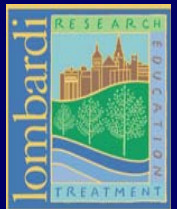


# Breast Cancer Updates 2010

Claudine Isaacs, MD  
Georgetown University



# Metastatic Breast Cancer

# Metastatic Breast Cancer

- Breast cancer that has spread beyond the breast and local lymph node area to distant sites
  - eg lungs, liver, bones, skin
- Unfortunately, incurable with current therapy

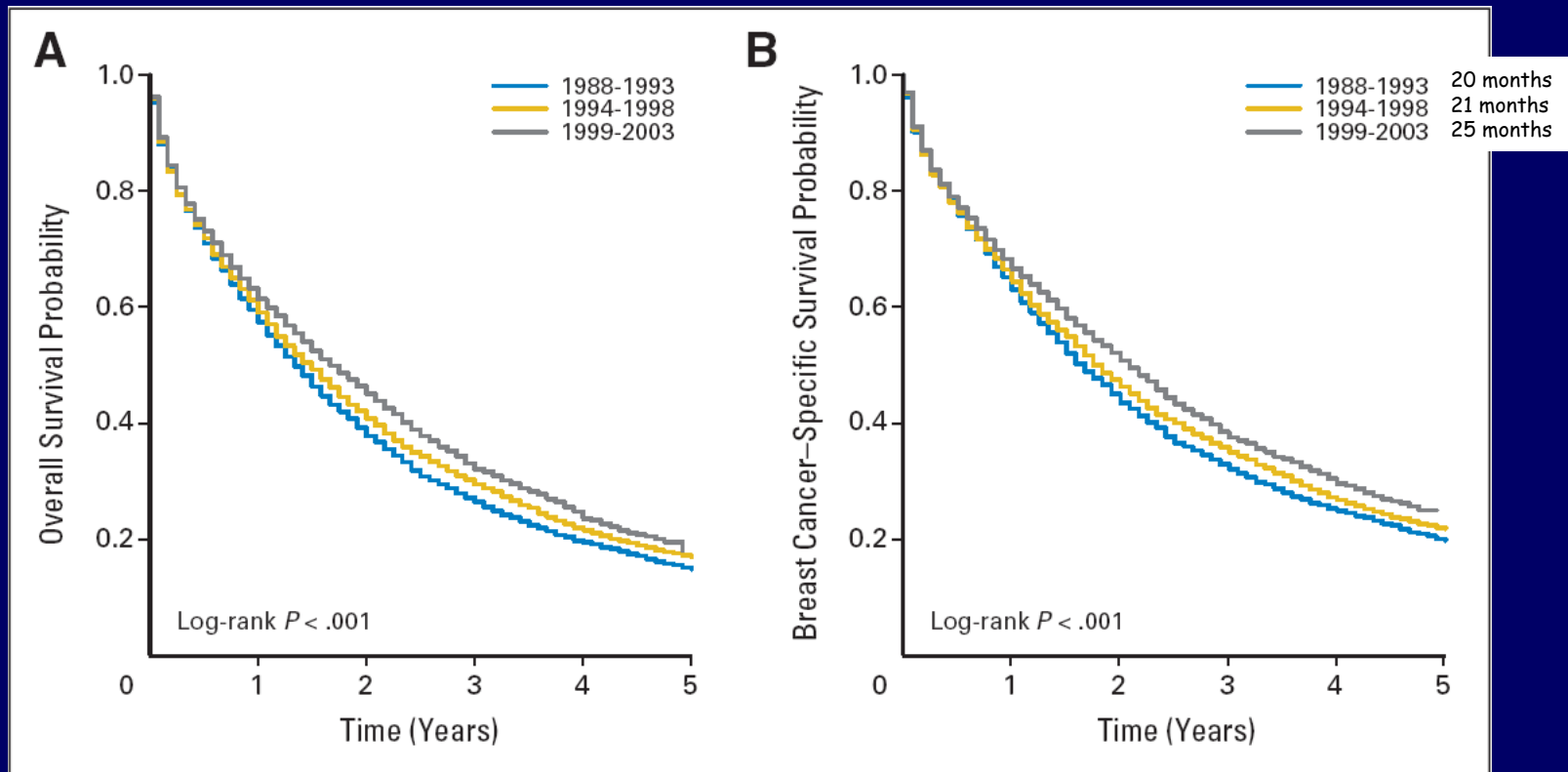
# Goals of treatment of MBC

- Prolongation of survival
- Improved quality of life
  - Improvement of symptoms
  - Acceptable toxicity

Number of very active treatment options

# Metastatic Breast Cancer Survival Improvement

15,438 pts from SEER Registry diagnosed with Stage IV disease



Do you biopsy at time of  
recurrence?

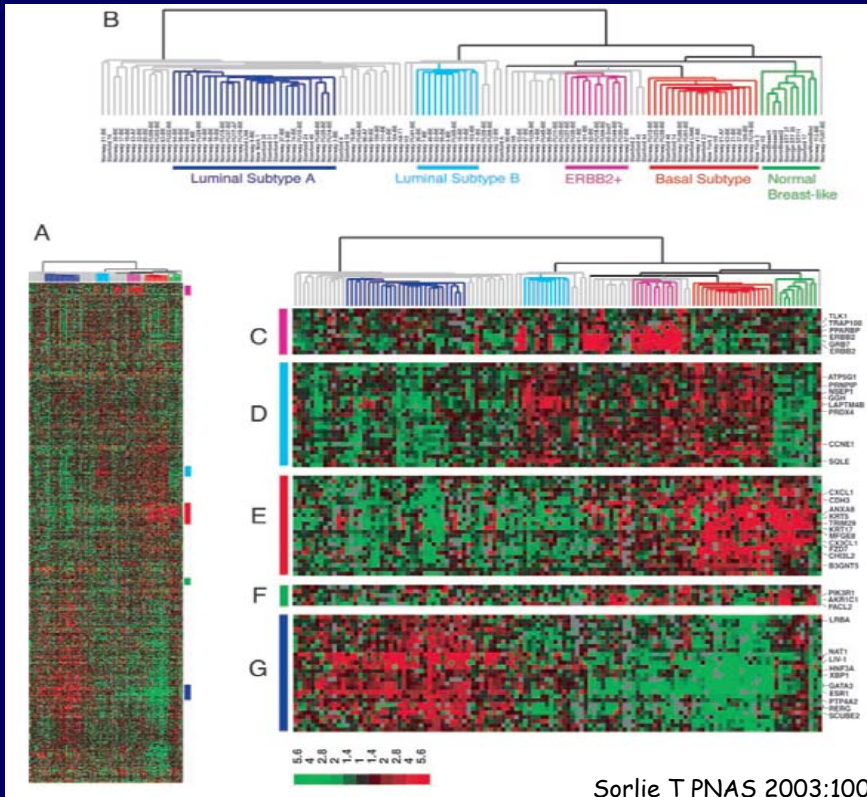
# Receptor Status

## Concordance Between Primary and Met

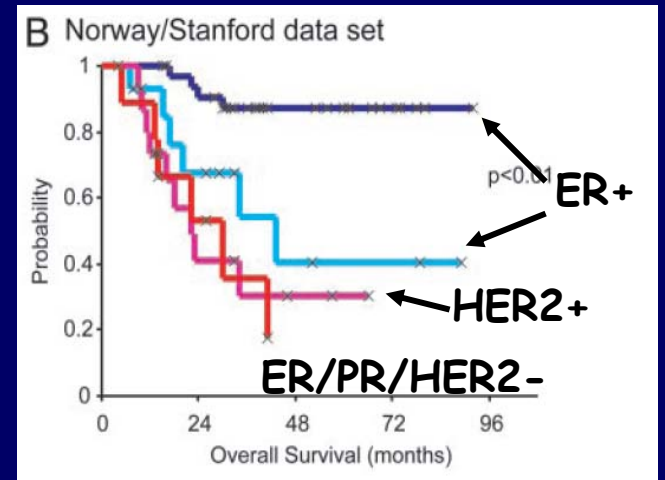
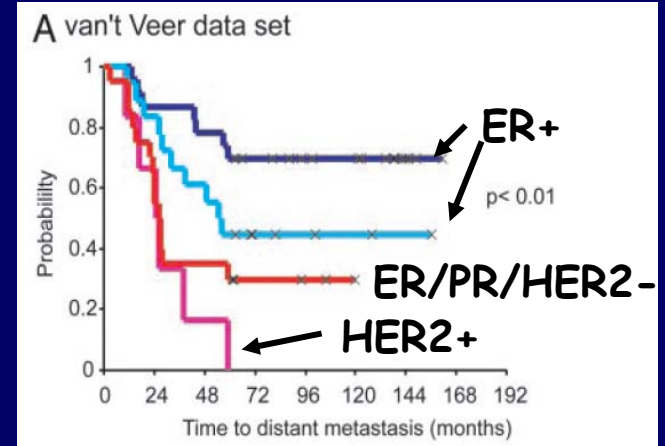
- Tissue microarrays (TMAs) from 160 patients with primary breast cancer matched to metastasis
  - Discordance on ER/PR in 14%
  - Discordance HER2 in 5%
- Abstracts ASCO 2010 similar findings

# Triple Negative Breast Cancer

# Triple Negative Breast Cancer



Sorlie T PNAS 2003;100:8418



# Triple Negative Breast Cancer

- Typically seen in young African-American women and *BRCA1* carriers (~65-80%)
- More aggressive subtype
  - No targeted therapy
  - Often respond well to chemotherapy but relapse early and with more visceral and CNS disease

# PARP Inhibitors

# Mechanisms of DNA Repair

## Environmental factors

(UV, radiation, chemicals)

## Normal physiology

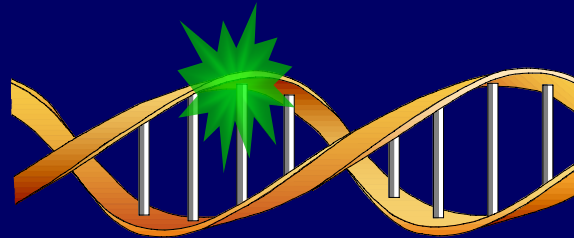
(DNA replication, ROS)

## Chemotherapy

(alkylating agents, antimetabolites)

## Radiotherapy

## DNA DAMAGE



---> Cell Death

## MAJOR DNA REPAIR PATHWAYS

### Single Strand Breaks

- Nucleotide excision repair
- Base excision repair
- PARP1

### Replication Lesions

- Base excision repair
- PARP1

### Double Strand Breaks

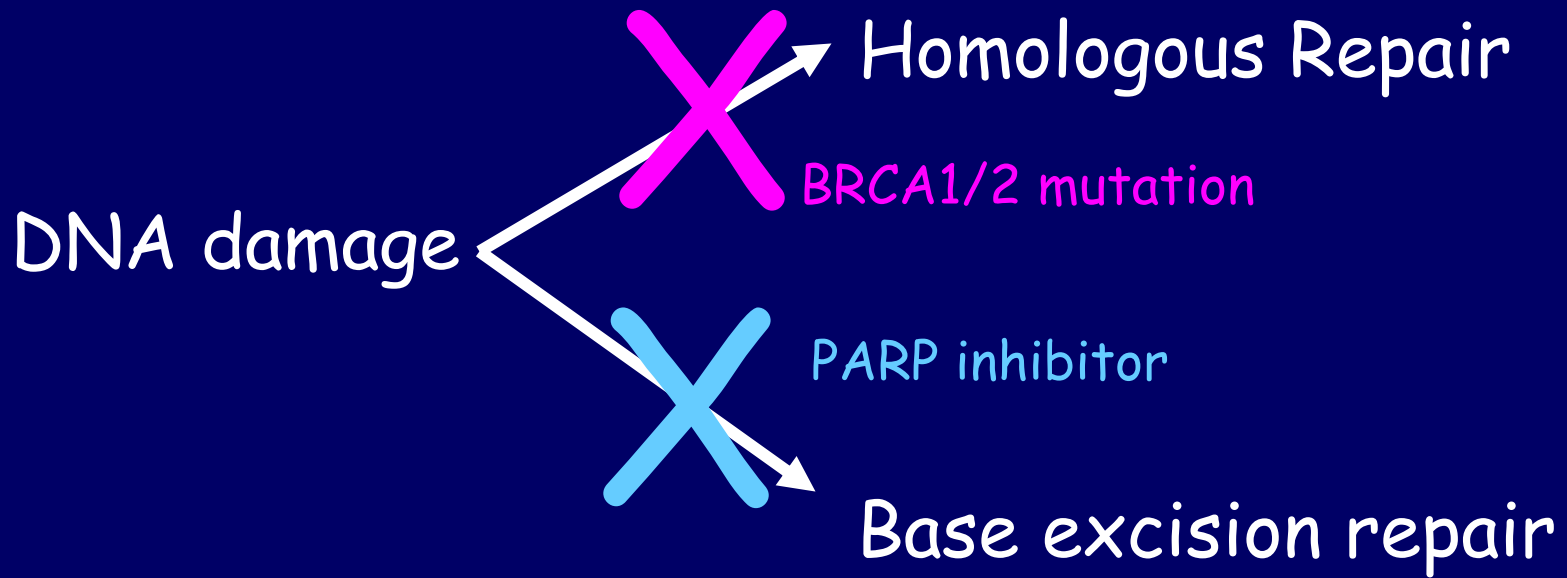
- Non-homologous end-joining
- Homologous recombination
- BRCA1/BRCA2
- Fanconi anemia pathway
- Endonuclease-mediated repair

### DNA Adducts/Base Damage

- Alkyltransferases
- Nucleotide excision repair
- Base excision repair
- PARP1

# PARP-inhibitors

## Mechanism of Action



# Triple Negative Breast Cancer PARP inhibitor

## Eligibility:

- Triple negative MBC
- Measurable disease
- $\leq 2$  prior CTX for MBC
- No prior gem, platinum, PARP inhibitor
- Stable brain mets allowed

Gemcitabine 1000 mg/m<sup>2</sup> d1,8  
Carbo AUC 2 d 1,8

Gemcitabine 1000 mg/m<sup>2</sup> IV d1,8  
Carbo AUC 2 d 1,8  
BSI-201 5.6 mg/kg IV d1,4,8,11

N = 120

Pts randomized to chemo alone could cross-over to chemo + BSI at PD

Prior chemo for MBC: ~ 60% no prior chemo for MBC; ~25% 1 prior;  
~15% 2 prior

# TN PARP Trial Results

	<b>Gem/Carbo (n = 44)</b>	<b>BSI + Gem/Carbo (n = 42)</b>	<b>P value</b>
ORR	16%	48%	0.002
CBR	21%	62%	0.0002
PFS	3.3 mos	6.9 mos	HR = 0.342 P<.0001
OS	5.7 mos	9.2 mos	HR = 0.348 P=.0005

~ 40% of patients on chemo alone arm x-over to BSI + chemo

# Phase II PARP Inhibitor (Olaparib)

## MBC in BRCA1/2 Carriers

- Advanced breast cancer relapsed after  $\geq 1$  chemotherapy
  - Heavily pretreated group (median 3 prior chemo regimens for MBC)
  - ~ 50% had triple negative disease
- ORR 49% in cohort receiving single agent Olaparib 400 mg bid

Bevacizumab

# Bevacizumab: Targeting Angiogenesis in MBC

- Tumor growth dependent on angiogenesis
- Bevacizumab is a humanized monoclonal antibody directed against VEGF
- Greater activity expected in less heavily pretreated patients

# Bevacizumab in the First-line Treatment of Locally Recurrent or MBC

- Eastern Cooperative Oncology Group (ECOG) 2100 trial
  - Planned interim analysis of a randomized, first-line, phase 3 trial

Patients with locally recurrent or metastatic breast cancer

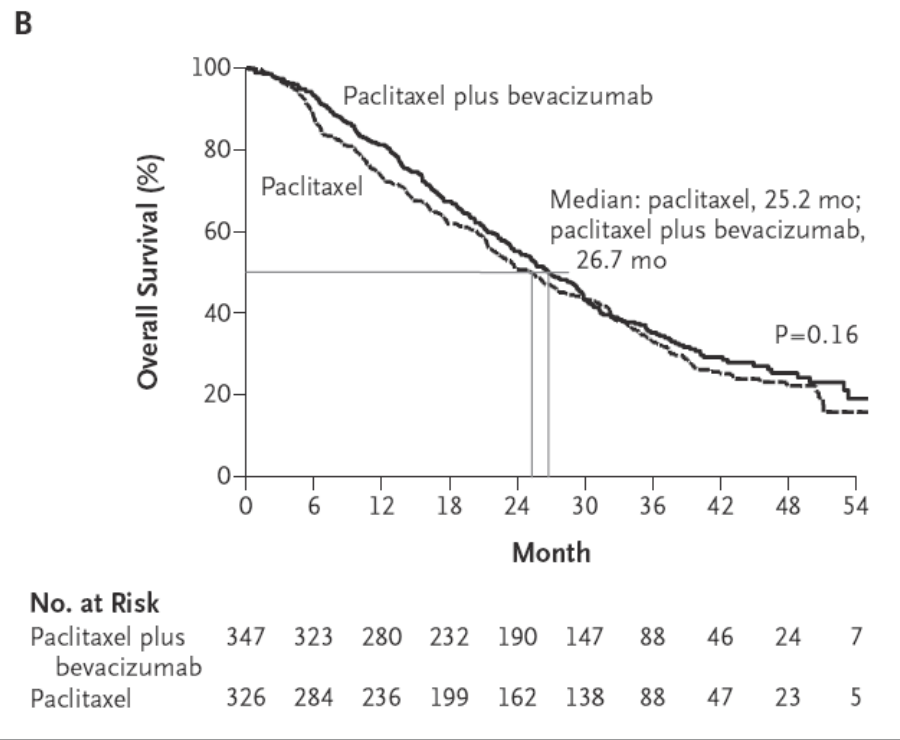
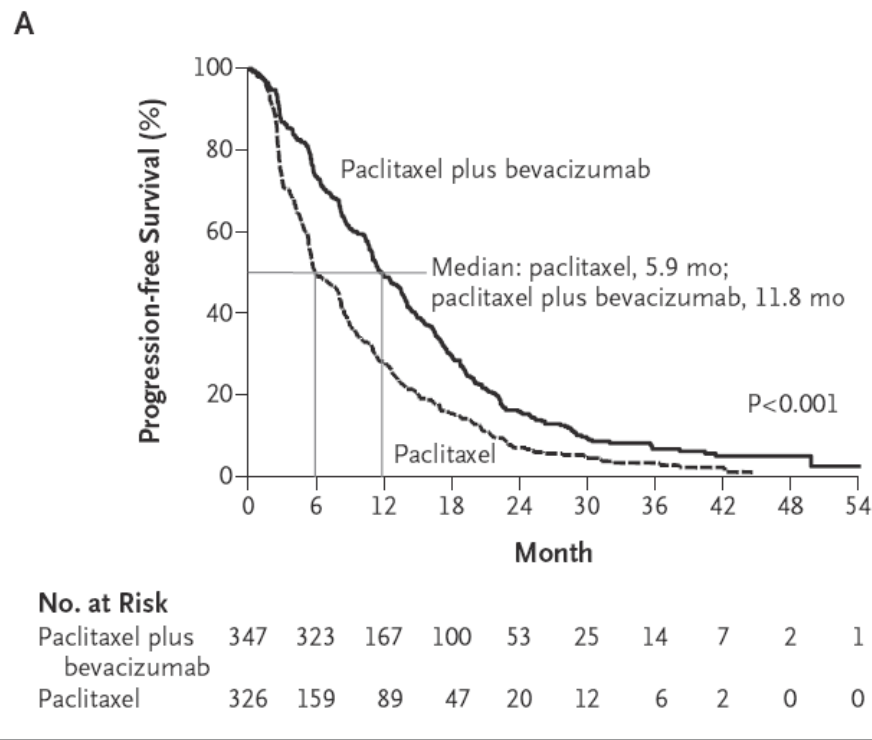
N = 722

Paclitaxel 90 mg/m<sup>2</sup> d 1, 8, 15 +  
Bevacizumab 10 mg/kg d 1, 15  
q 28 days  
(n = 365)

Paclitaxel 90 mg/m<sup>2</sup> d 1, 8, 15  
q 28 days  
(n = 350)

Treatment on both arms continued until disease progression or unacceptable toxicity

# ECOG 2100 Phase III Trial Outcomes



**Figure 2. Survival Analyses.**

Progression-free survival (Panel A) and overall survival (Panel B) in all eligible patients were analyzed with the use of the Kaplan–Meier method. Analyses including all patients assigned to treatment yielded similar results (data not shown).

# E2100 Phase III Trial Toxicity Results

Grade 3/4 Event	Paclitaxel, % (n = 332)	Bevacizumab + Paclitaxel, % (n = 350)
Hypertension*	0	15
Thromboembolism	1.5	1.9
CV Ischemia*	0	1.9
Hemorrhage	0	0.5
Proteinuria*	0	3.5
Neuropathy*	18	23
Fatigue*	5	9
Neutropenia/FN	0.8	0.3
Decreased LVEF	0	< 1
GI perforation	0	0.5

\* $P < .05$

Quality of life scores similar between treatment groups

# Bevacizumab in MBC

Trial	Regimen	N	ORR, %	Median PFS (mo)	Median OS (mo)
E2100 <sup>1</sup>	Paclitaxel vs	326	21.2	5.9	25.2
	Paclitaxel + bevacizumab	347	36.9*	11.8*	26.7
AVADO <sup>2</sup>	Docetaxel	241	46.4	8.2	31.9
	Docetaxel + LD bevacizumab	248	55.2	9.0*†	30.8
	Docetaxel + HD bevacizumab	247	64.1*†	10.1*	30.2
RIBBON-1 <sup>3,4</sup>	Capecitabine +/- bev	615	35 vs 24*	8.6 vs 5.7*	29 vs 21.2
	Taxane +/- bev	307	50 vs 35*	9.2 vs 8.2	25.5 vs 23.8
	anthracycline +/- bev	315	52 vs 40	9.2 vs 7.9*	(pooled analysis)

\*Statistically significant; †P value of exploratory nature; ‡Stratified analysis.

# Adverse Effects in Phase III Trials

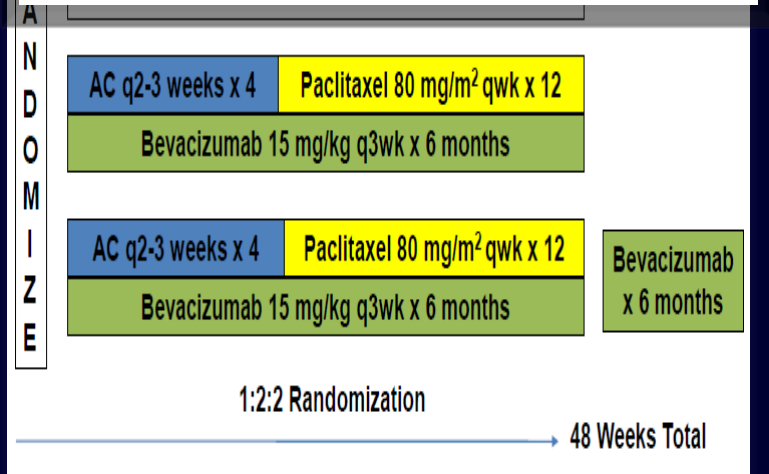
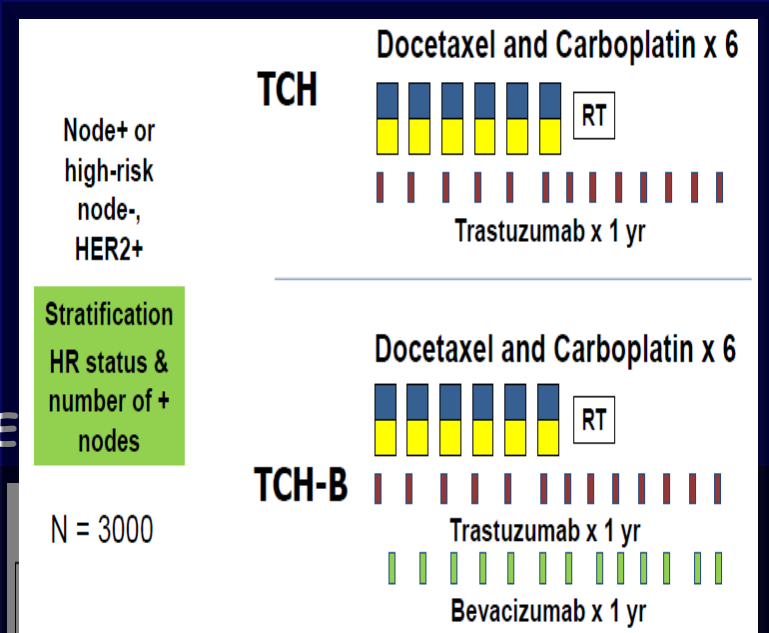
Grade $\geq$ 3 Adverse Events	E2100	AVADO		RIBBON 1		
	Pac / Bev (n = 363)	Doc / Bev		Cap /Bev (n = 404)	Tax /Bev (n = 203)	Anthra /Bev (n = 210)
		Bev 7.5 mg/kg (n = 252)	Bev 15 mg/kg (n = 247)			
<b>Bleeding*</b>	2%	1%	1%	0.2%	5%	0
<b>Hypertension†</b>	16%	0%	3%	10%	9%	10%

\*Rates of bleeding in placebo arms ranged from 0 to 0.9%.

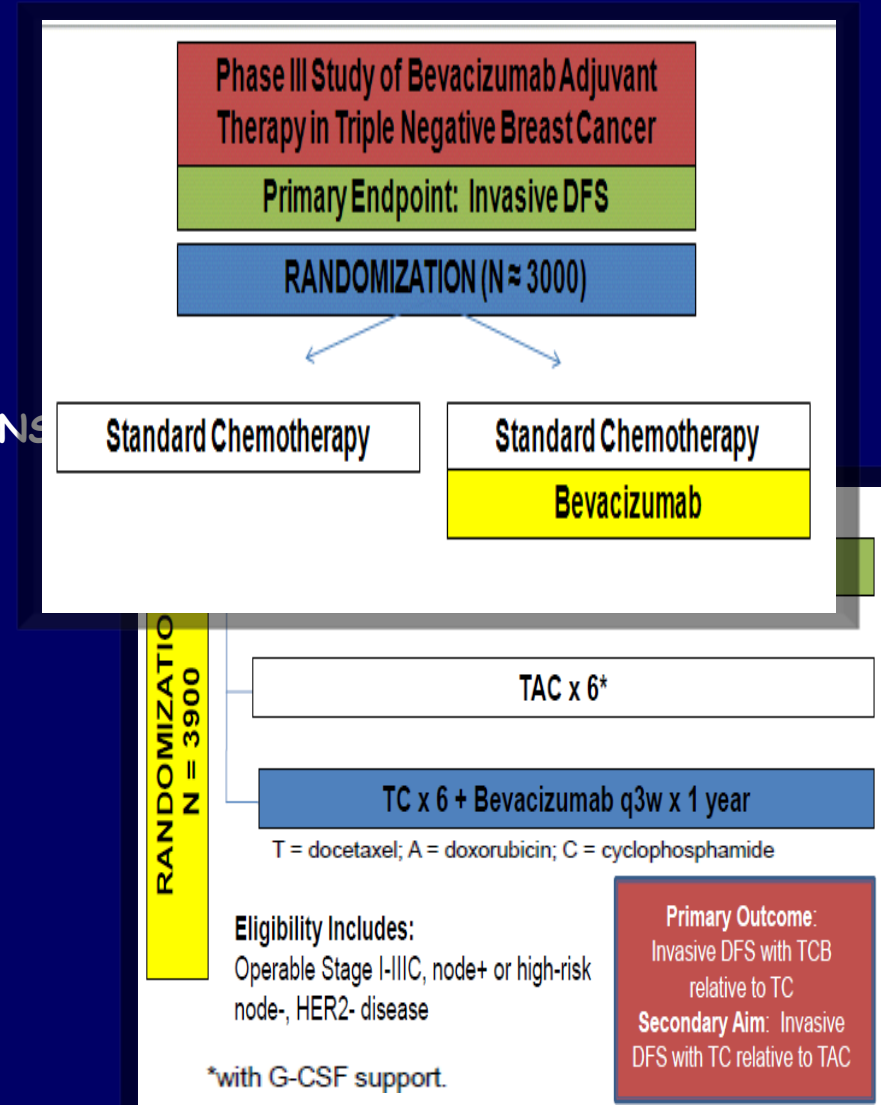
†Rates of hypertension in placebo arms ranged from 0 to 2%.

# Bevacizumab in the Adjuvant Setting

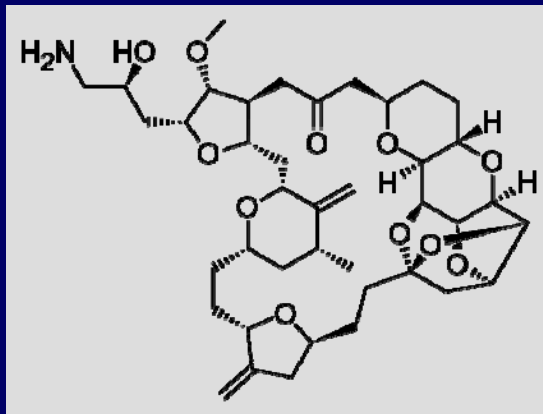
## BETH (NSABP B44 / CIRG)



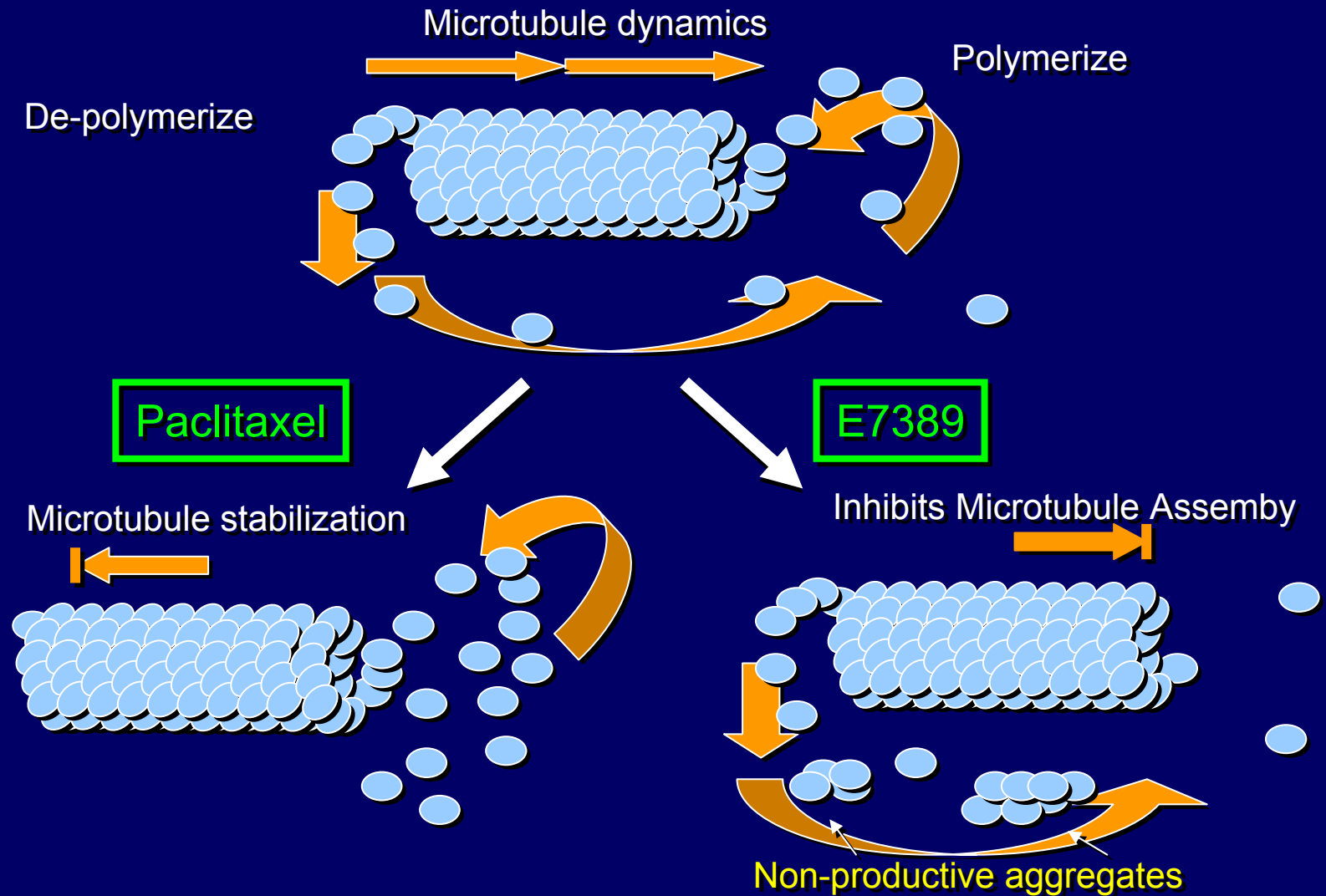
## BEATRICE



# Eribulin



# Eribulin Mesylate: Mechanism of Action





# EMBRACE Study

## Eribulin

### Eligibility:

- MBC or LABC
- 2-5 Prior CTX
  - $\geq 2$  CTX for ABC
  - Prior anthra and taxane
- PD < 6mos since last CT
- ECOG  $\leq 2$

N = 762



Eribulin 1.4 mg/m<sup>2</sup> over 2-5 mins  
d1,d8 q21days

Randomization 2:1

Tx of Physician Choice (TPC)  
Any monox (CT, HT, biolog)  
or supportive care

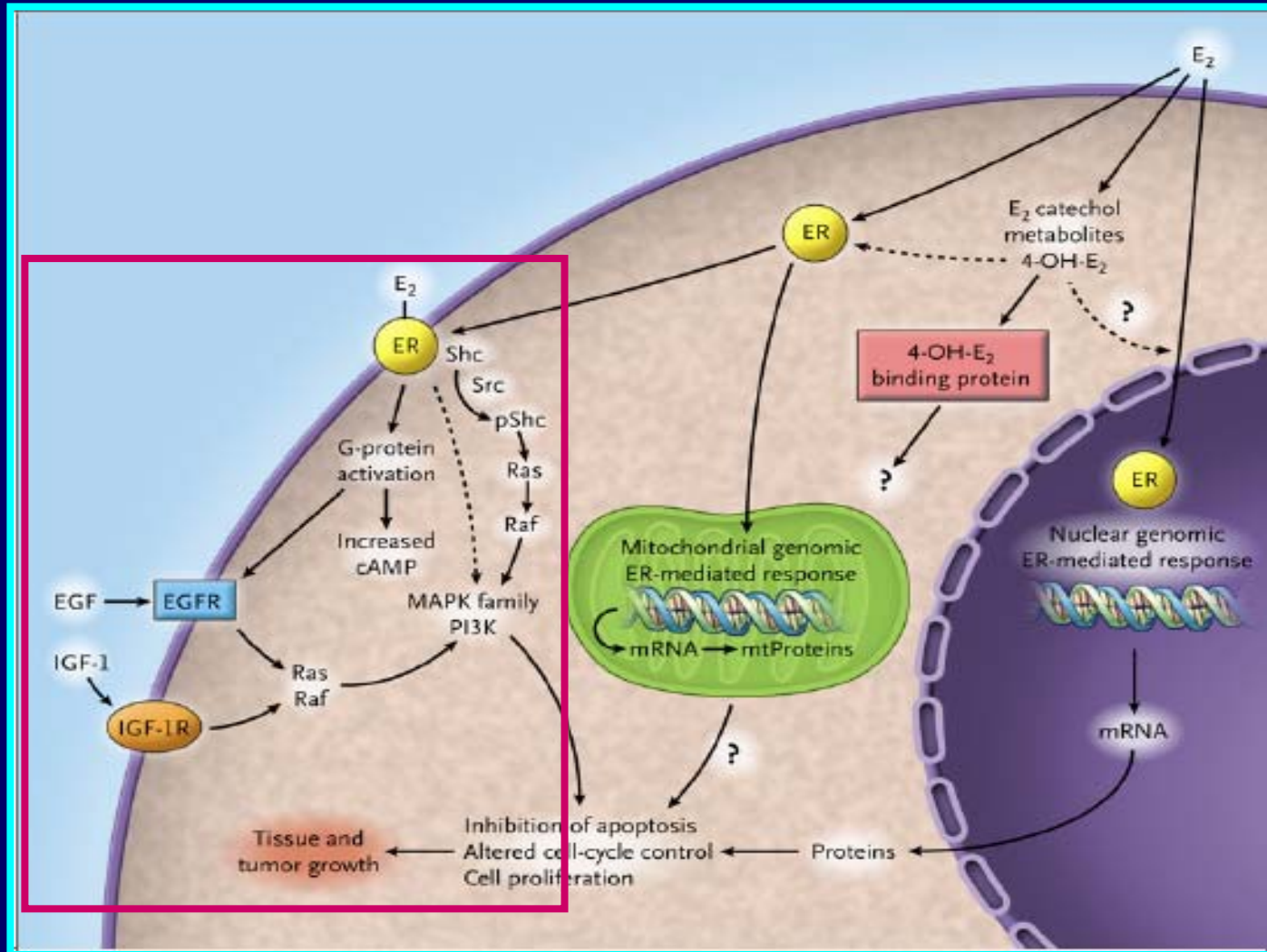
- Median # prior chemos 4
- 96% of pts on TPC received CT

	Eribulin	TPC	P value
ORR	12.2%	4.7%	0.02
OS	13.1 mos	10.6 mos	0.04

# Endocrine Therapy Resistance

# Endocrine Resistance

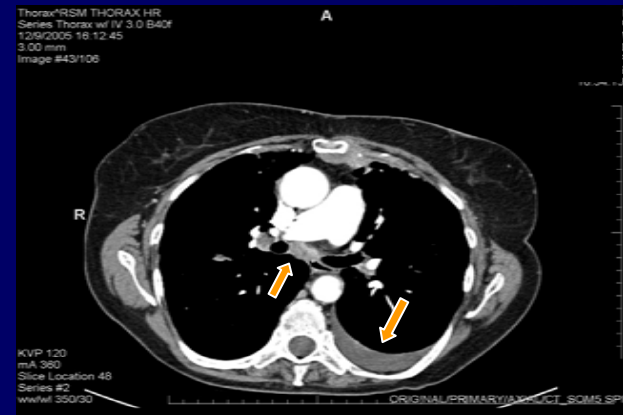
## Sorafenib + Anastrozole



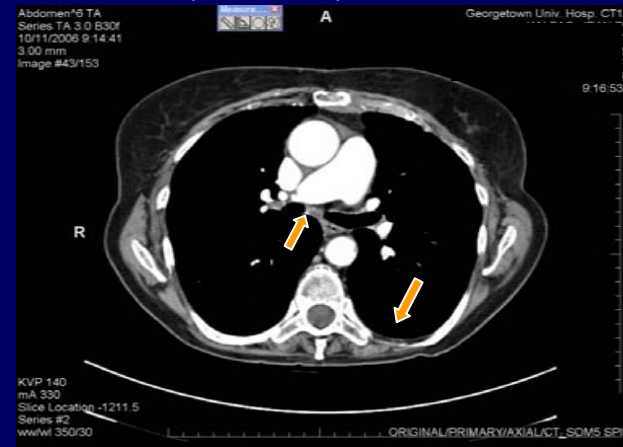
# Endocrine Resistance Sorafenib + Anastrozole

- Added sorafenib to Anastrozole in pts progressing on prior AI
- 23% of patients had tumor shrinkage or stable disease  $\geq$  24 weeks

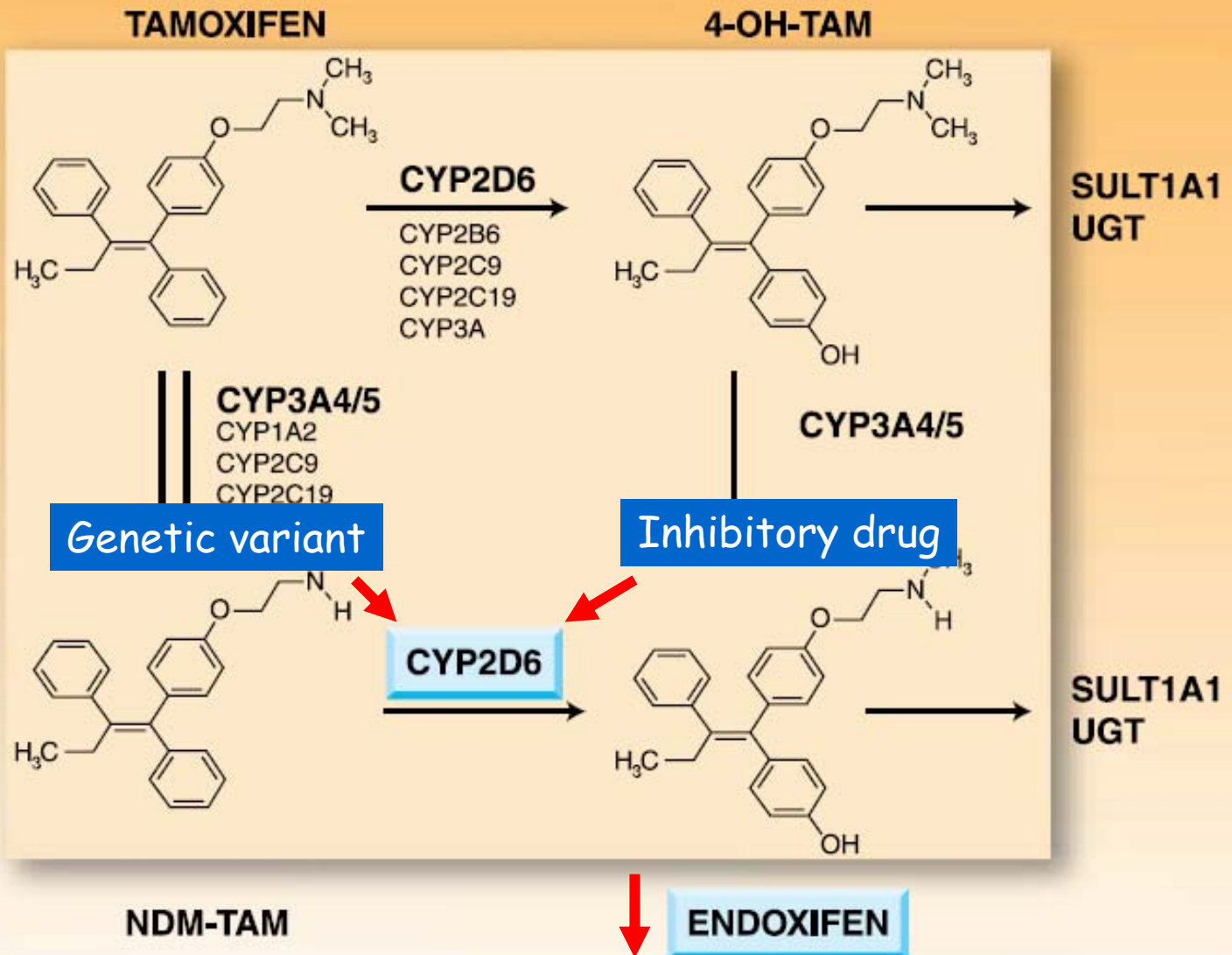
Before sorafenib and AI



After sorafenib and AI



# Adjuvant Setting



# CYP2D6 genotype association studies

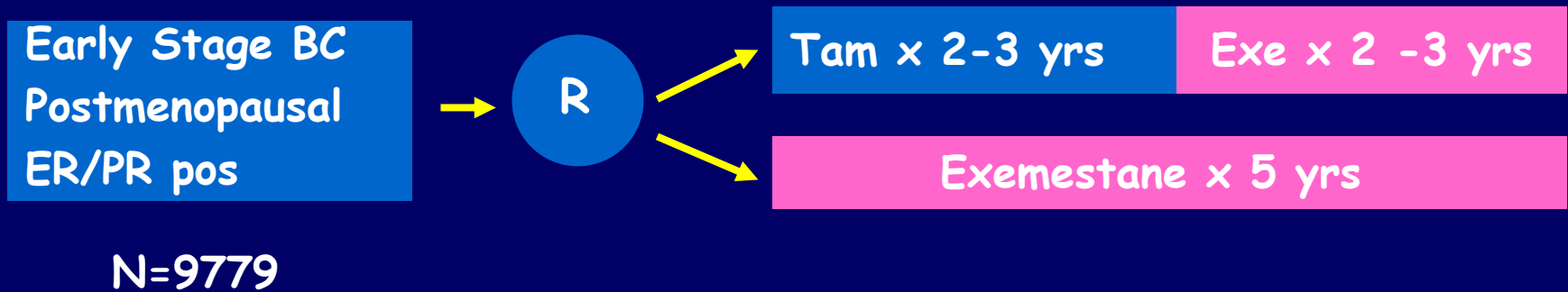
Positive studies			
	N	HR	p
Goetz '05	190	1.86	.08
Schroth '07	197	1.89	.02
Newman '08	68	3.6	.09
Ramon '09	91	>1	.02
Bijl '09	85	2.1	.03
Kiyotani '08/'10	282	9.5	<.001
Xu '08	152	4.7	.04
Lim '07	21		.02
Bonanni '06/'10	182		.04
Schroth '09	1325	1.29	.02

Negative studies			
	N	HR	p
Wegman '05	76	<1	NS
Wegman '07	677	<1	.055
Nowell '05	162	.67	.19
Okishiro '09	173	.6	.39
Toyamo '09	154		NS
Dieudonné '09			

## Presentation SABCS '09

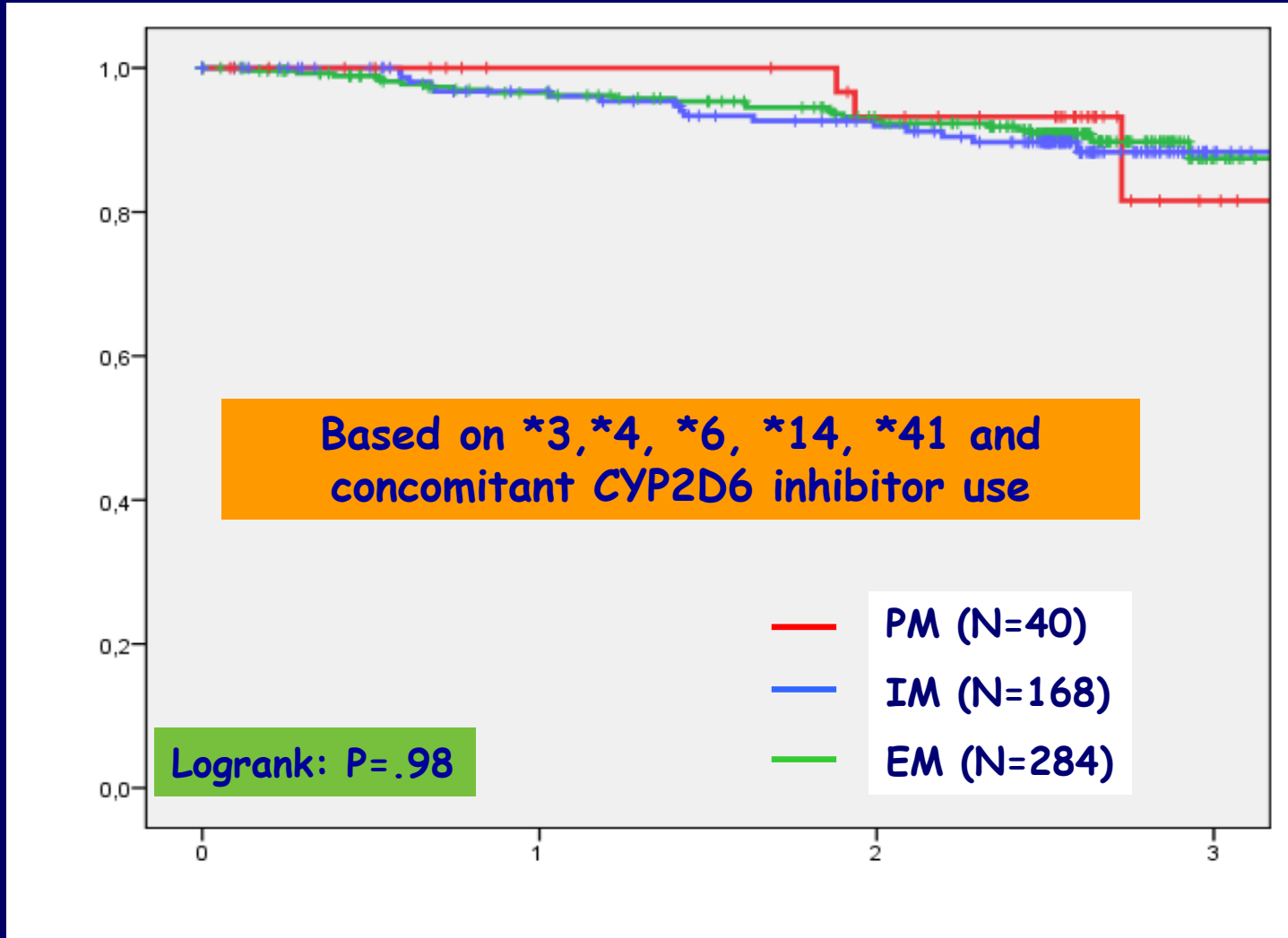
Goetz	2,880	NS
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# CYP2D6 TEAM Substudy



- Genotyped 747 Dutch patients randomized to Tam → Exe arm for genes involved metabolic and pharmaco-dynamic pathway of tamoxifen
  - 29 germline genetic variants and 12 candidate genes

# Results CYP2D6 phenotype



PM= poor metabolizer; IM= intermediate metabolizer; EM= extensive metabolizer

# Risk Reducing Salpingo-Oophorectomy

## Mortality Reduction

	No RRSO	RRSO	HR [95% CI]
All cause mortality	10%	3%	0.40 [95% CI, 0.26-0.61]
Breast cancer specific mortality	6%	2%	0.44 [95% CI, 0.26-0.76]
Ovarian cancer specific mortality	3%	0.4%	0.21 [95% CI, 0.06-0.80]

# QUESTIONS?

