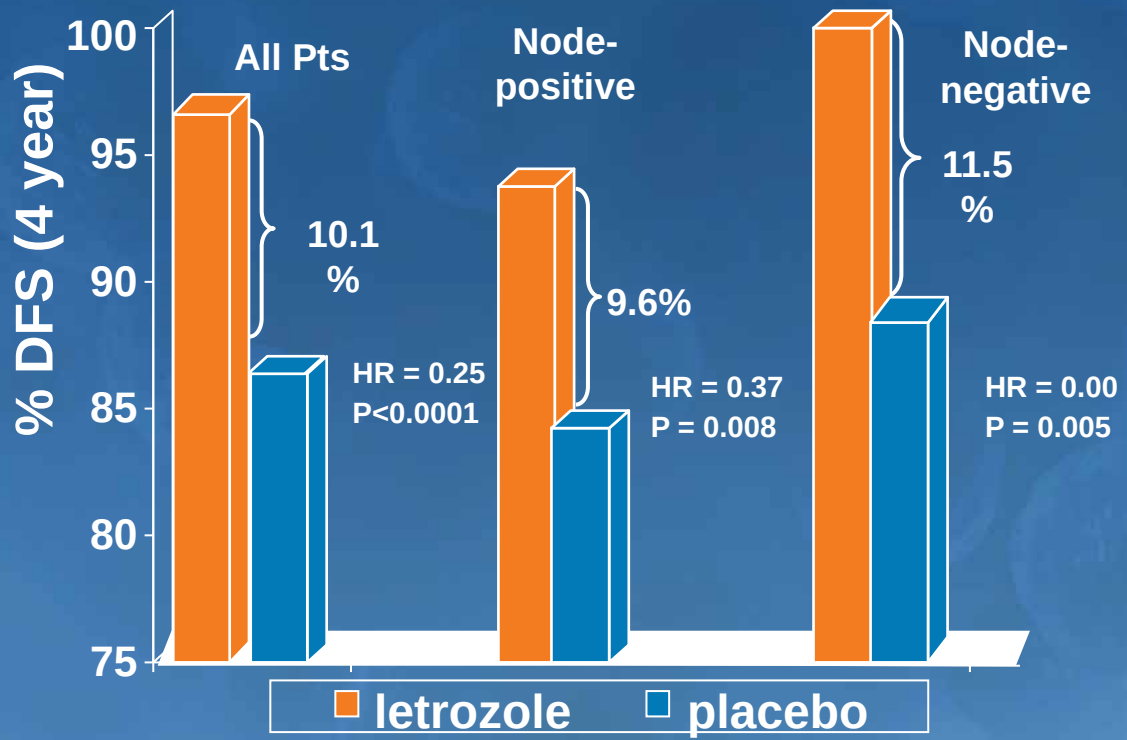
Post-menopausal n = 4,277

a) ≥50 years of age without menses at diagnosis **or**

b) <50 years of age without menses and considered postmenopausal at diagnosis **or**

c) considered post-menopausal by virtue of menopausal LH/FSH

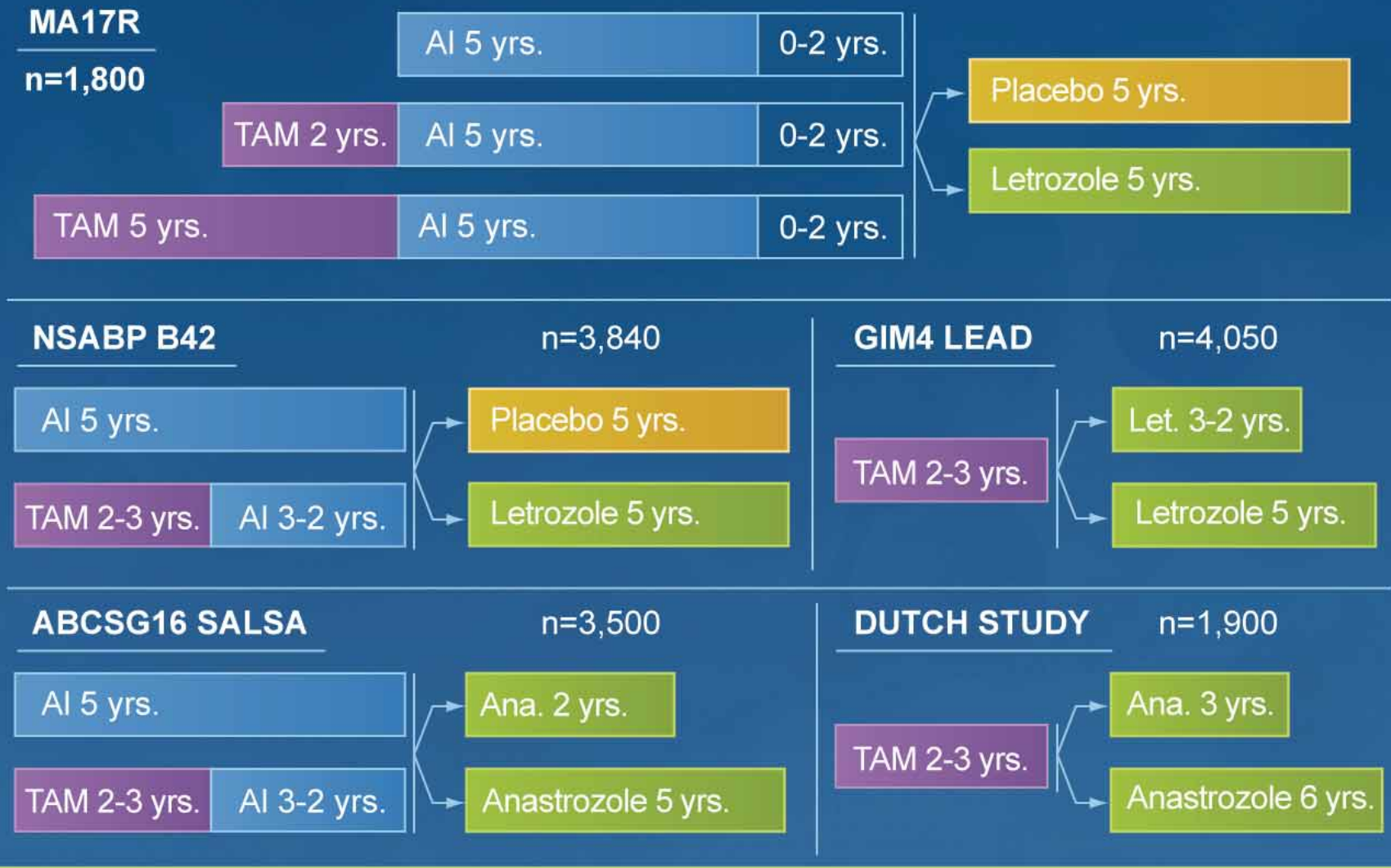
Extended Endocrine Therapy in Premenopausal Breast Cancer



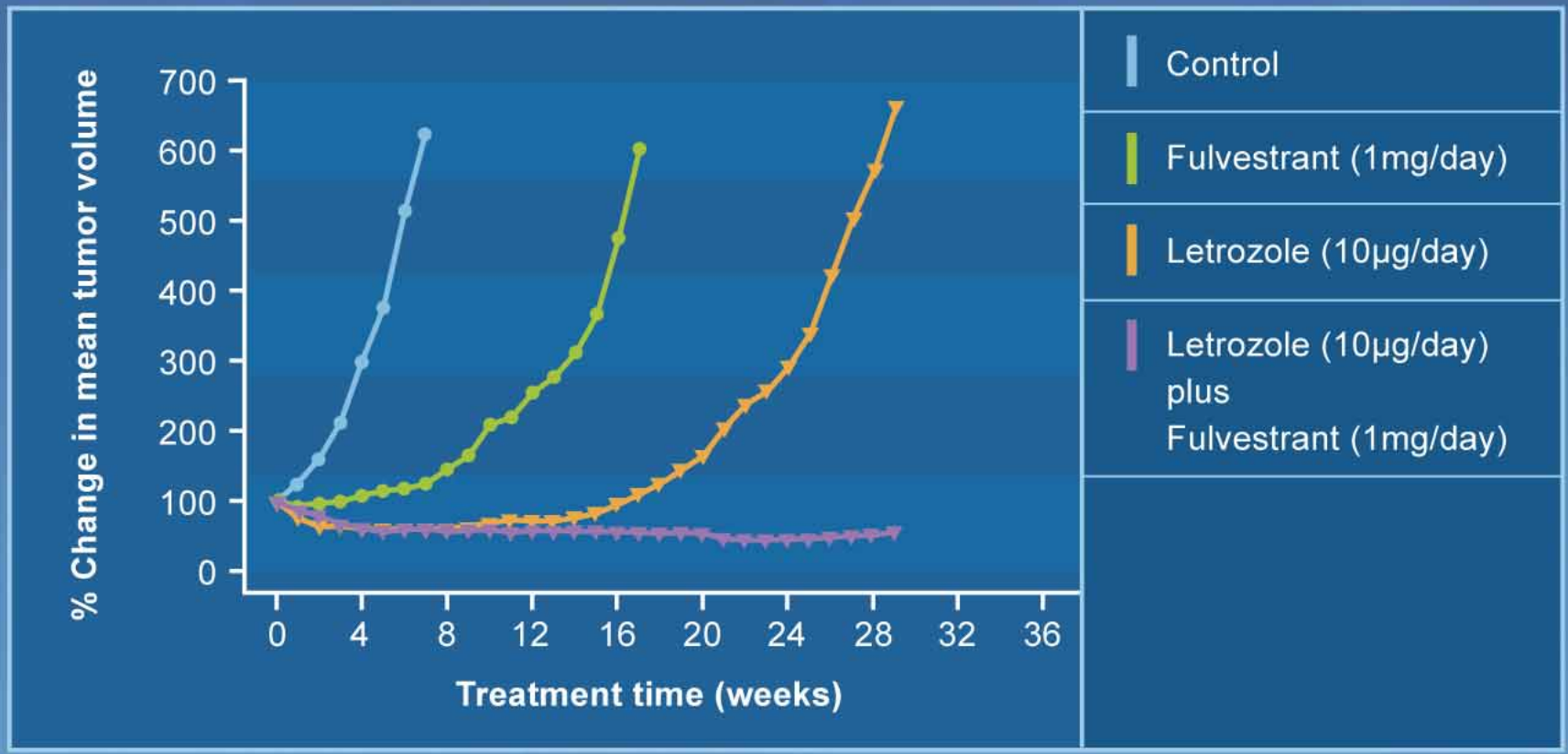
1. Premenopausal patients with ER-positive breast cancer benefit significantly from extended AI therapy after they become menopausal
2. The benefit was similar in women who delayed endocrine therapy up to 6 years after tamoxifen

Goss PE et al. San Antonio Breast Cancer Symposium 2009;Abstract 13.

Adjuvant Endocrine Therapy (AI) > 5 Years



Letrozole vs Letrozole + Fulvestrant "Total E2 Block"
a) On the Growth of MCF-7Ca Aromatase Xenograft
b) In Ongoing Clinical Trials



Reprinted with permission from Brodie A et al. *Clin Cancer Res* 2005;11(2 Pt 2):884s-8s. Figure 2.

Total Estrogen Blockade (continued)

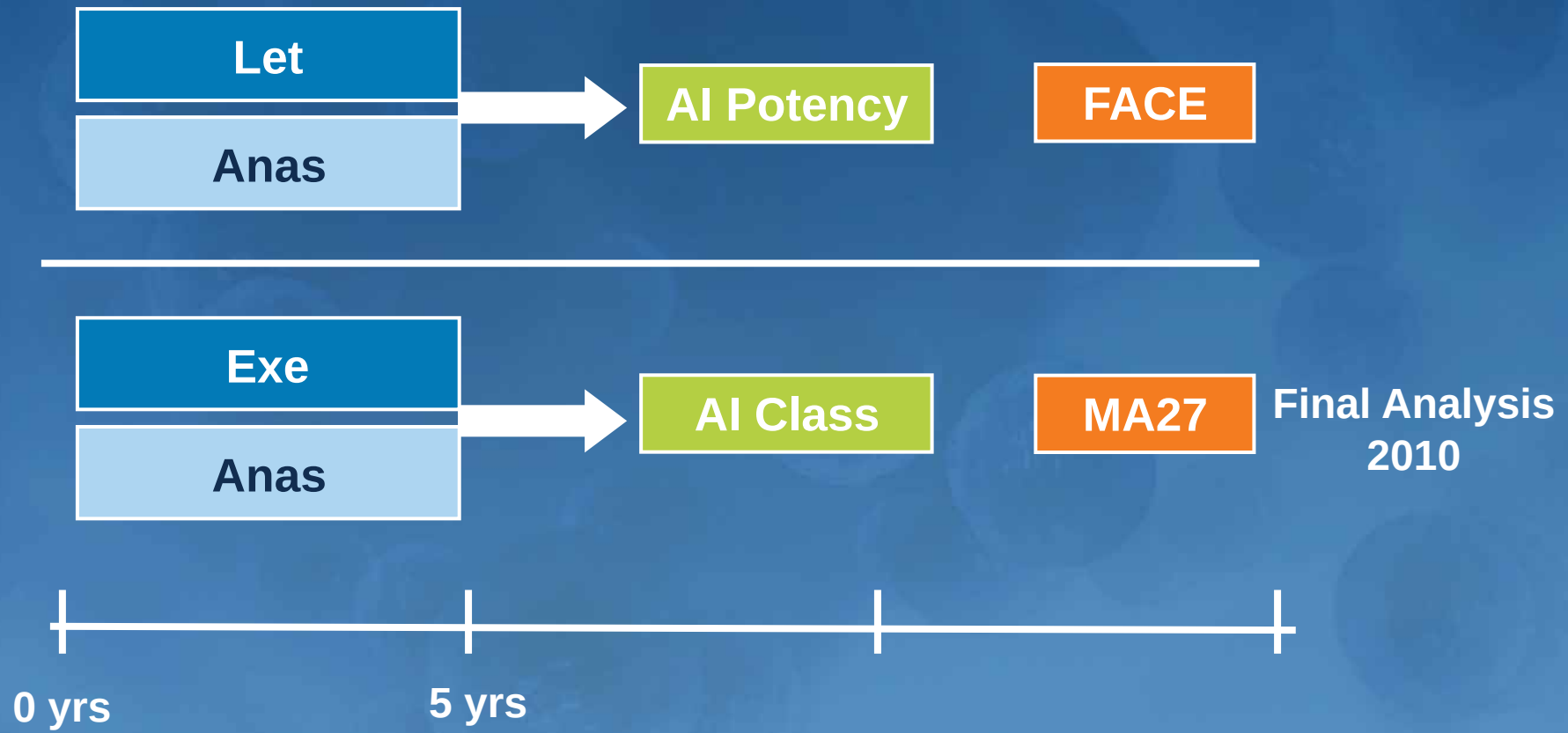
	Fulvestrant + Anastrozole n=258	Anastrozole n=256
Number progressed (%)	200 (77.5%)	200 (78.1%)
Median TTP (months)	10.8	10.2
Hazard Ratio (95% CI)	0.99 (0.81, 1.20)	
p-value	0.91	

TTP per-protocol analysis (unadjusted model)		
	Fulvestrant + Anastrozole n=175	Anastrozole n=175
Hazard Ratio (95% CI)	1.05 (0.83, 1.32)	
p-value	0.70	

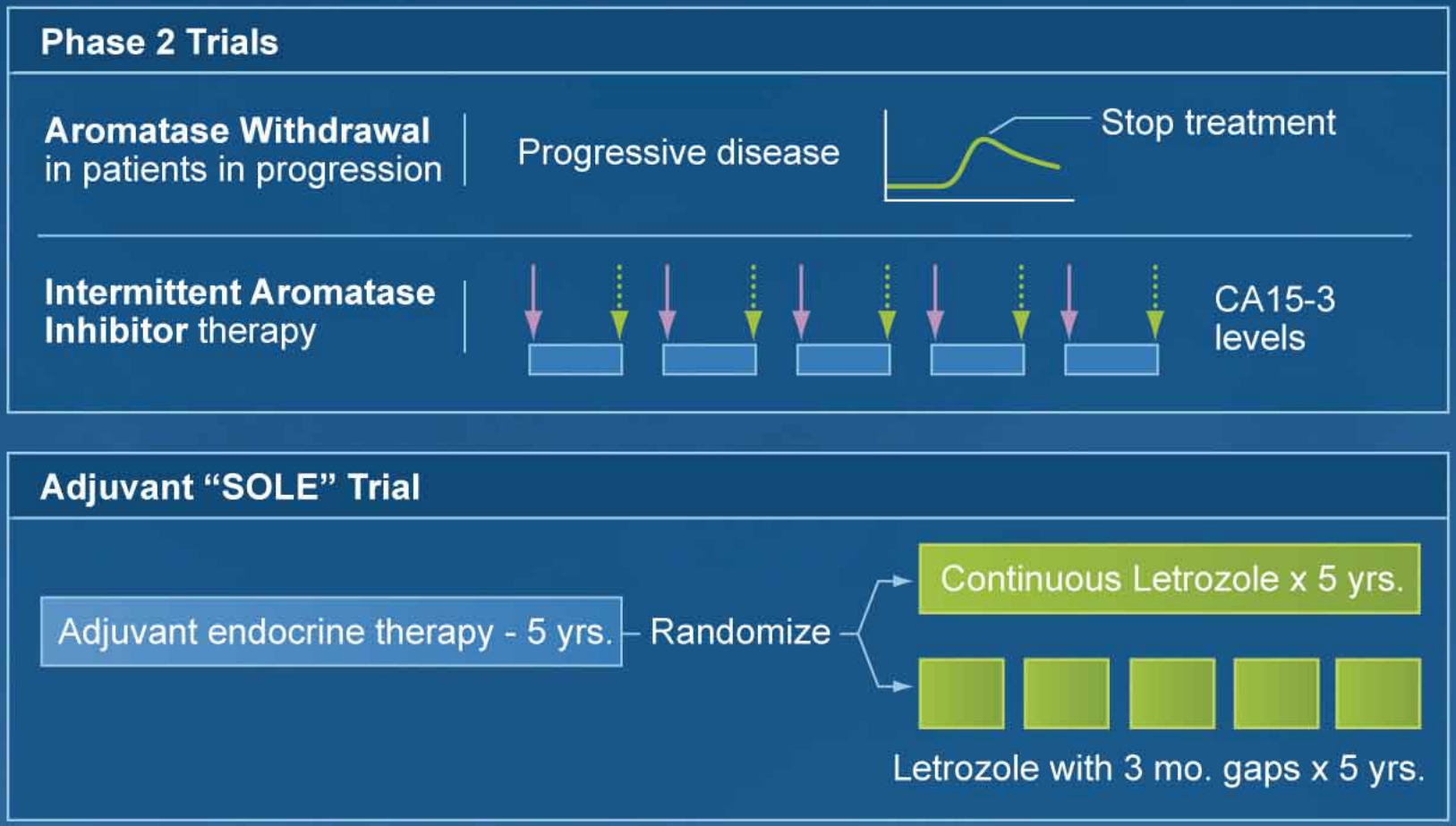
Bergh J et al. San Antonio Breast Cancer Symposium 2009;Abstract 23.

Current Adjuvant Endocrine Therapy
Optimal Aromatase Inhibitor

Postmenopausal Women



Ongoing Intermittent Aromatase Inhibitor Trials



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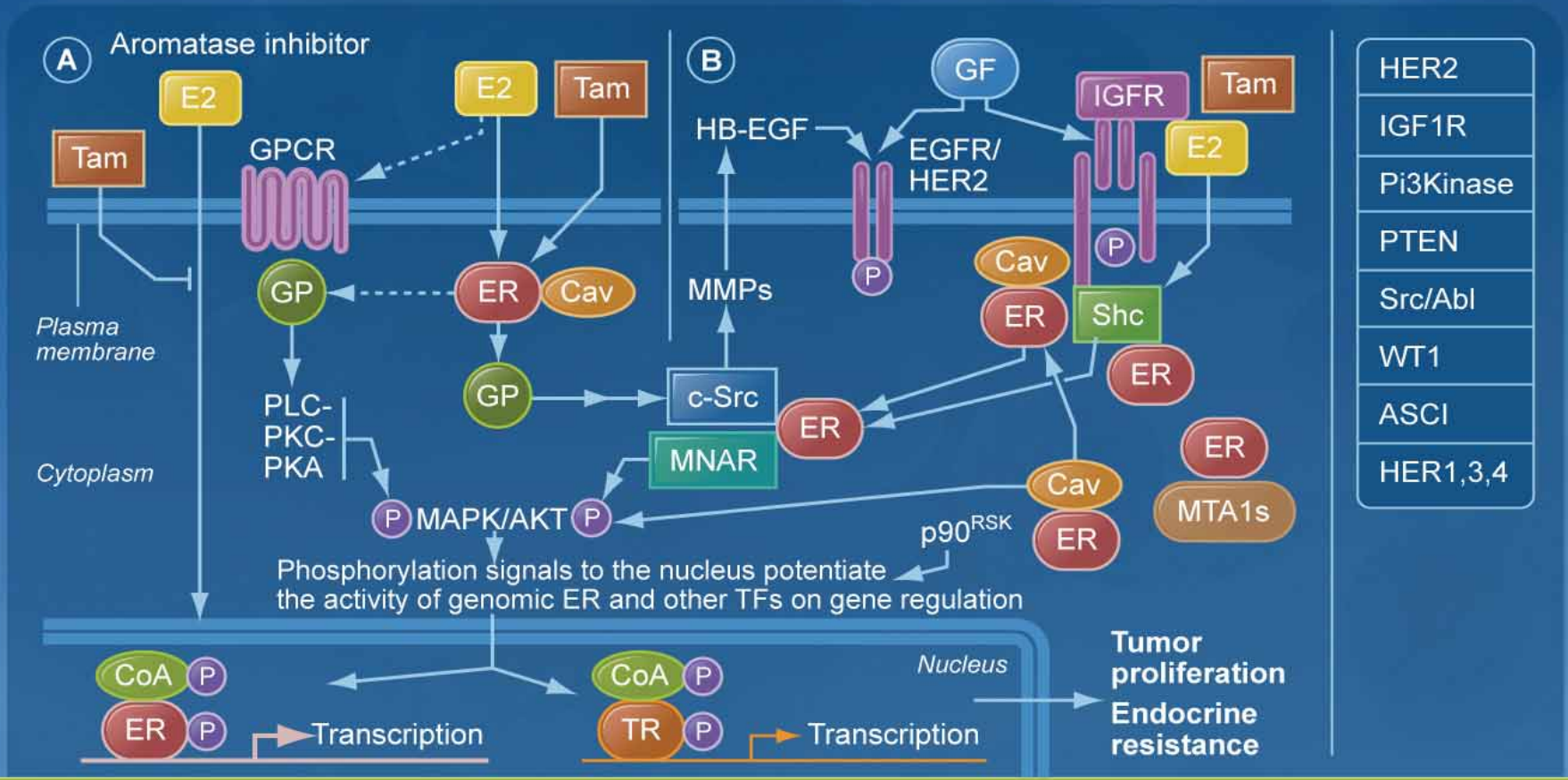
Genomic and Non-genomic (Rapid) ER Signaling Crosstalk with Growth Factors and Growth Factor Receptors and Cell Kinase Pathways – Endocrine Resistance



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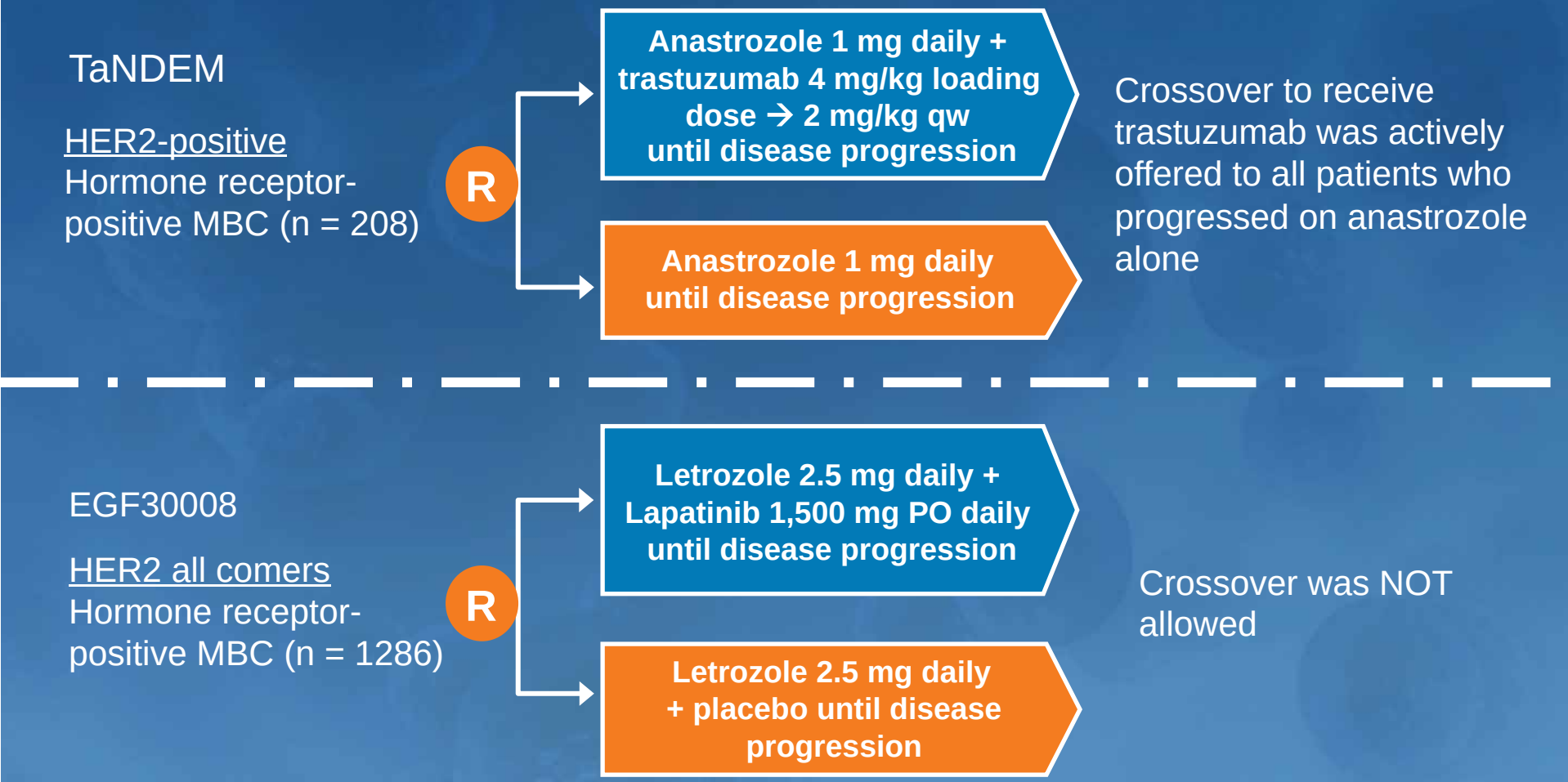
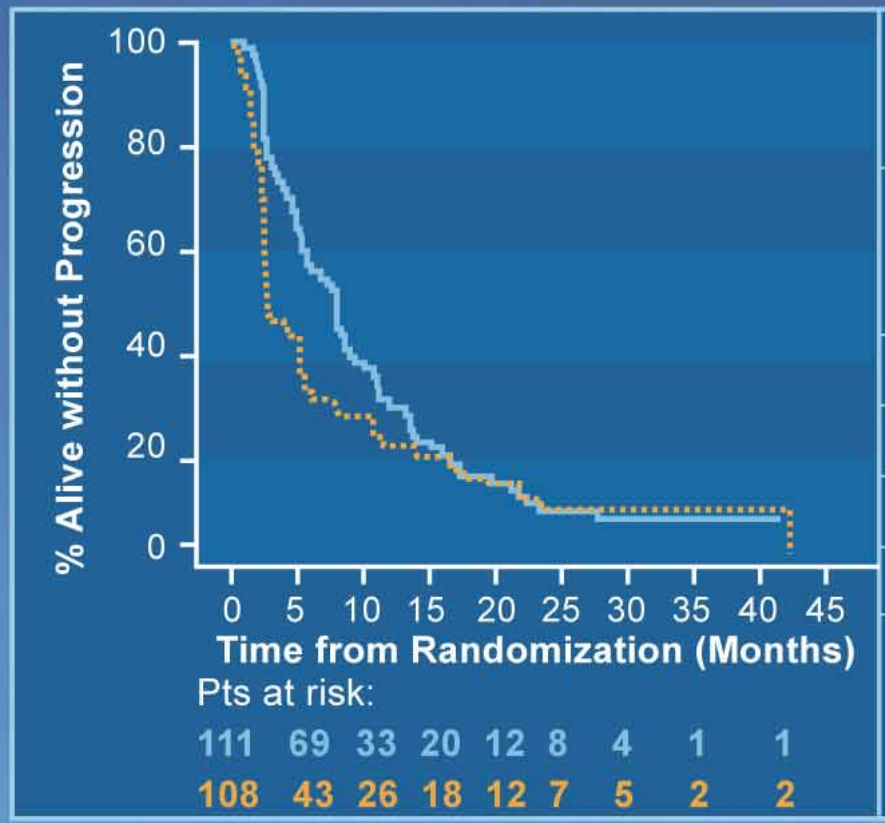
Anti-Estrogen + Anti-HER2 Therapy in HER2-Positive Breast Cancer



Letrozole +/- Lapatinib: Progression-Free Survival (PFS) in Patients with HER2-Positive Disease (N=219)



Letrozole + Lapatinib

Letrozole

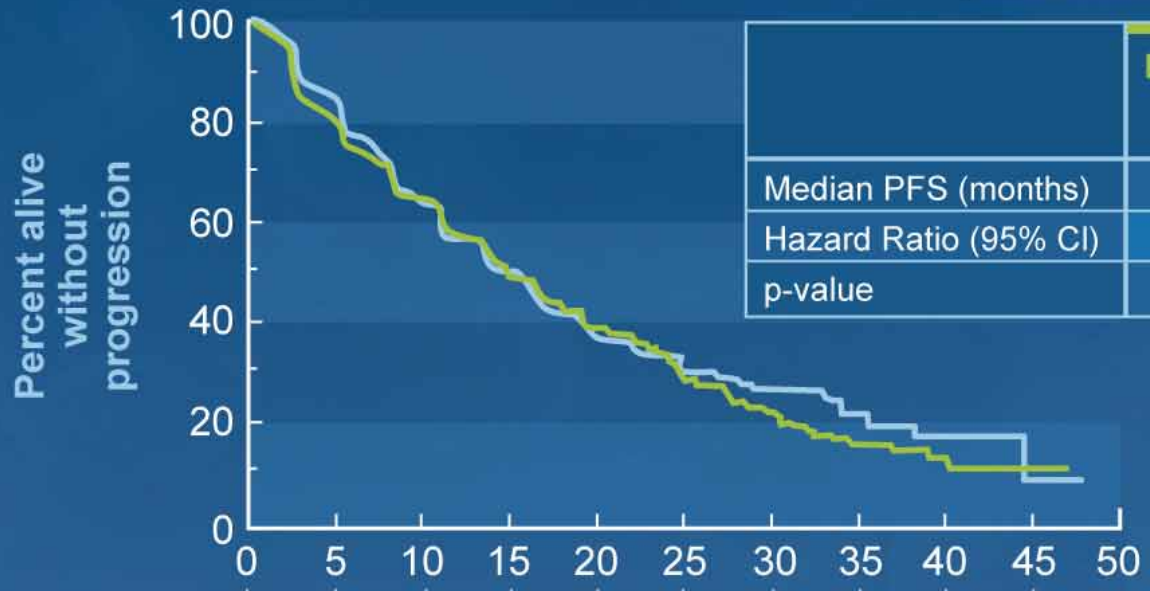
	Letrozole (N = 108)	Letrozole + Lapatinib (N = 111)
Progressed or died	89 (82%)	88 (79%)
Median PFS, mo	3.0	8.2
Hazard ratio (95% CI)	0.71 (0.53, 0.96)	
p-value	**0.019**	

With permission from Schwarzberg LS et al. *Oncologist* 2010;15(2):122-9; Johnston S et al. San Antonio Breast Cancer Symposium 2008;Abstract 46.

Letrozole +/- Lapatinib: PFS in Patients with HER2-Negative Disease (N=952)

≥ 6 months since D/C of TAM (33%) or No TAM (67%)

Median TAM duration: 5 yrs.
Median time since D/C: 3.5 yrs.



	Letrozole n=370	Letrozole + Lapatinib n=382
Median PFS (months)	15	14.7
Hazard Ratio (95% CI)	0.94 (0.79, 1.13)	
p-value	0.522	

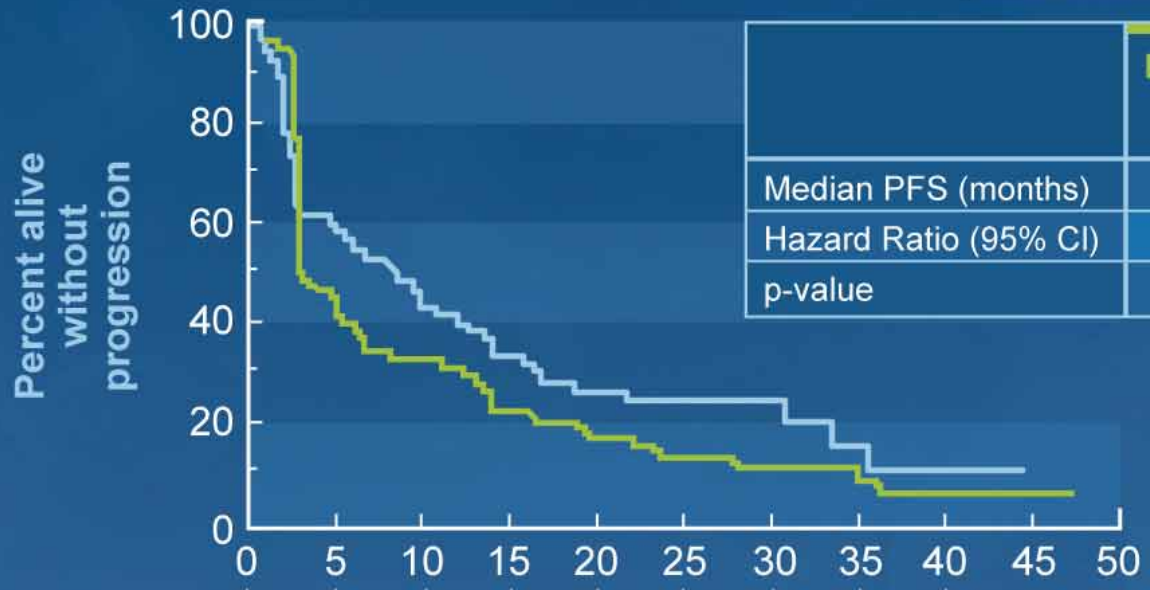
Patients at risk										
Letrozole	370	283	214	158	106	62	41	16	9	6
Letrozole + Lapatinib	382	282	202	147	87	55	37	20	7	1

With permission from Johnston S et al. San Antonio Breast Cancer Symposium 2008;Abstract 46.

Letrozole +/- Lapatinib: PFS in Patients with HER2-Negative Disease (N=952) (continued)

< 6 months since D/C of TAM

Median TAM duration: 2.8 yrs.
Median time since D/C: 1 mo.

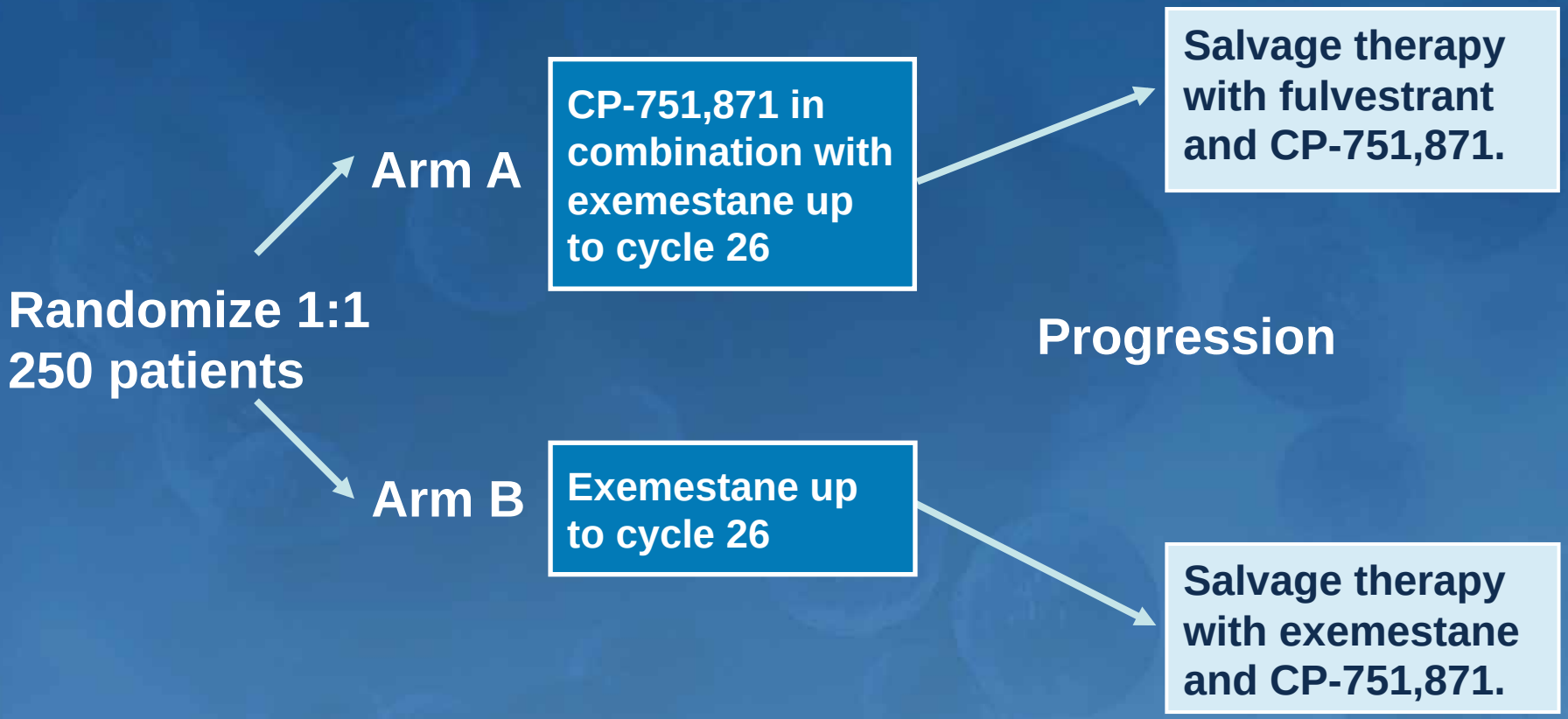


	Letrozole n=104	Letrozole + Lapatinib n=96
Median PFS (months)	3.1	8.3
Hazard Ratio (95% CI)	0.78 (0.57, 1.07)	
p-value	0.117	

Patients at risk									
Letrozole	104	43	31	21	14	9	5	4	1
Letrozole + Lapatinib	96	53	36	25	15	10	8	3	

With permission from Johnston S et al. San Antonio Breast Cancer Symposium 2008;Abstract 46.

Anti-Estrogen + Anti-IGF1R



Patients in Arm A experiencing exemestane toxicity will continue CP-751,871 until disease progression before switching to salvage therapy and vice versa.

CONCLUSIONS: Estrogen and Progesterone Receptor Pathways and Agents

- Optimal endocrine therapy in early stage pre- and postmenopausal ER-positive breast cancer continues to be defined:
  - Duration
  - Combination
  - Aromatase inhibitor
  - Optimal schedule
- Anti-estrogen agents + targeted therapies being investigated in metastatic disease
- Identifying tumor and host signatures will enable personalized approach to endocrine therapies