

Case #3: HER2-Negative Metastatic Breast Cancer Previously Treated with an Anthracycline and Taxane: What's the Best Approach?



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Case Summary

- **58-year-old general practitioner**
- **ER-positive tumor (ER 50%, PR 0%)**
- **Recurrence of disease to lung and liver 1.5 years following completion of adjuvant anthracycline and taxane chemotherapy while on AI**
- **Symptomatic (cough, loss of appetite)**
- **ECOG PS: 1**
- **Comorbidity: Hypertension (well controlled)**

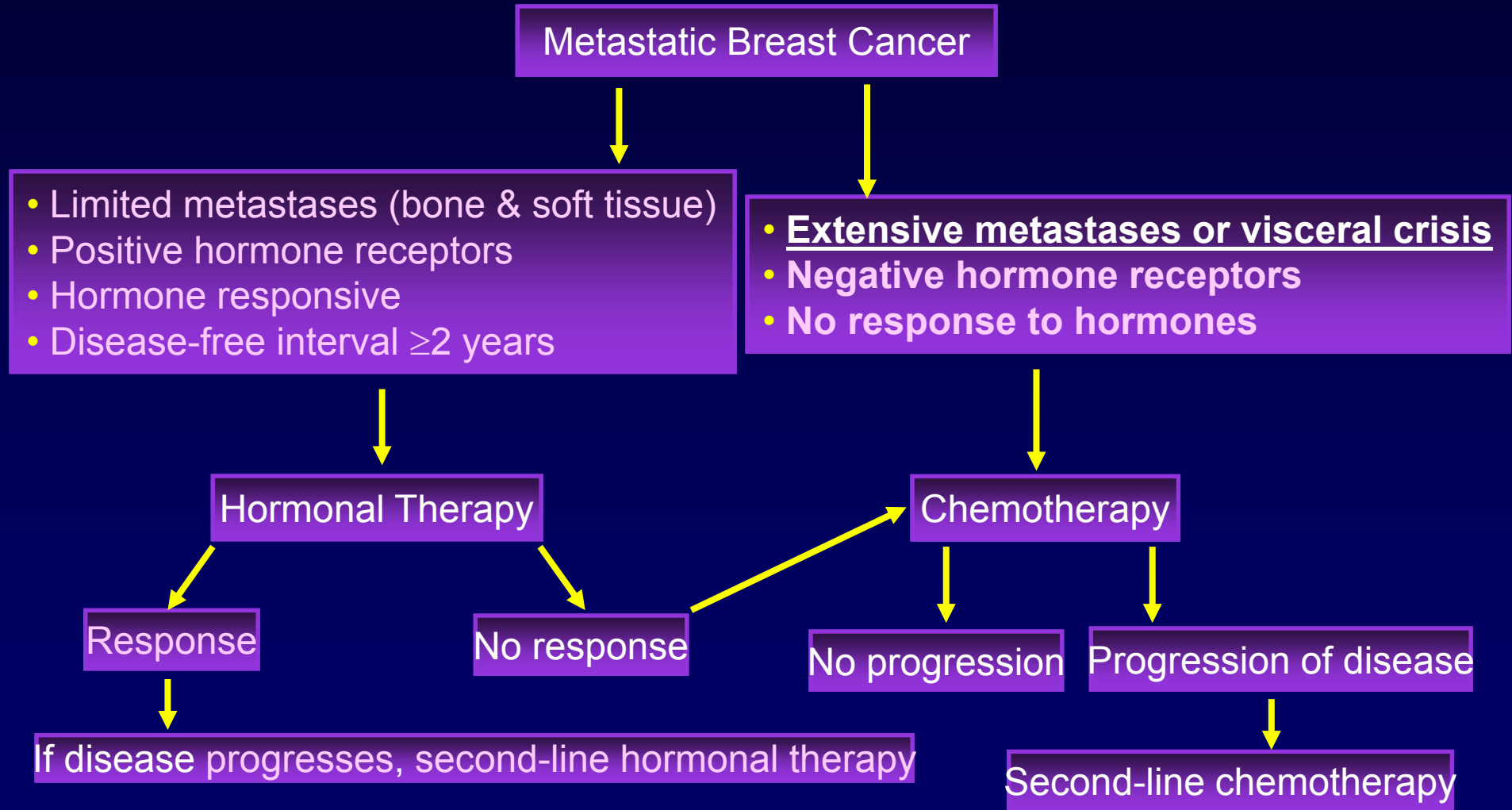
Is this patient resistant to anthracyclines/taxanes?

- **No evidence from literature since the lower rate of OR to consider a disease sensitive is not defined**
- **12 months was chosen in the ixabepilone registration trial (after amendment!)**
- **Some parameters could help:**
 - **For example: The “theoretical” time before relapse without treatment (stage + Ki67)**

Which therapy at the time of progression?

- **First-line therapy**
- **Second-line therapy**

Systemic Treatment Approach for Metastatic Breast Cancer



Choosing the Right Chemotherapy Regimen for Advanced Breast Cancer

“Friendly”

Agent/Regimen

“Aggressive” Regimen

**Slowly-progressing
disease**

**Rapidly progressing/life-
threatening disease**

**Any site provided limited
visceral involvement**

**Massive visceral
involvement**

Asymptomatic patient

Symptomatic patient

**Indication for “aggressive”
regimen but frail**

Fit

Chemotherapy for MBC

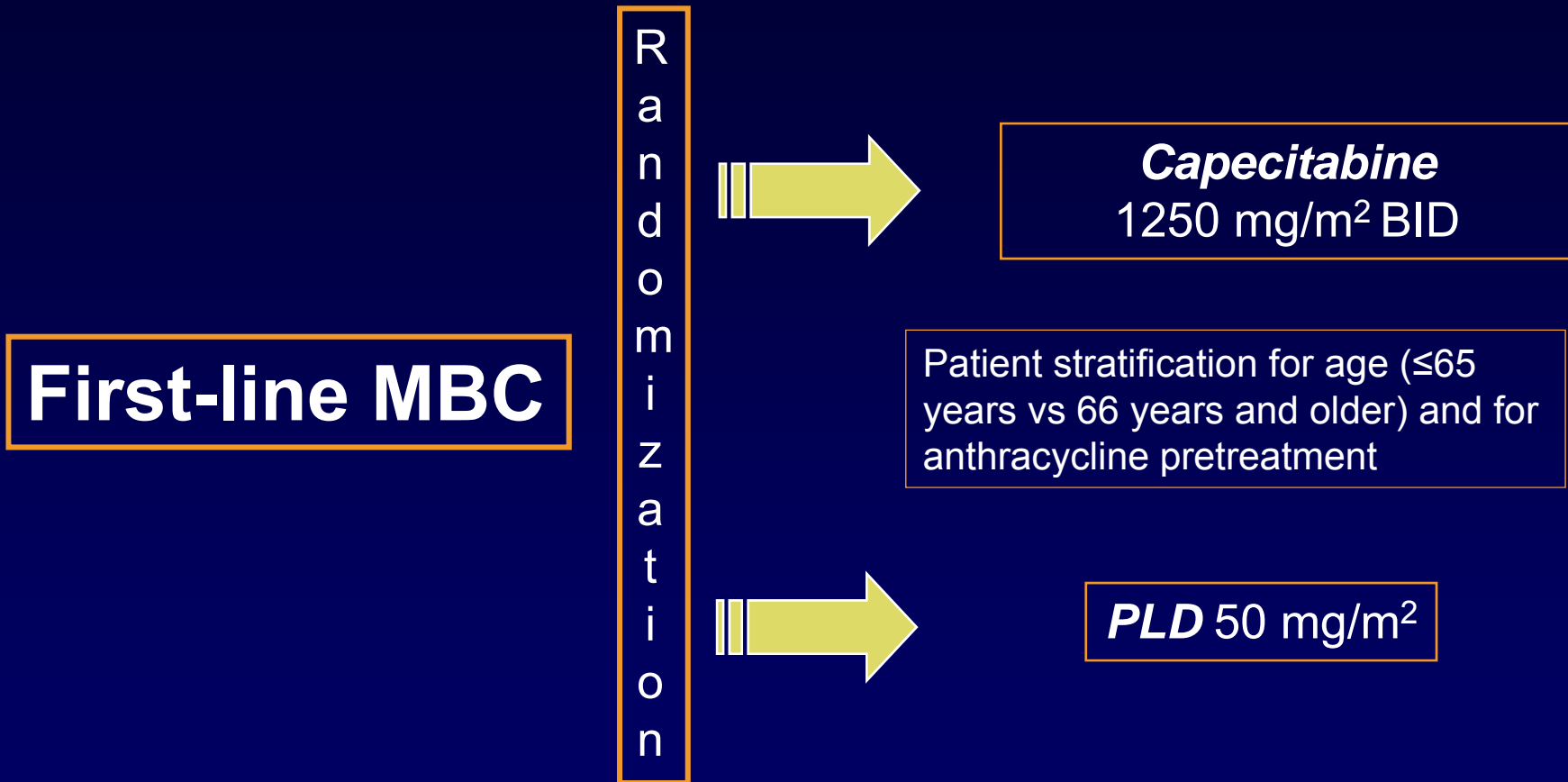
- **Sequential single agents preferred for most patients**
 - Variety of options—no single ‘gold standard’
 - Limits toxicity
 - Supported by clinical trial data
- **Combinations appropriate for rapidly progressive symptomatic disease**
 - Reduction in symptoms outweighs potential toxicity
 - May not be candidate for subsequent therapy if continued progression

Capecitabine in Taxane-Pretreated MBC: Consistent Efficacy Data

No.	CR+PR, %	ORR+SD, %	Median TTP, months	Median OS, months
163	20 ¹	63	3.0	11.6
75	26 ²	57	3.2	12.2
136	15 ³	62	3.3	10.4
126	28 ⁴	63	4.6	15.2
230	19 ⁵	NA	4.2	NA

1. Blum JL, et al. *Eur J Cancer*. 2001;37(Suppl. 6): Abstract 693. 2. Blum JL, et al. *Cancer*. 2001;92(7):1759-1768.
3. Reichardt P, et al. *Ann Oncol*. In press. 4. Updated from Fumoleau P, et al. *Proc Am Soc Clin Oncol*. 2002;21:
Abstract 247. 5. Maung K. *Clin Breast Cancer*. 2003;3:375-377.

PELICAN Trial: PLD vs Capecitabine Study Design



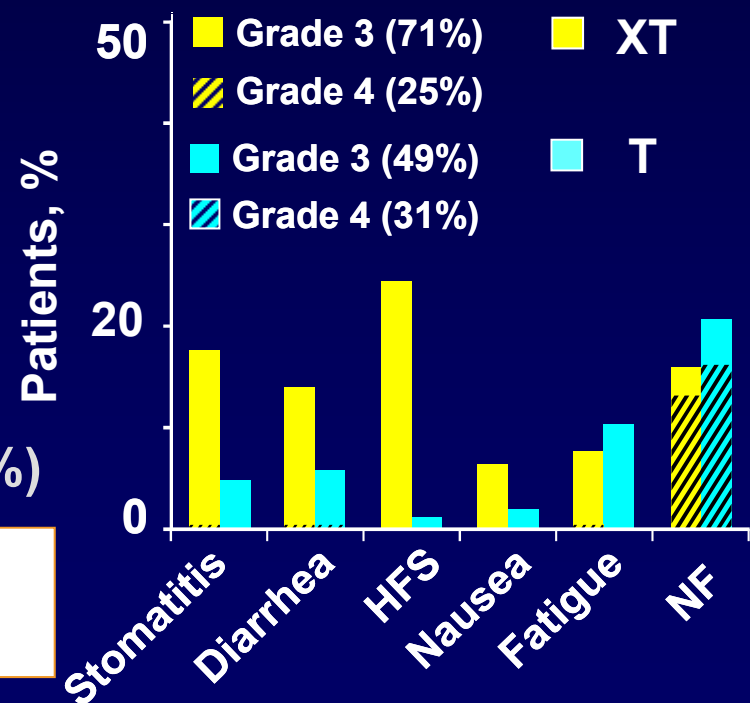
Cycles in both arms will be repeated as scheduled until disease progression or unacceptable toxicity

Polychemotherapy: XT

- **XT** (capecitabine 1250 mg/m² BID days 1-14 plus docetaxel 75 mg/m², day 1) vs **T** (docetaxel 100 mg/m²) q 21

- ↑ RR: 42% vs 30%, $P = .006$
- ↑ TTP: HR 0.65
- ↑ OS: HR 0.77
- Median OS (CI)
- 14.5 (12.3–16.1)
- 11.5 (9.8–12.7) (crossover rate 17%)

Selected patients, ie, good PS & aggressive disease



Polychemotherapy: GT

- **GT** (gemcitabine 1250 mg/m² days 1-8 plus paclitaxel 175 mg/m²) vs **T** (paclitaxel 175 mg/m²) q 21
 - ↑ RR: 41% vs 26%,
 $P = .0002$
 - ↑ TTP: HR 0.70
 - ↑ OS: HR 0.82
 - Median OS 18.5 vs 15.8
(crossover rate 16%)
 - GT mainly hematologic toxicity (febrile neutropenia 5% vs 1.2%, transfusion need: n = 28 vs 10)
 - Grade 3-4 nonhematologic toxicity low in both arms



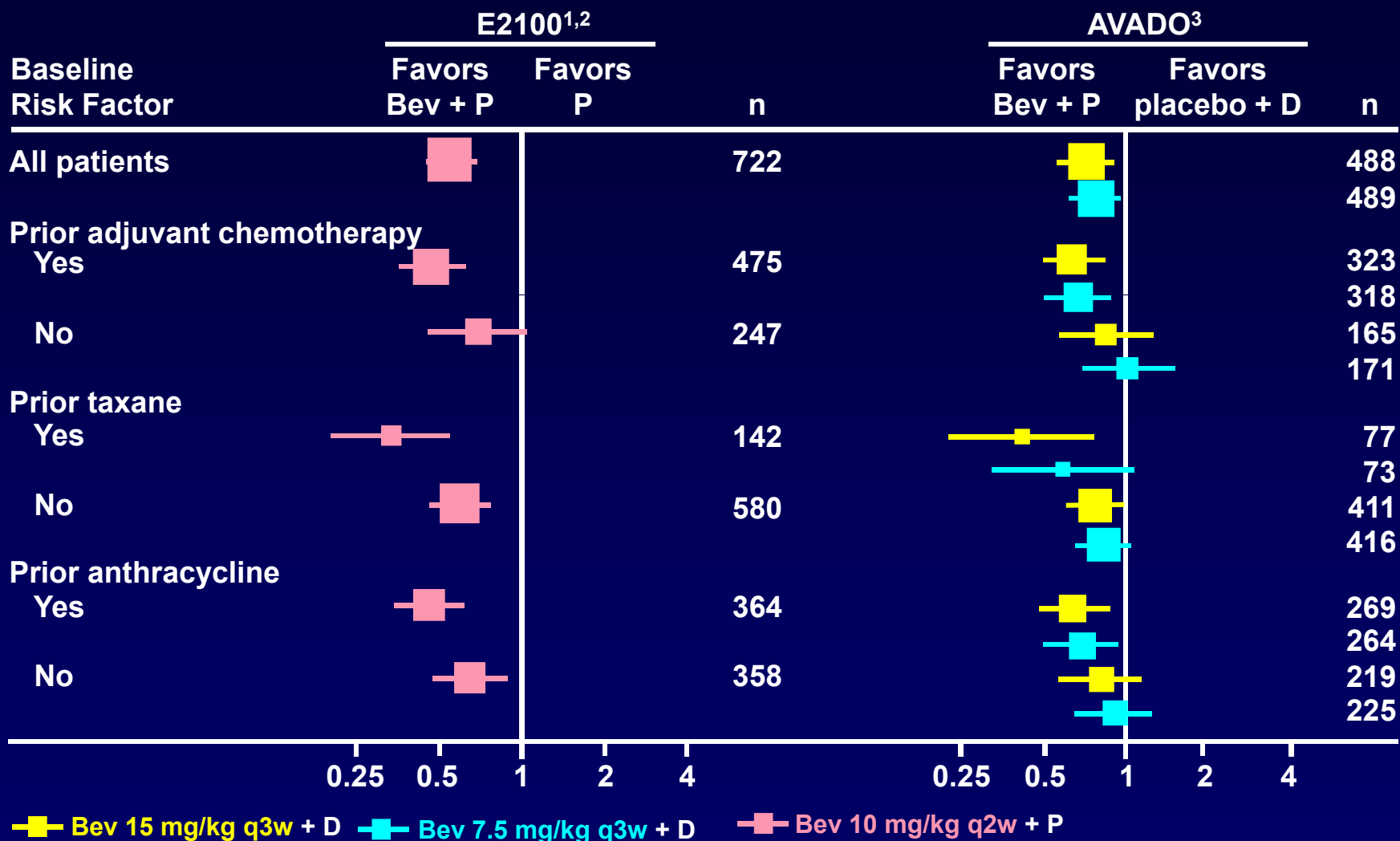
GT: High therapeutic index

Anti-VEGF Therapy (Bevacizumab) in Metastatic Breast Cancer (MBC)

	E2100 ¹		AVADO ²		RIBBON-1: Capecitabine ³		RIBBON-1: A/T ³	
Placebo (PI) controlled	No		Yes		Yes		Yes	
Chemotherapy	Weekly paclitaxel (P)		q 3 wk docetaxel (D)		Capecitabine (C)		q 3 wk docetaxel/nabPAC/FAC/EC/FEC	
Dose of bevacizumab (B)	10 mg/kg q 2 wk		7.5 or 15 mg/kg q 3 wk		15 mg/kg q 3 wk		15 mg/kg q 3 wk	
	P	P+B	D+PI	D+B	C+PI	C+B	A/T+PI	A/T+B
ORR	25%	49%	46%	55%/64%	24%	35%	38%	51%
PFS, months	5.9	11.8	8.1	9.0/10.0	5.7	8.6	8.0	9.2
HR	0.60 <i>P</i> < .0001		0.80 (7.5 mg) <i>P</i> = .0450 0.67 (15 mg) <i>P</i> = .0002		0.69 <i>P</i> = .0002		0.64 <i>P</i> < .0001	
OS, months	25.2	26.7	31.9	30.8/30.2	21.2	29	23.8	25.2
HR	0.88 <i>P</i> = .16		1.05 (7.5 mg) <i>P</i> = .72 1.03 (15 mg) <i>P</i> = .85		0.85 <i>P</i> = .27		1.03 <i>P</i> = .83	

1. Miller K, et al. *N Eng J Med*. 2007;357(26):2666-2676. 2. Miles DW, et al. *Cancer Res*. 2009;69(Suppl):Abstract 41. 3. Robert NJ, et al. *J Clin Oncol*. 2009;27(15S): Abstract 1005.

Bevacizumab + Taxane Is Active Even in Taxane Pretreated Patients

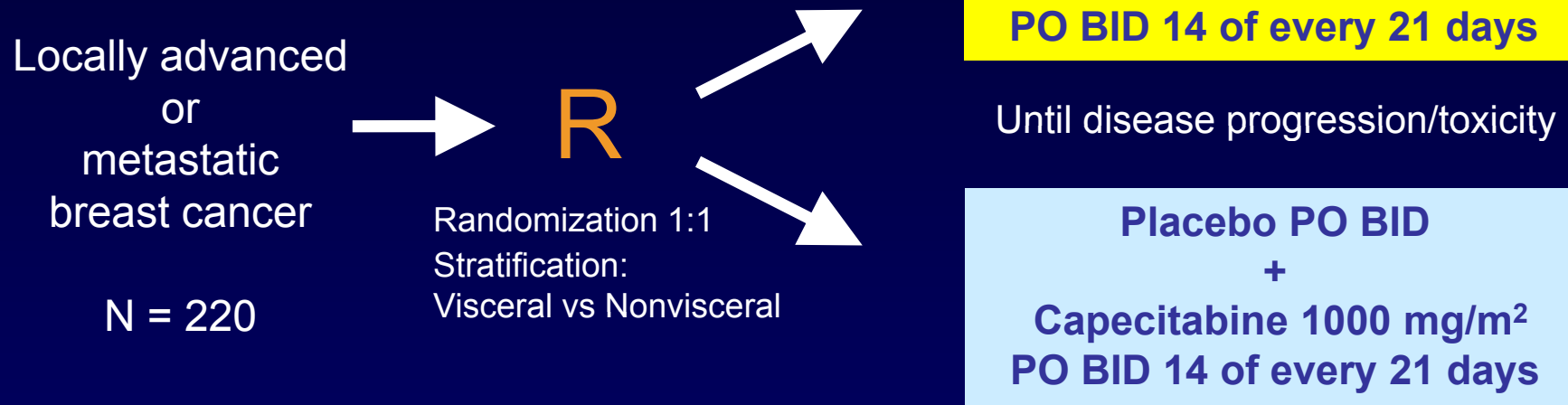


Andreas Schneeweiss ESMO 2008 presentation

1. Klencke BJ, et al. *J Clin Oncol.* 2008;26(May 20 Suppl): Abstract 1036. 2. Roche data on file 2007. 3. Miles D, et al. *J Clin Oncol.* 2008;26(May 20 Suppl): Abstract LBA1011.

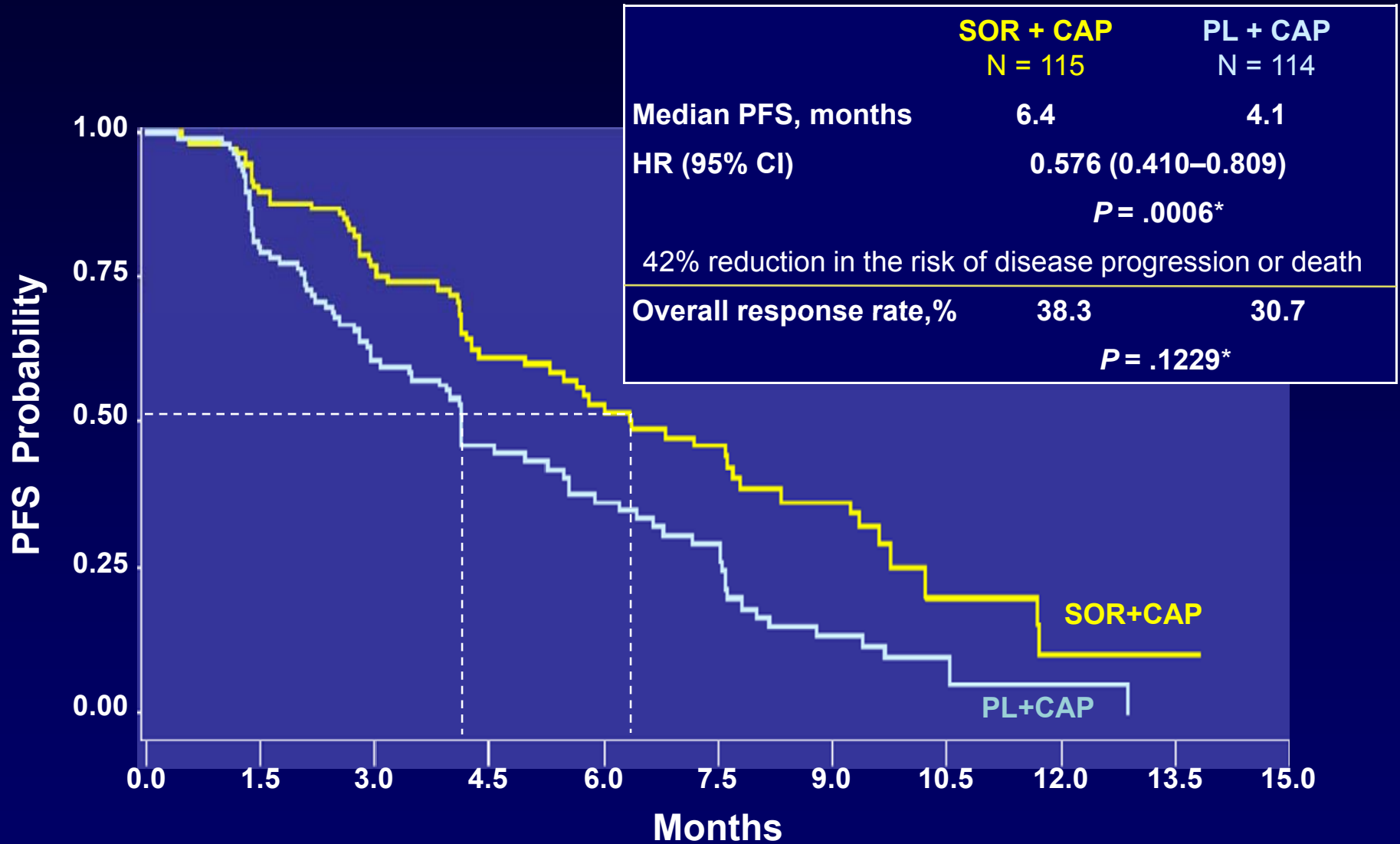
SOLTI-0701: Study Design

Multinational, double-blind, randomized, placebo-controlled, **phase IIb**



- **Primary endpoint: PFS**
- **Secondary endpoints: OS, TTP, RR, duration of response, safety**
- **Target enrollment: N = 220**
- **Sample size calculation: hazard ratio (HR) of 0.65 (90% power and 1-sided $\alpha = 0.14$)**
- **Countries: Spain, France, Brazil**

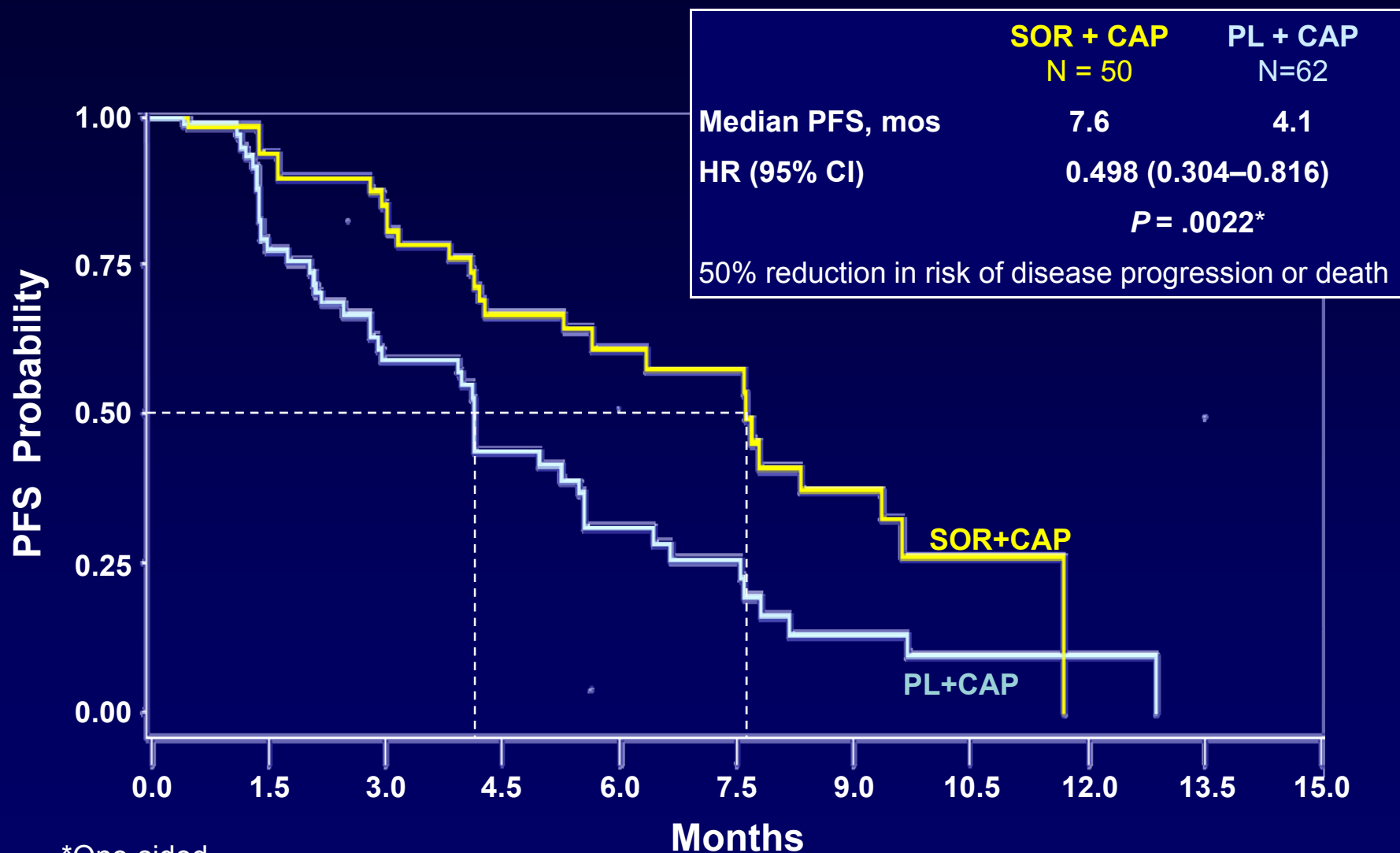
SOLTI-0701:PFS and ORR (ITT Population)



*One-sided

Baselga J, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 45.

PFS: First-Line Patients



Baselga J, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 45.

Adverse Event Rates*

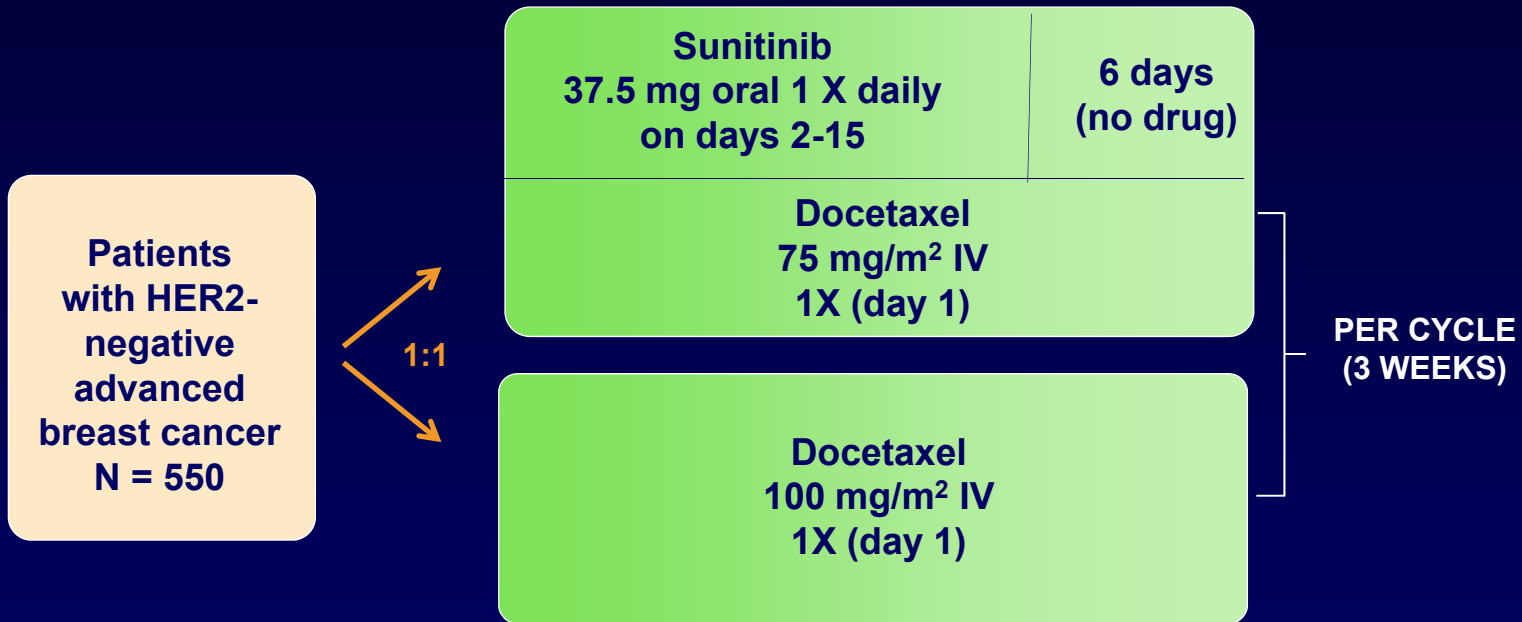
Overall incidence > 10% and Grade 3/4 ≥ 2% in either treatment arm

	Sorafenib + Capecitabine (N = 112)			Placebo + Capecitabine (N = 112)		
	All, %	Grade 3, %	Grade 4, %	All, %	Grade 3, %	Grade 4, %
HFSR / HFS	89	45	-	63	13	-
Diarrhea	53	5	0	30	5	0
Mucosal inflammation	32	1	0	19	3	1
Asthenia	24	0	0	27	2	0
Rash	22	3	0	8	0	0
Hypertension	17	1	0	12	2	0
Fatigue	14	2	0	13	1	0
Musculoskeletal pain	12	2	0	6	0	0
Dyspnea	12	5	0	12	3	1
Neutropenia	11	4	1	4	2	1

*Treatment-emergent

Baselga J, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 45.

SUN 1064: Sunitinib Malate + Docetaxel vs Docetaxel in First-Line Advanced Breast Cancer



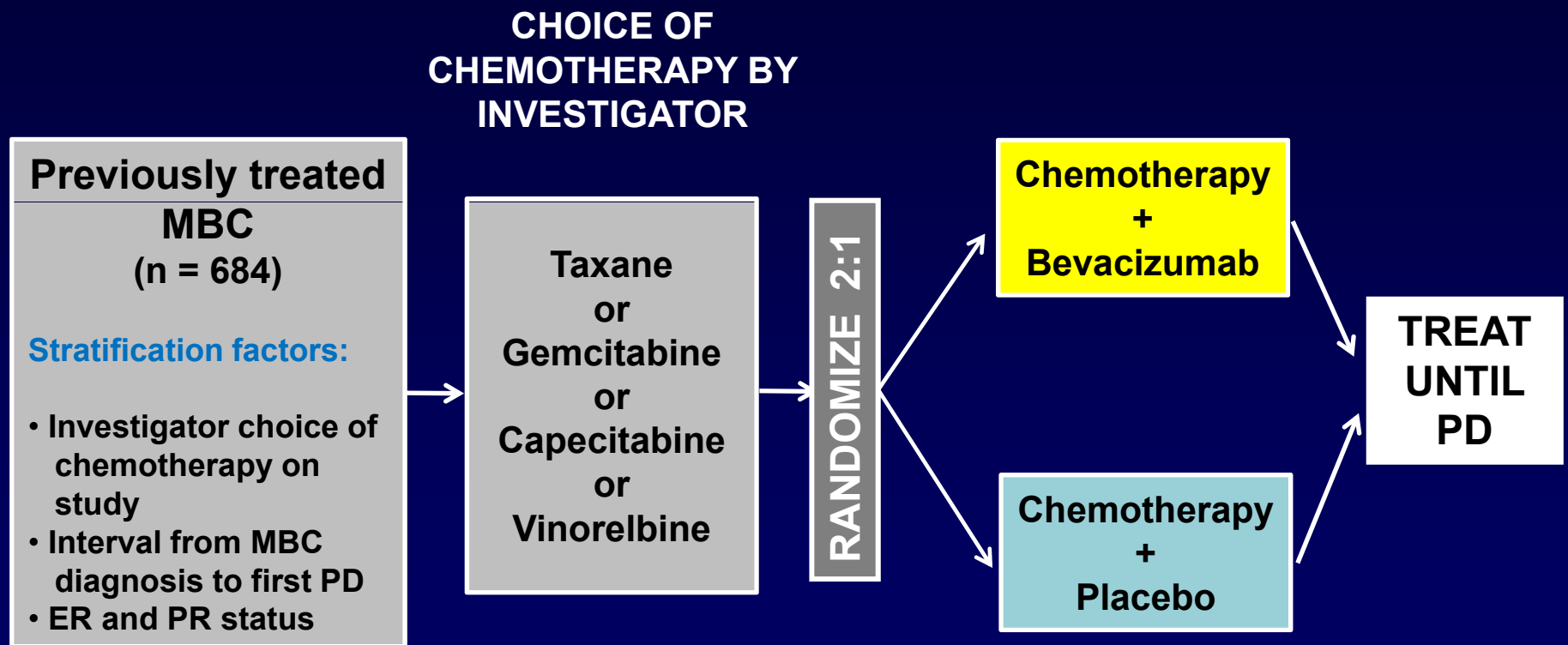
Trial Design	Endpoints	Study Sites	Indication
Multinational, multi-center, randomized, open label	Primary: PFS Secondary: ORR, DR, safety, QoL, pharm-economics	Global	First-line

Accrual completed

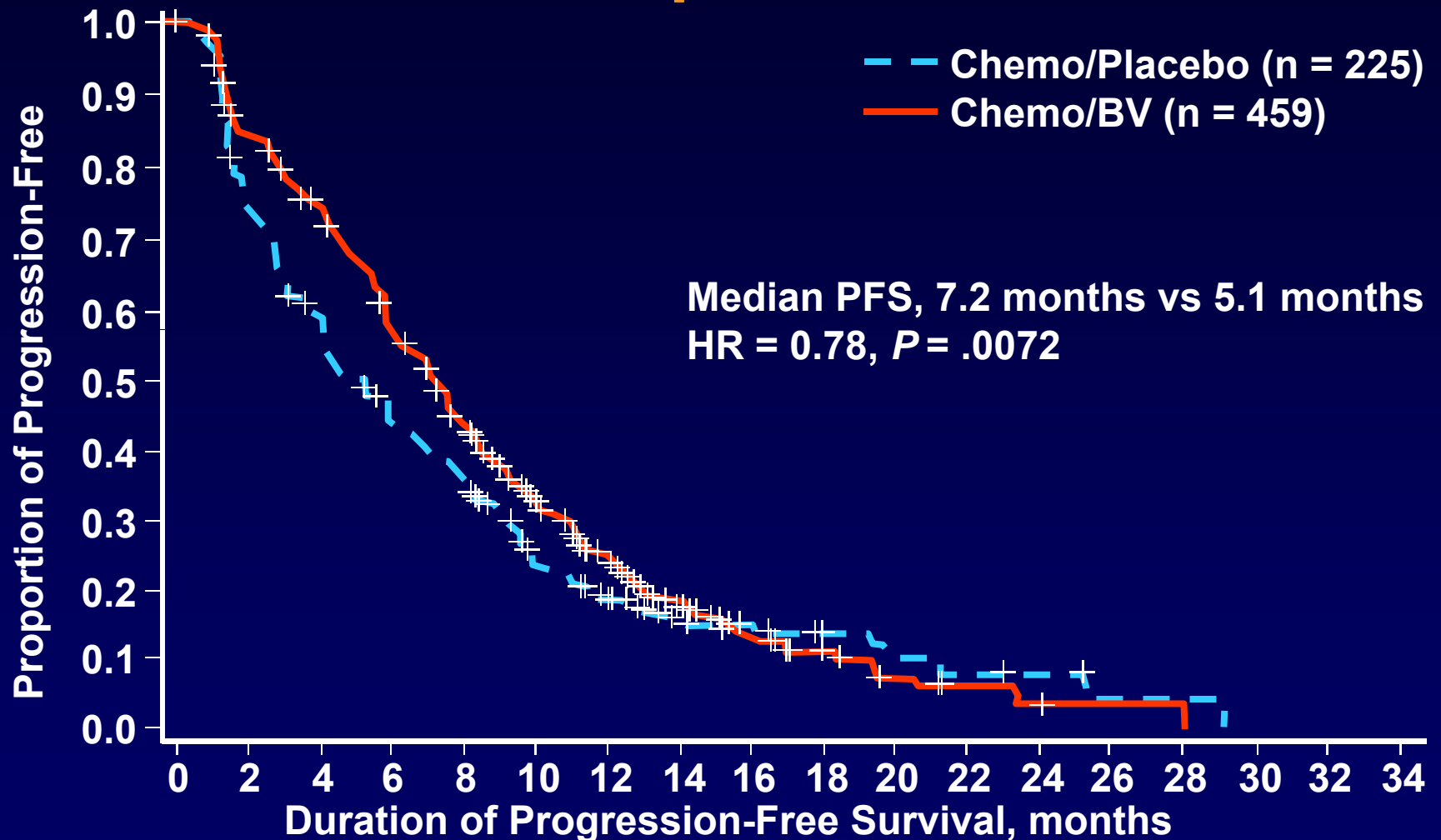
Phase II Study: Sunitinib in MBC

- Sunitinib is an oral, multitargeted tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, stem cell factor receptor (KIT), and colony-stimulating factor-1 receptor
- N = 64 MBC patients pretreated with A and T
- Sunitinib malate 50 mg/day for 4 weeks q 6
- ORR = 11% (7 PRs), median response duration 19 weeks
- Clinical benefit (ORR+NC \geq 6 months) = 16% (10 patients/64)
- Median time to progression = 10 weeks

RIBBON-2: Trial Design



RIBBON-2: Primary Endpoint of PFS ITT Population



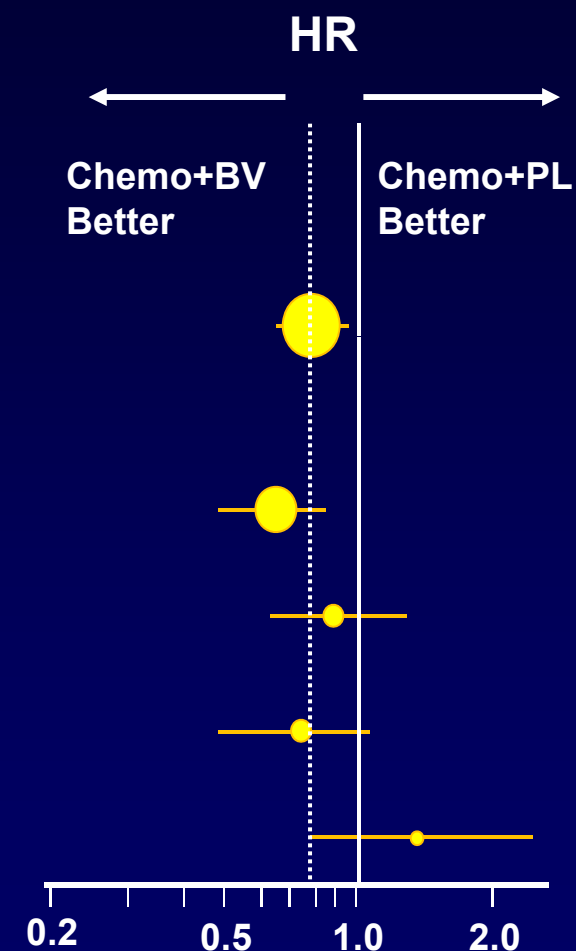
Number at risk:

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Chemo/Placebo	225	165	129	93	77	44	33	19	12	8	5	4	3	1	1	0	0	0
Chemo/BV	459	381	334	254	190	130	87	47	27	18	9	5	2	1	1	0	0	0

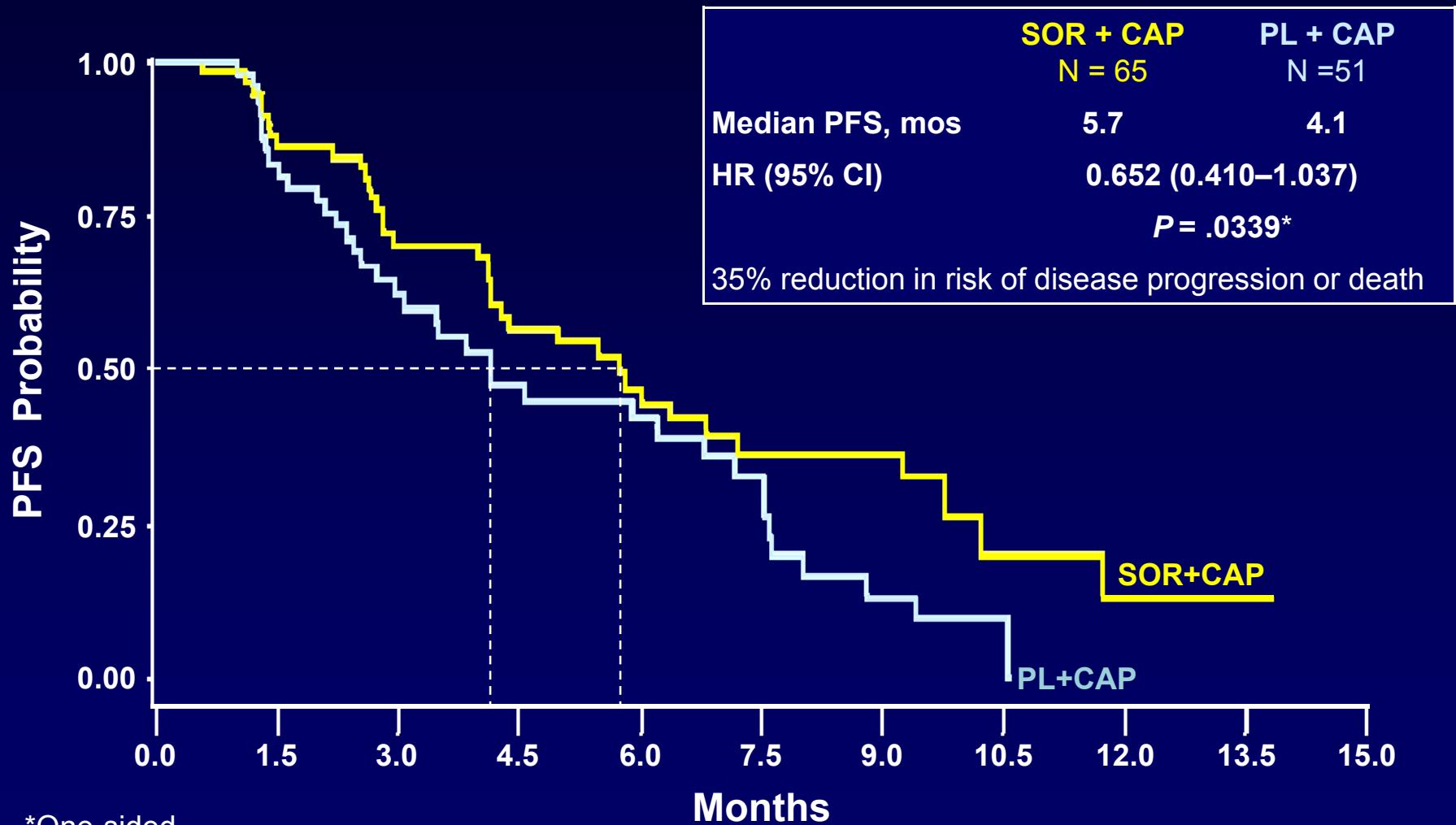
Brufsky A, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 42.

RIBBON-2: Cohort-Specific Analysis PFS ITT Population

Cohort	Total, n	Chemo + PL n = 225		Chemo + BV n = 459		HR (95% CI)
		Events	Media, months	Events	Median, months	
All subjects	684	184/255	5.1	372/459	7.2	0.78 (0.64-0.93)
Chemo						
Taxanes	304	84/103	5.8	151/201	8.0	0.64 (0.49-0.84)
Gemcitabine	160	43/52	5.5	84/108	6.0	0.90 (0.61-1.32)
Capecitabine	144	39/47	4.1	87/97	6.9	0.73 (0.49-1.08)
Vinorelbine	76	18/23	7.0	50/53	5.7	1.42 (0.78-2.59)



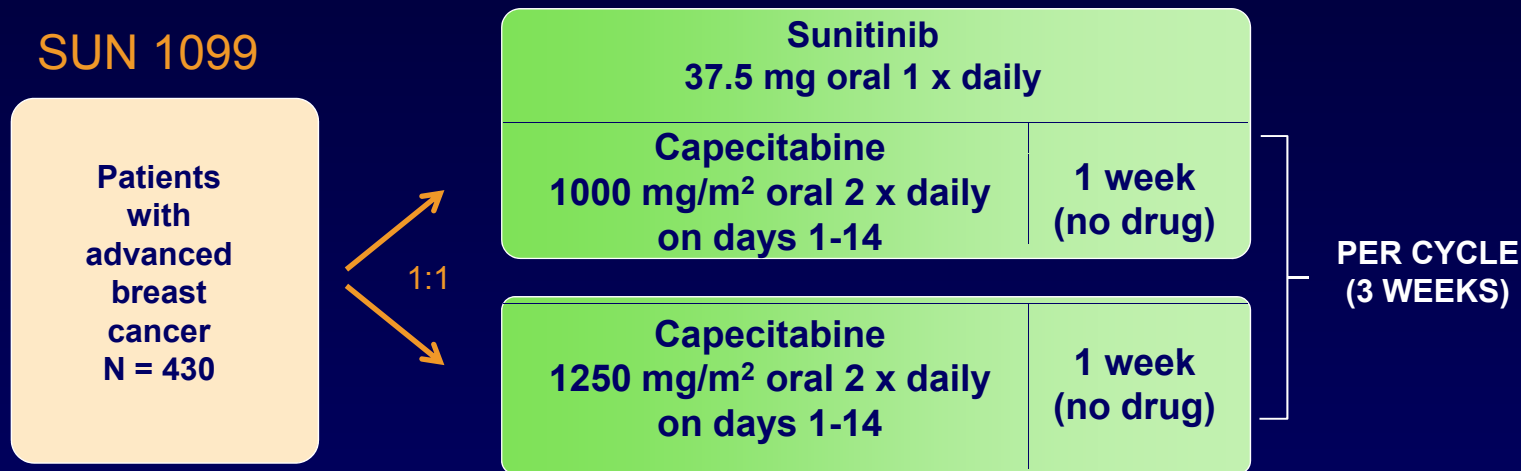
SOLTI-0701 PFS: Second-Line Patients



*One-sided

Baselga J, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 45.

SUN 1099: Sunitinib + Capecitabine vs Capecitabine in Second-Line Advanced Breast Cancer



Trial Design	Endpoints	Study Sites	Indication
Multinational, multi-center, randomized, open label Phase III	Primary: PFS Secondary: ORR, OS, QoL, safety, pharm-economics	US, EU, Canada	Second-line

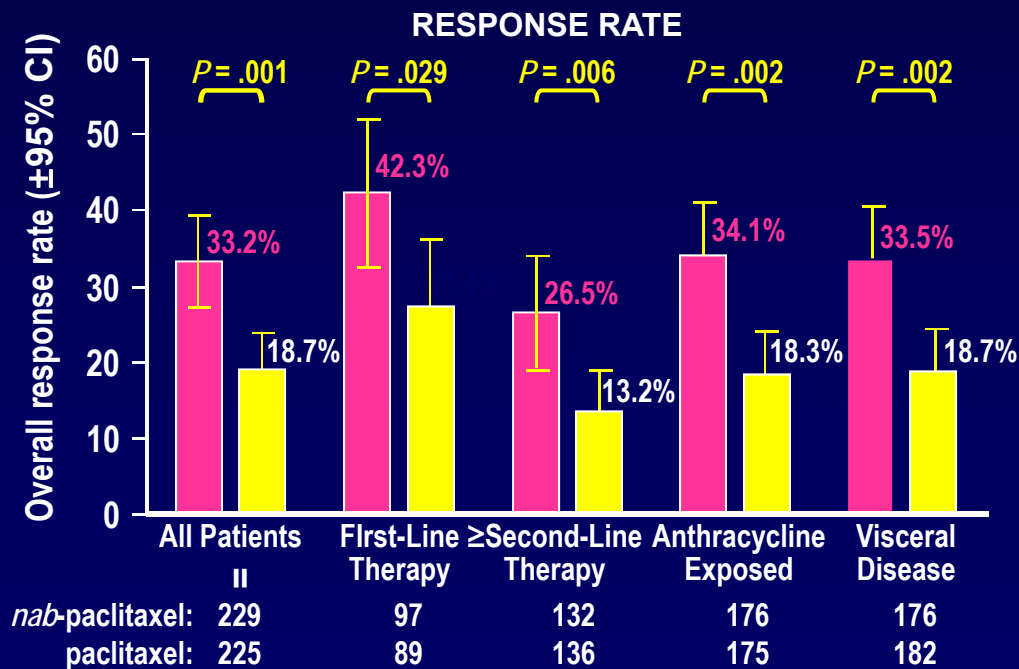
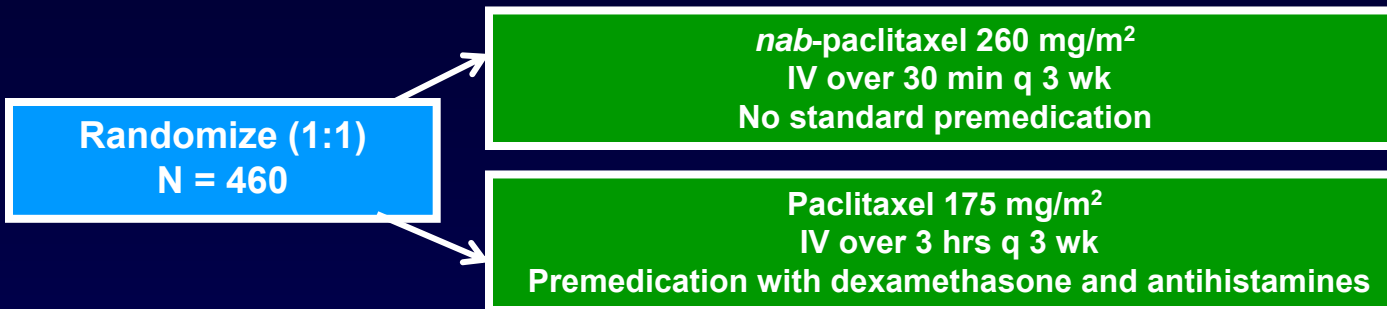
Accrual completed

***Nab*-Paclitaxel in Breast Cancer**

- ***Nab*-paclitaxel is albumin-bound, polyethoxylated castor oil-free paclitaxel → no steroids premedication and short duration infusion**
- **Previous study testing *nab*-paclitaxel in taxane pretreated advanced breast cancer patients (N = 181 patients; ORR 31%)***

*Blum JL, et al. *Clin Breast Cancer*. 2007;7(11):850-856.

Phase III Trial: *nab*-Paclitaxel vs Paclitaxel in mBC



- Significantly improved response rate: 33% vs 19%, P = .001
- Increased time to tumor progression: 22.7 weeks vs 16.6 weeks, P = .003
- Prolonged survival in > first-line patients: 56.4 weeks vs 46.7 weeks, P = .016

A Phase III Trial in M+ Patients Resistant to Anthracyclines and Taxanes

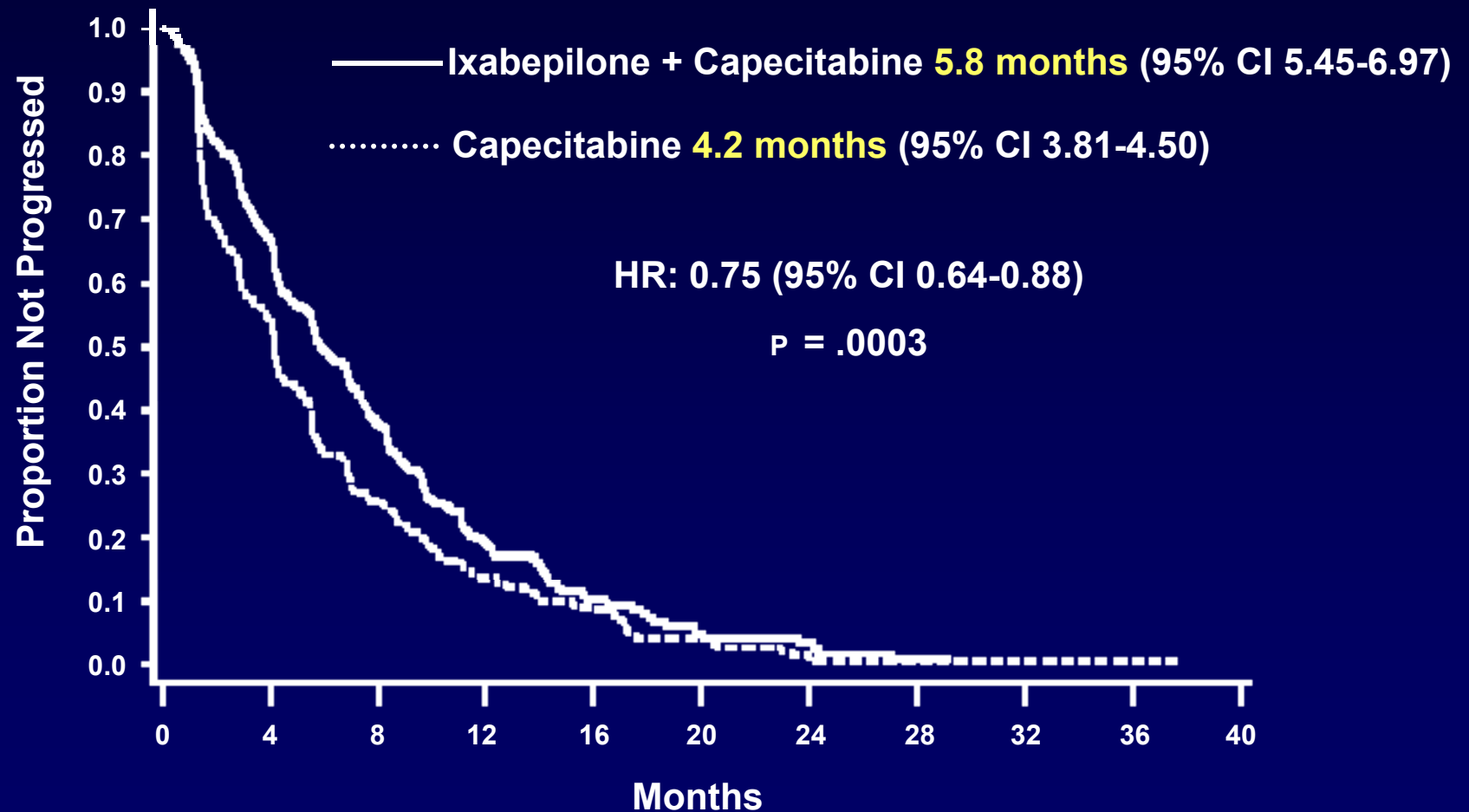
**N = 752
patients**

Ixabepilone 40 mg/m² IV 3 hr day 1 q 3 weeks + Capecitabine 2000 mg/m²/day PO days 1-14 q 3 weeks

Capecitabine 2500 mg/m²/day PO days 1-14 q 3 weeks

Stratification by visceral metastases, prior CT, anthracycline resistance, study site

Progression-Free Survival by Treatment Arm (Independent Radiology Review)



Ixabepilone + Capecitabine Phase III Trial

Grade 3/4 Treatment-Related Toxicities

Adverse Event Grade 3/4	I + C, % (N = 369)	C, % (N = 368)
Neutropenia	68	11
Febrile Neutropenia	4.8	0.5
Peripheral neuropathy	22.8	0
Resolution of neuropathy*, median wks after dose reduction (range)	6.0 (4.6–7.6)	NA
Hand-foot syndrome	18	17
Fatigue	9	3.3
Myalgia	8	0.3
Diarrhea	6	8.5
Vomiting	4	2.3
Nausea	3	2
Mucositis	2.3	2
Arthralgia	3	0

*Defined as the time from onset of worst grade to baseline or grade 1; NA: neuropathy not seen

Thomas ES, et al. *J Clin Oncol*. 2007;25(33):5210-5217.

Eribulin as a Novel Antimicrotubule Cytotoxic Agent

- Eribulin is a synthetic analogue of the marine natural product halichondrin B
- Eribulin is a microtubule dynamics inhibitor with a novel mechanism of action (it suppresses microtubule growth and it sequesters tubulin into nonfunctional aggregates)
- Phase I studies have shown that neutropenia is the dose-limiting toxicity (DLT). Other side effects include alopecia, fatigue, and nausea

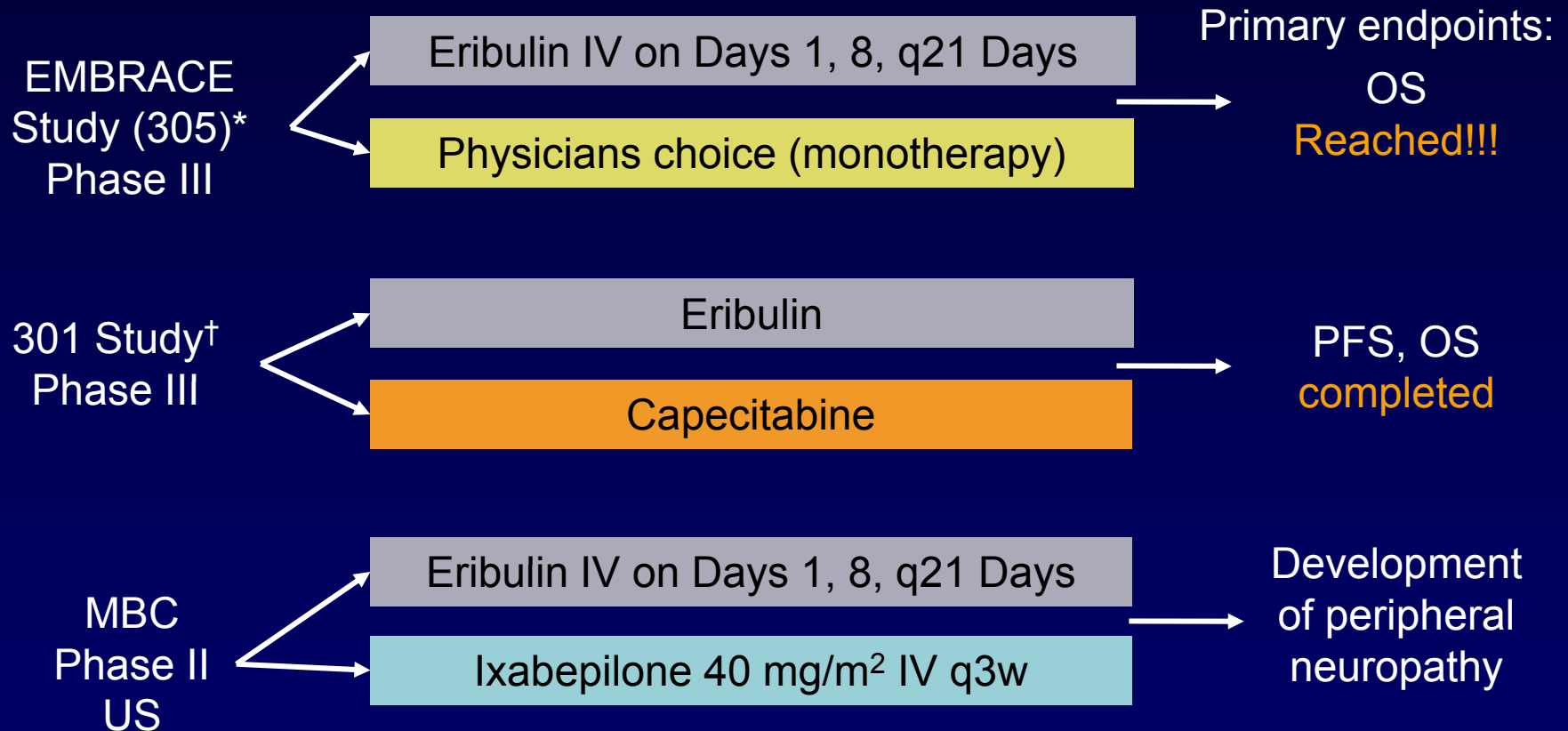
Phase II Trials with Eribulin in Patients with Advanced Breast Cancer Previously Treated With Anthracyclines And Taxanes

	Vahdat et al* <i>J Clin Oncol</i> 2009 ¹	Vahdat et al** ASCO 2008 ²
Number of patients	103	269
Median number of prior chemotherapy regimens for M+ disease	4	4
Eribulin dose	1.4 mg/m ² IV bolus d 1 + 8 q 21 days	1.4 mg/m ² IV bolus d 1 + 8 q 21 days
ORR, % (95% CI)	16 (10-25)	9 (6-13)
FN/G3 fatigue/G3 neurotox, %	4/5/5	5/10/5

*70/103 patients received d 1 + 8 +15 q 28 days; **previously treated with A, T, and capecitabine

1. Vahdat LT, et al. *J Clin Oncol*. 2009;27(18):2954-2961. 2. Vahdat LT, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract 1084.

Additional Studies of Eribulin in Metastatic Breast Cancer



*Third-line breast cancer treatment.

†Second-line breast cancer treatment.

My Opinion

- **First-line combination approach:**
 1. Chemo-based clinical trial
 2. Docetaxel + bevacizumab (need to improve disease as soon as possible)
 - RR: 64%
- **Second-line approach**
 1. Clinical trial
 2. Chemo + bevacizumab