

Case #4

Managing Metastatic Breast Cancer in a Patient Previously Treated with an Anthracycline and Taxane

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Issues to be discussed

- 1. Therapeutic approaches following a surgery for local recurrence (Luminal B)**
- 2. Systemic therapy for metastatic disease after adjuvant FEC/Docetaxel, tamoxifen and non-steroidal aromatase inhibitor**
- 3. Therapy of metastatic disease:**
 - Monotherapy versus combination**
 - Chemotherapy plus molecular-targeted therapy**

👉 Taking into account 2 episodes of FN despite G-CSF in the adjuvant

Treatment of Local Recurrence

Systemic therapy for treating locoregional recurrence in women with breast cancer

Rauschecker HHE, Clarke MJ, Gatzemeier W, Recht A

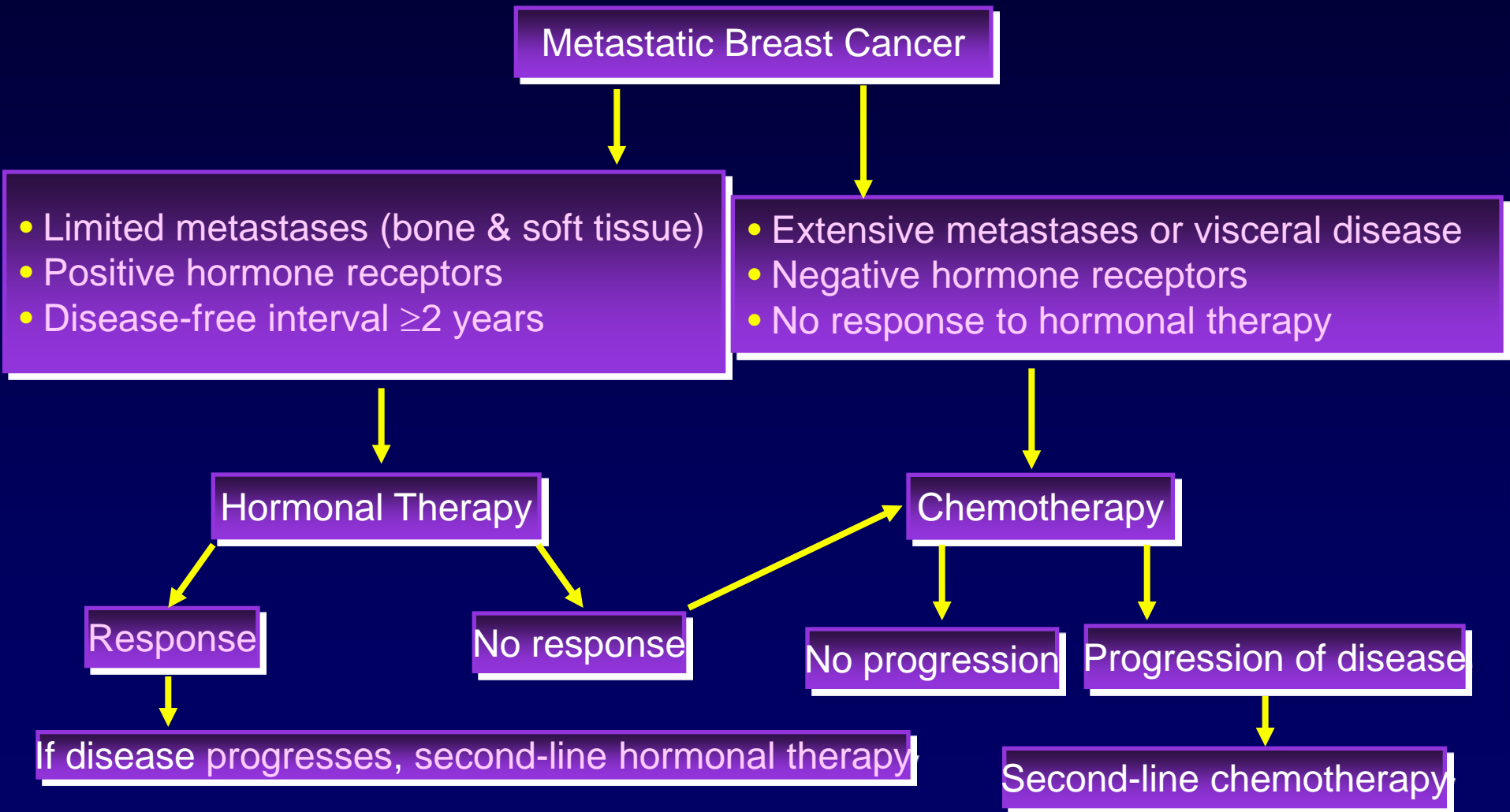
- **10% - 35% of women with operable breast cancer will experience an isolated locoregional recurrence following their primary treatment.**

AUTHORS' CONCLUSION

This review of randomized trials provides insufficient evidence to support systemic treatment in women with locoregional recurrence of breast cancer. Participation in randomized trials of systemic treatment versus observation is appropriate.

**Treatment of Symptomatic Distant
Progression Following Adjuvant
FEC/Docetaxel and Endocrine Therapy**

Algorithm For Systemic Treatment Approach for HER2-Negative, Metastatic Breast Cancer



Chemotherapy for MBC

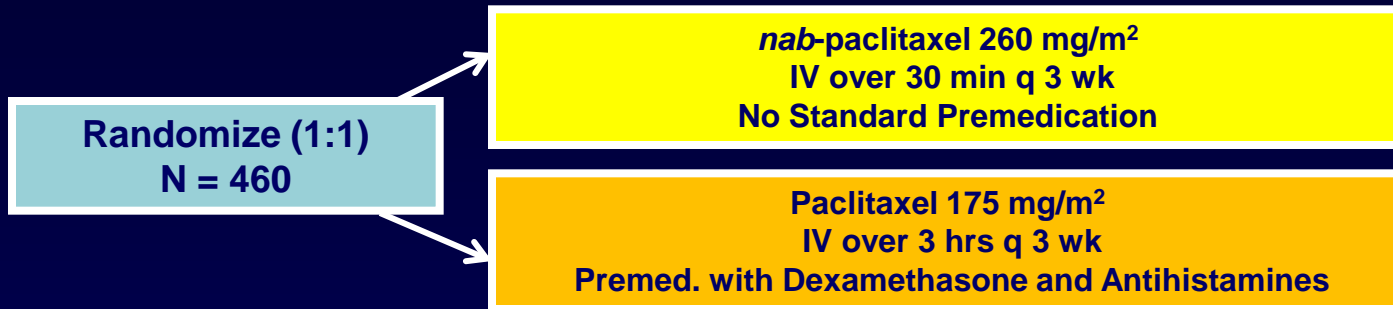
- **Sequential single agents (at MTD) preferred for most patients**
 - Variety of options—no single ‘gold standard’
 - Limited toxicity regimens are preferred
- **Combinations appropriate for rapidly progressive, symptomatic disease**
 - Reduction in disease symptoms outweighs potential toxicity
 - May not be candidate for subsequent therapy if rapid progression continued

Rechallenge With Pegylated Liposomal Doxorubicin Plus Cyclophosphamide for First-Line Therapy of MBC After Adjuvant Anthracyclines

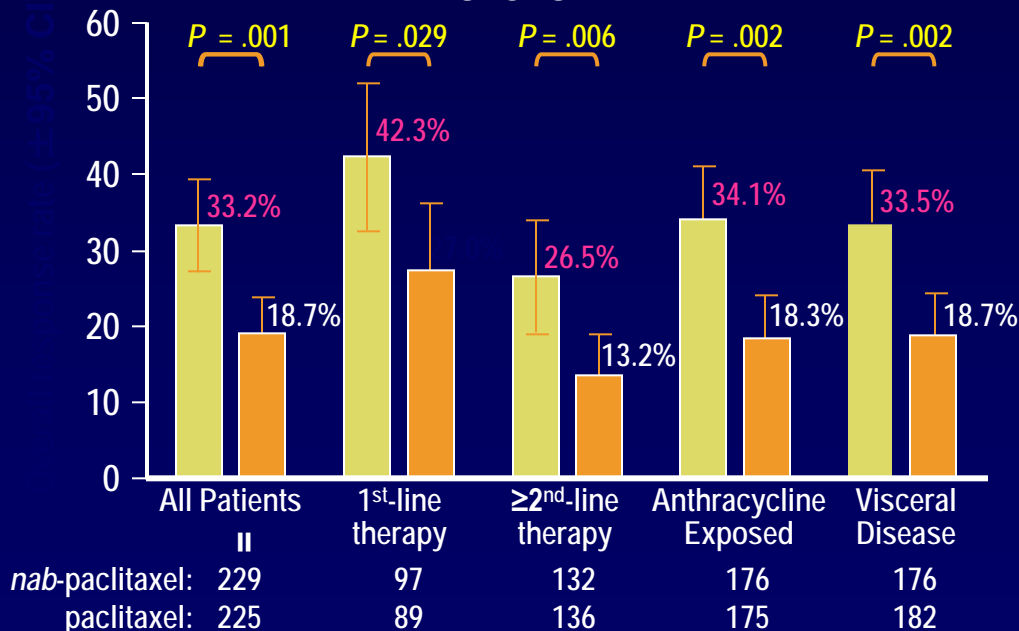
Response	Disease-Free Interval							
	Overall		1 to 3 years		3 to 5 years		> 5 years	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
CR	2	3	0	0	1	6	1	3
PR	22	35	4	24	6	33	12	40
SD ≤6 months	21	33	5	29	4	25	12	40
PD	18	29	8	47	5	31	5	17
Total	63		17		16		30	

SD, stable disease; PD, progressive disease

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



RESPONSE RATE



- Significantly improved response rate: 33 vs 19%, $P = .001$
- Increased time to tumor progression: 22.7 wk vs 16.6 wk, $P = 0.003$
- Prolonged survival in > first-line patients: 56.4 weeks vs 46.7 weeks, $P = .016$

***nab*-Paclitaxel “Targeted 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%)***

Capecitabine in Taxane-Pretreated MBC: Consistent Efficacy Data

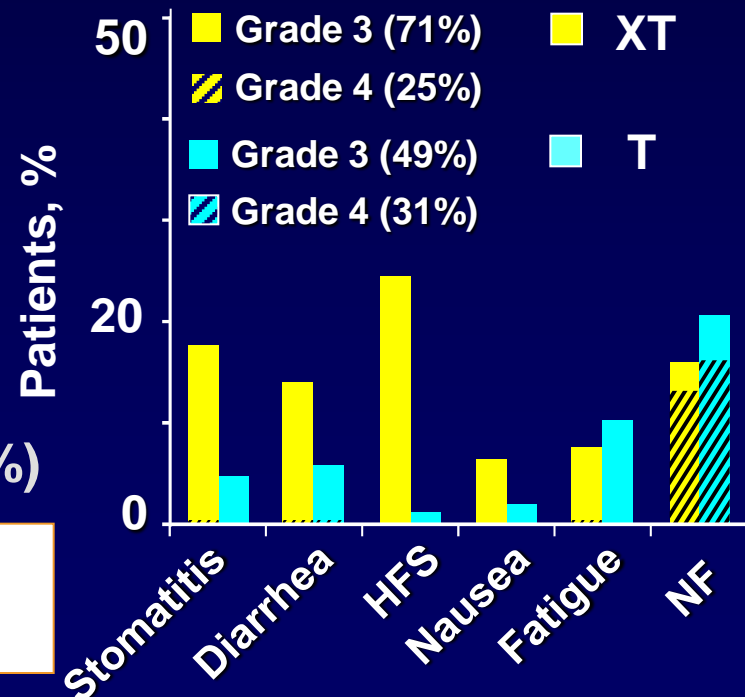
No.	CR+PR, %	ORR+SD, %	Median TTP, months	Median OS, months
163	20 ¹	63	3.0	11.6
75	26 ²	57	3.2	12.2
136	15 ³	62	3.3	10.4
126	28 ⁴	63	4.6	15.2
230	19 ⁵	NA	4.2	NA

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.

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



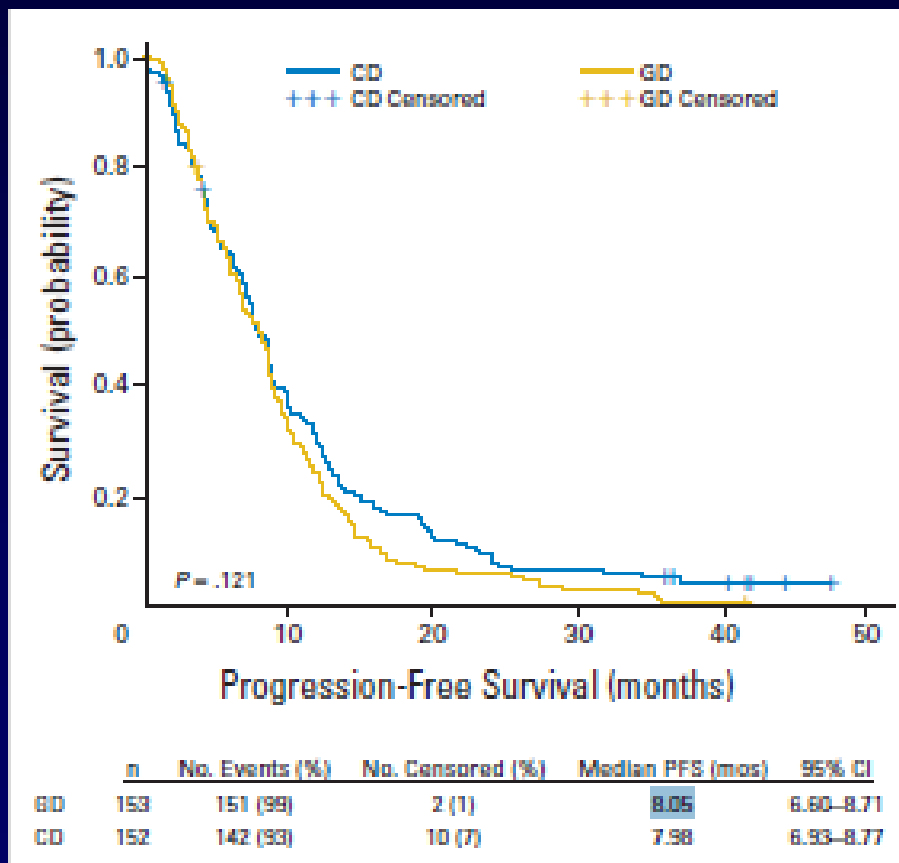
Gemcitabine Plus Paclitaxel vs Paclitaxel

- **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)
 - G3-4 nonhematologic toxicity: low in both arms



GT: Favorable therapeutic index

Phase III Study of Gemcitabine Plus Docetaxel vs Capecitabine Plus Docetaxel for Anthracycline-Pretreated Patients With Metastatic Breast Cancer



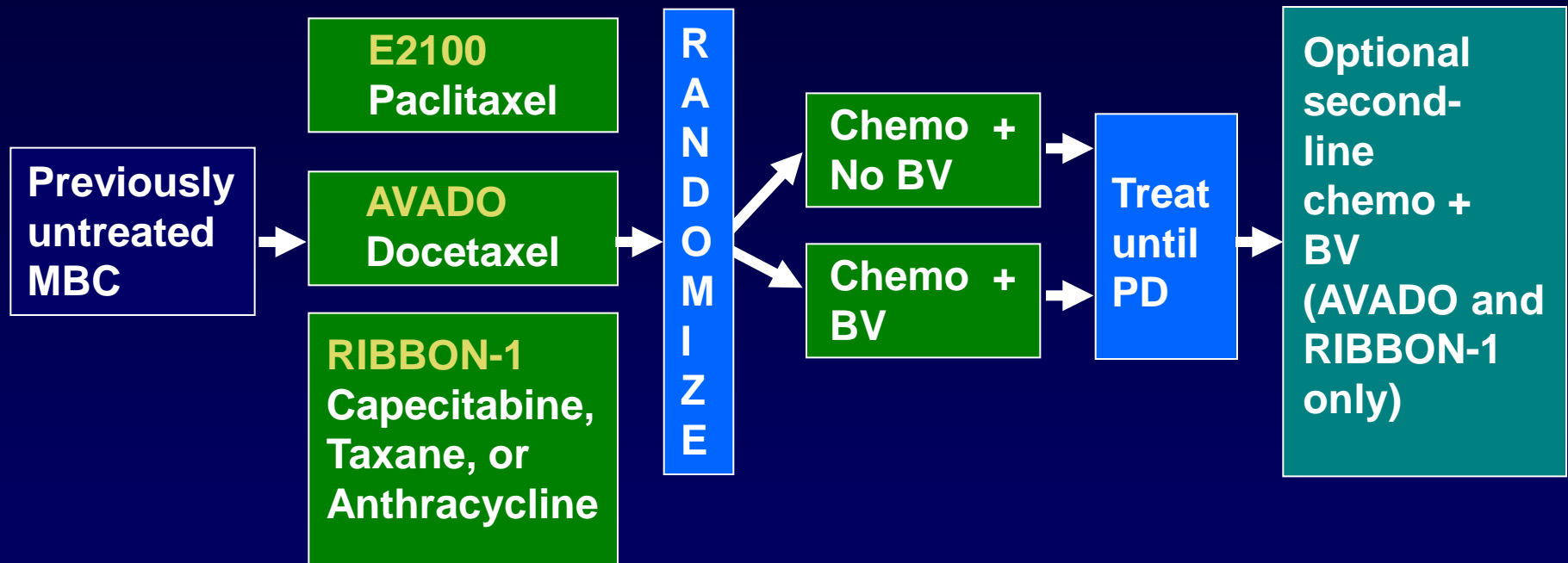
No significant difference in outcome, but a different toxicity profile

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	6.2	9.8	8.3	10.7
HR	0.60 P<.0001		0.80 (7.5 mg) P = .0450 0.67 (15 mg) P = .0002		0.68 P = .0011		0.77 P = .04	
OS, months	25.2	26.7	31.9	30.8/30.2	21.2	29	23.8	25.2
HR	0.88 P = .16		1.05 (7.5 mg) P = .72 1.03 (15 mg) P = .85		0.85 P = .27		1.03 P = .83	

1. Miller K, et al. *N Eng J Med*. 2007;357(26):2666-2676.
2. Miles DW, et al. *J Clin Oncol* 2010;28(20):3239-3247.
3. Robert NJ, et al. *J Clin Oncol*. 2009;27(15S): Abstract 1005.

A Meta-Analysis of Overall Survival Data from Three Randomized Trials of Bevacizumab (BV) and First-Line Chemotherapy as Treatment for Patients with MBC



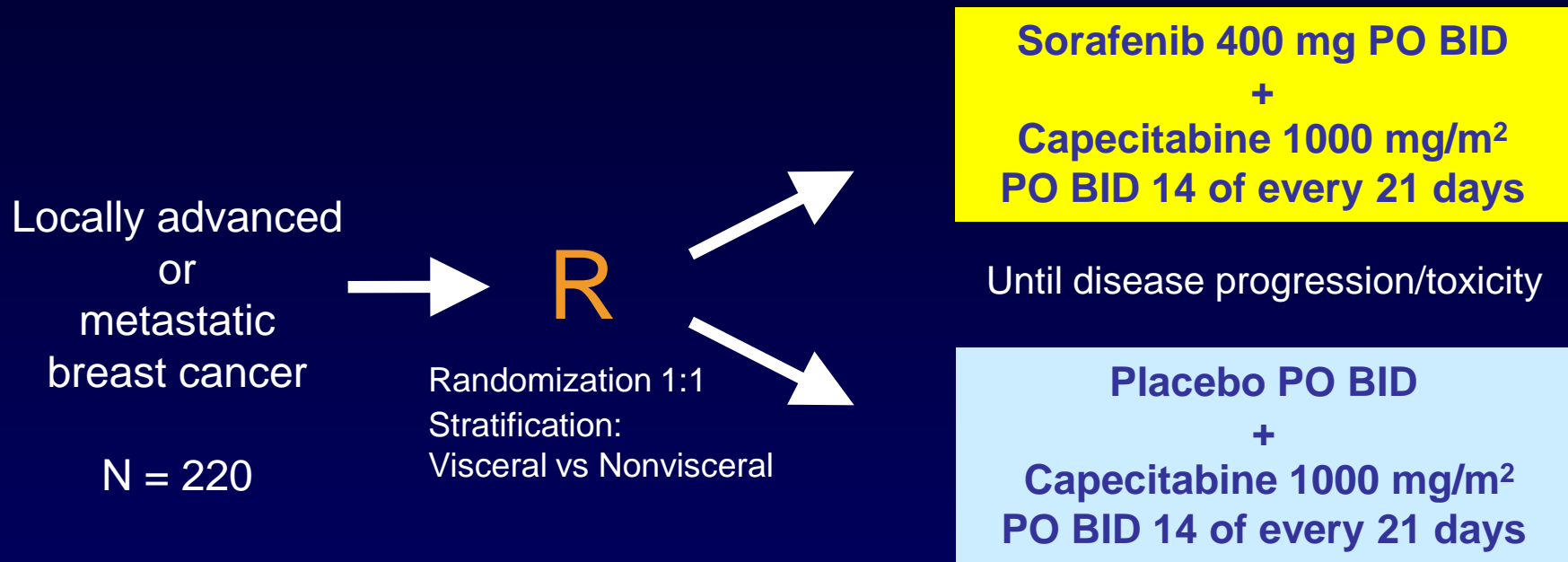
Pooled Efficacy Analysis of Bevacizumab + Chemotherapy vs Chemotherapy Alone

Outcome	Chemotherapy + Bevacizumab (n = 1439)	Chemotherapy Alone (n = 1008)
Median PFS, mos	9.2	6.7
HR (95% CI)	0.64 (0.57-0.71)	
ORR,* %	49	32
Median OS, mos	26.7	26.4
HR (95% CI)	0.97 (0.86-1.08)	
1-yr OS, %	82	77

*Assessed in patients with measurable disease at baseline: n = 1105 for chemotherapy plus bevacizumab; n = 788 for chemotherapy alone.

SOLTI-0701: Study Design

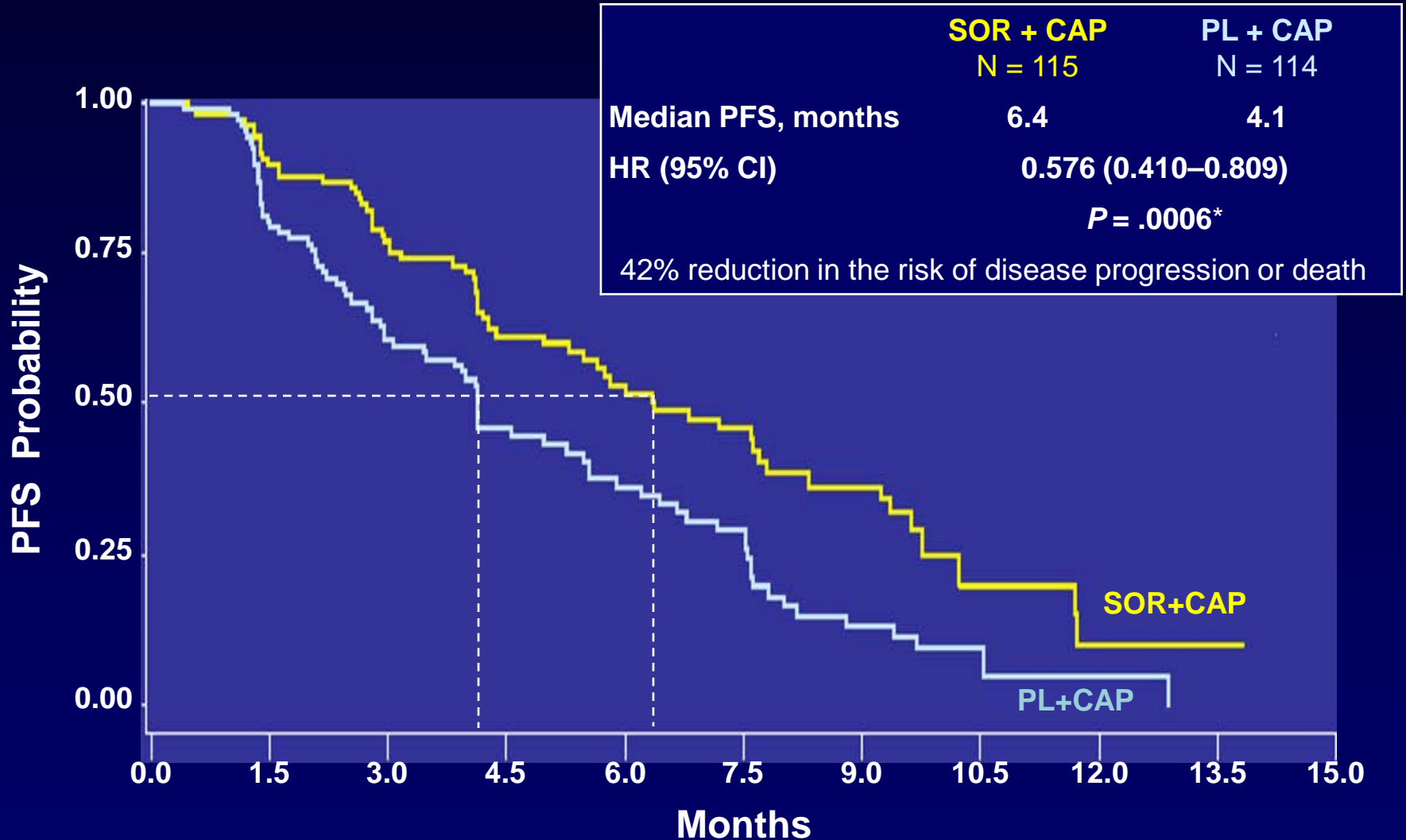
Multinational, double-blind, randomized, placebo-controlled, **phase IIb**



- **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 ITT Population



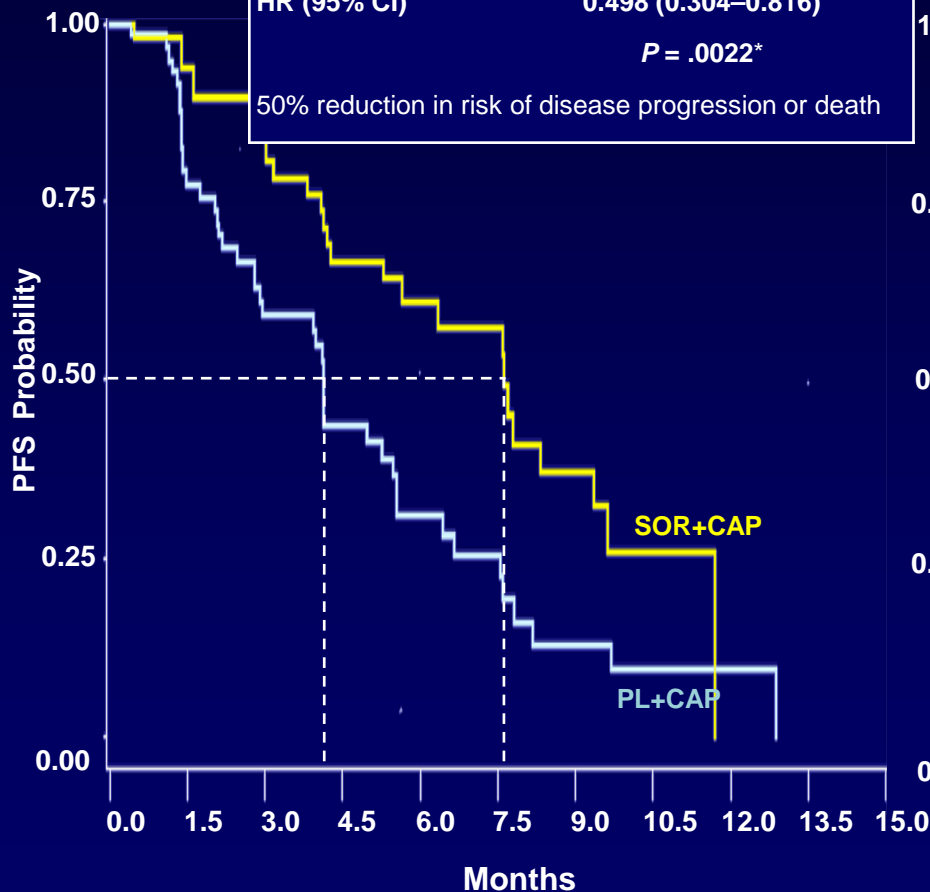
*One-sided

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

SOLTI-0701 Progression-Free Survival

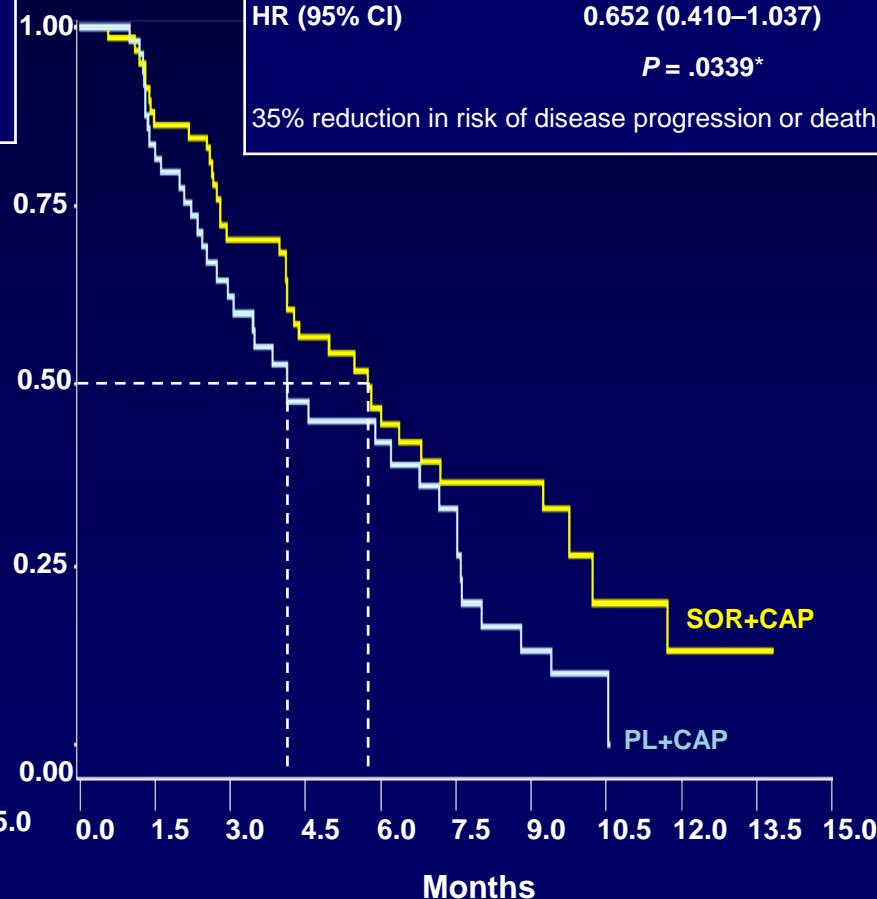
First-Line Patients

	SOR + CAP N = 50	PL + CAP N=62
Median PFS, mos	7.6	4.1
HR (95% CI)	0.498 (0.304–0.816)	
	<i>P</i> = .0022*	
	50% reduction in risk of disease progression or death	



Second-Line Patients

	SOR + CAP N = 65	PL + CAP N = 51
Median PFS, mos	5.7	4.1
HR (95% CI)	0.652 (0.410–1.037)	
	<i>P</i> = .0339*	
	35% reduction in risk of disease progression or death	



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

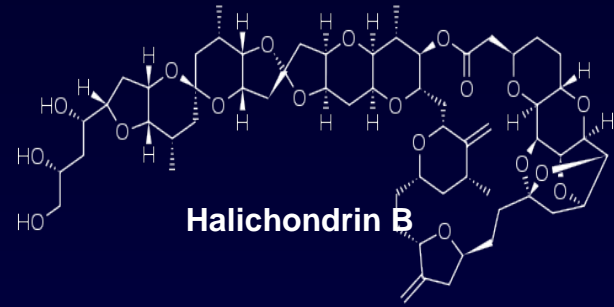
*Treatment-emergent

SUMMARY OF ANTI VEGF(R) TRIALS IN BREAST CANCER

	BEVACIZUMAB (approved)	SUNITINIB	SORAFENIB
(1st line) with Paclitaxel	E2100: POSITIVE Ph III (722 pts) Bevacizumab (BV)+Paclitaxel vs Paclitaxel PFS 11.8 vs 5.9 mos; P<0.001, OS ns	SUN1094 NEGATIVE Ph III (493 pts) Sunitinib+ Paclitaxel vs BV + Paclitaxel Terminated for futility	Randomised Ph II (237 pts) Sorafenib+Paclitaxel vs Placebo + Paclitaxel PFS 6.9 vs 5.6 mos p=0.085 TTP 8.1 vs 5.6 mos p=0.017
(1st line) with Docetaxel	AVADO: POSITIVE Ph III (736 pts in 3 arms) BV+Docetaxel vs Docetaxel+Placebo PFS 10.0 vs 8.1 mos, P<0.001, OS ns	SUN 1064 NEGATIVE Ph III (593 pts) Sunitinib + Docetaxel vs Docetaxel PFS 8.6 vs 8.3 mos; p=0.265	Ongoing Ph II
(1st line) with Taxanes or Capecitabine	RIBBON1: POSITIVE Ph III (1237 pts) BV+cape vs cape + placebo (615 pts) PFS 9.8 vs 6.2 mos p=0.0011 BV+T/A vs T/A+placebo (617pts) PFS 10.7 vs 8.3 mos, p=0.004		POSITIVE Ph II (250 pts) 1 st & 2 nd lines Sorafenib+Cape vs placebo + Cape PFS 6.4 vs. 4.1 mos; p<0.0006
In 2nd line with others: GEM, Navelbine)	RIBBON 2: POSITIVE Ph III trial (684 pts) Bevacizumab + CT vs CT PFS 7.2 vs 5.1 mos, p=0.0072, OS ns	SUN 1107: NEGATIVE Ph III (482 pts) Sunitinib vs Cape ; 2 nd line PFS 2.8 vs 4.2; p=0.002	ONGOING Ph II
(3rd line) with Capecitabine	AVF2119 NEGATIVE Ph III (462 pts) BV + Cape vs Cape better RR (19.8% vs 9.1%, P=0.001) PFS 4.86 vs 4.17 mos; p=0.85	SUN 1099: NEGATIVE Ph III (442 pts) Sunitinib+Cape vs Cape PFS 5.5 vs 5.9 mos, p=0.941	

Adapted from Miles DW, et al. *J Clin Oncol* 2010;28(20):3239-3247.

Eribulin Mesylate



- Halichondrins – a new class of antineoplastic agents
- Eribulin is a synthetic analogue of halichondrin B, a natural marine sponge product
- Nontaxane microtubule dynamics inhibitor with a novel mode of action
- Potent antiproliferative agent *in vitro* and *in vivo*
- Active against β -tubulin mutated cell lines
- Wide therapeutic window and induces less neuropathy in mice than paclitaxel

EMBRACE Study Design

Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389

Global, randomized, open-label Phase III trial (Study 305)

Patients (N = 762)

- Locally recurrent or MBC
- 2-5 prior chemotherapies
 - ≥ 2 for advanced disease
 - Prior anthracycline and taxane
- Progression of ≤ 6 months of last chemotherapy
- Neuropathy \leq grade 2
- ECOG ≤ 2

Eribulin mesylate

1.4 mg/m², 2-5 min IV
Day 1, 8 q21 days

Randomization 2:1

Treatment of Physician's Choice (TPC)

Any monotherapy (chemotherapy, hormone, biologic)* or supportive care only†

Primary endpoint

- Overall survival

Secondary endpoints

- PFS
- OR
- Safety

•Stratification:

- Geographic region, prior capecitabine, HER2/*neu* status

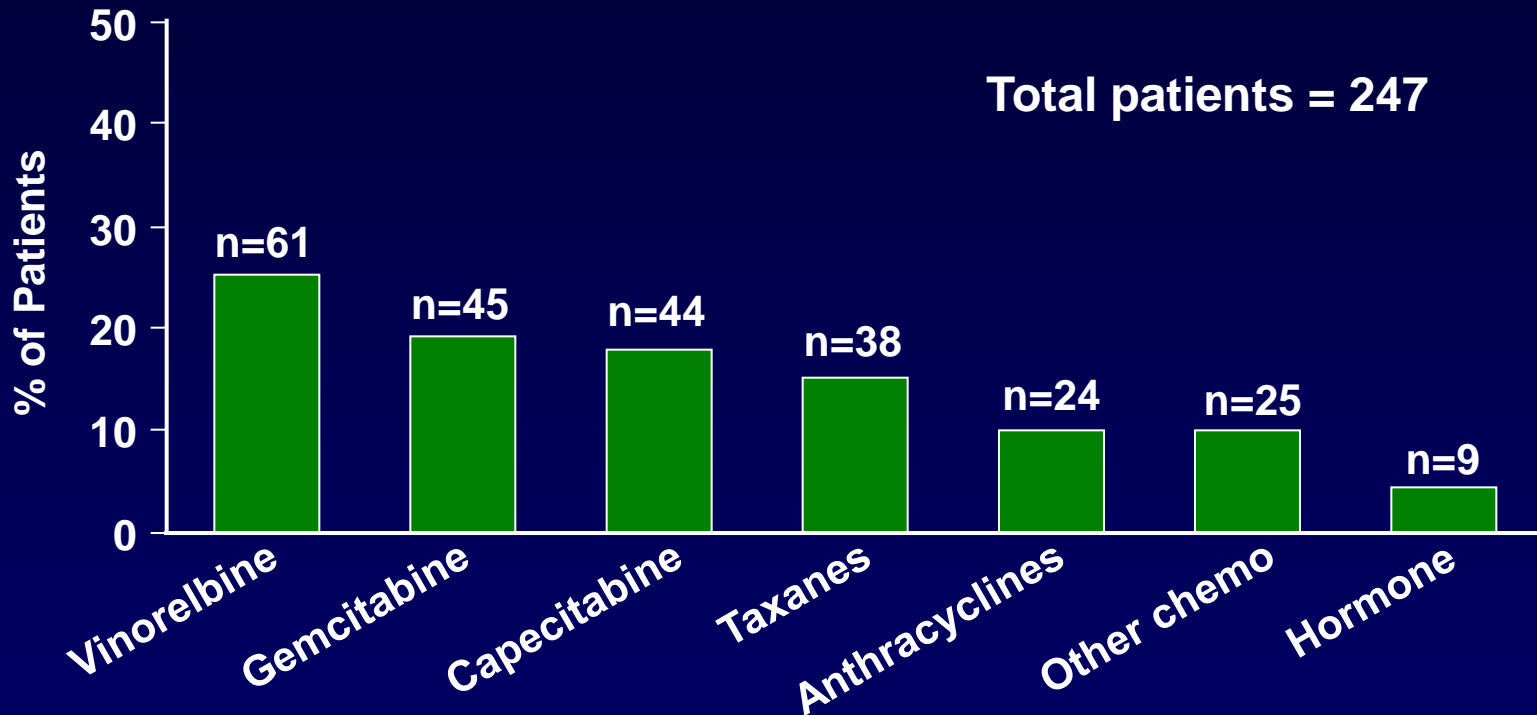
*Approved for treatment of cancer

†Or palliative treatment or radiotherapy administered according to local practice, if applicable

ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PFS, progression-free survival; HER2/*neu*, human epidermal growth factor receptor 2.

TPC Treatment Received

95% of patients treated with chemotherapy



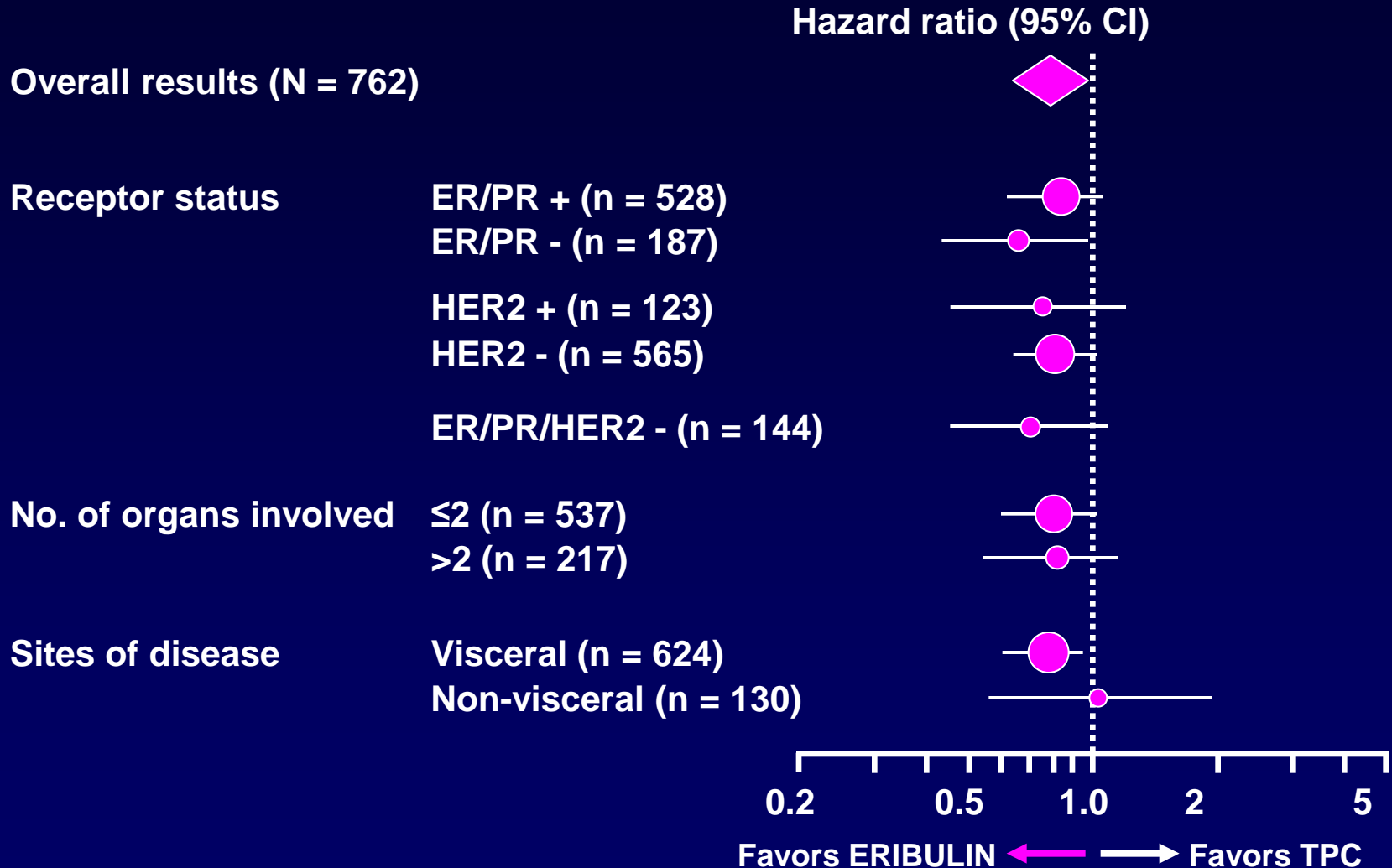
No patient received best supportive care or “biologic” therapies only

ITT population; Taxanes: paclitaxel, docetaxel, abraxane (ixabepilone)
Anthracyclines: doxorubicin, liposomal doxorubicin, mitoxantrone

EMBRACE: Overall and Progression-Free Survival (ITT)

Outcome	Eribulin (n = 508)	Physician's Choice (n = 254)
Median OS (independent review), mos	13.12	10.65
HR (95% CI)		0.81 (0.66-0.99)
<i>P</i> value		.041
1-yr survival, %	53.9	43.7
Median PFS (independent review), mos	3.7	2.2
HR (95% CI)		0.87 (0.71-1.05)
<i>P</i> value		.14
Median PFS (investigator review), mos	3.6	2.2
HR (95% CI)		0.76 (0.64-0.90)
<i>P</i> value		.002

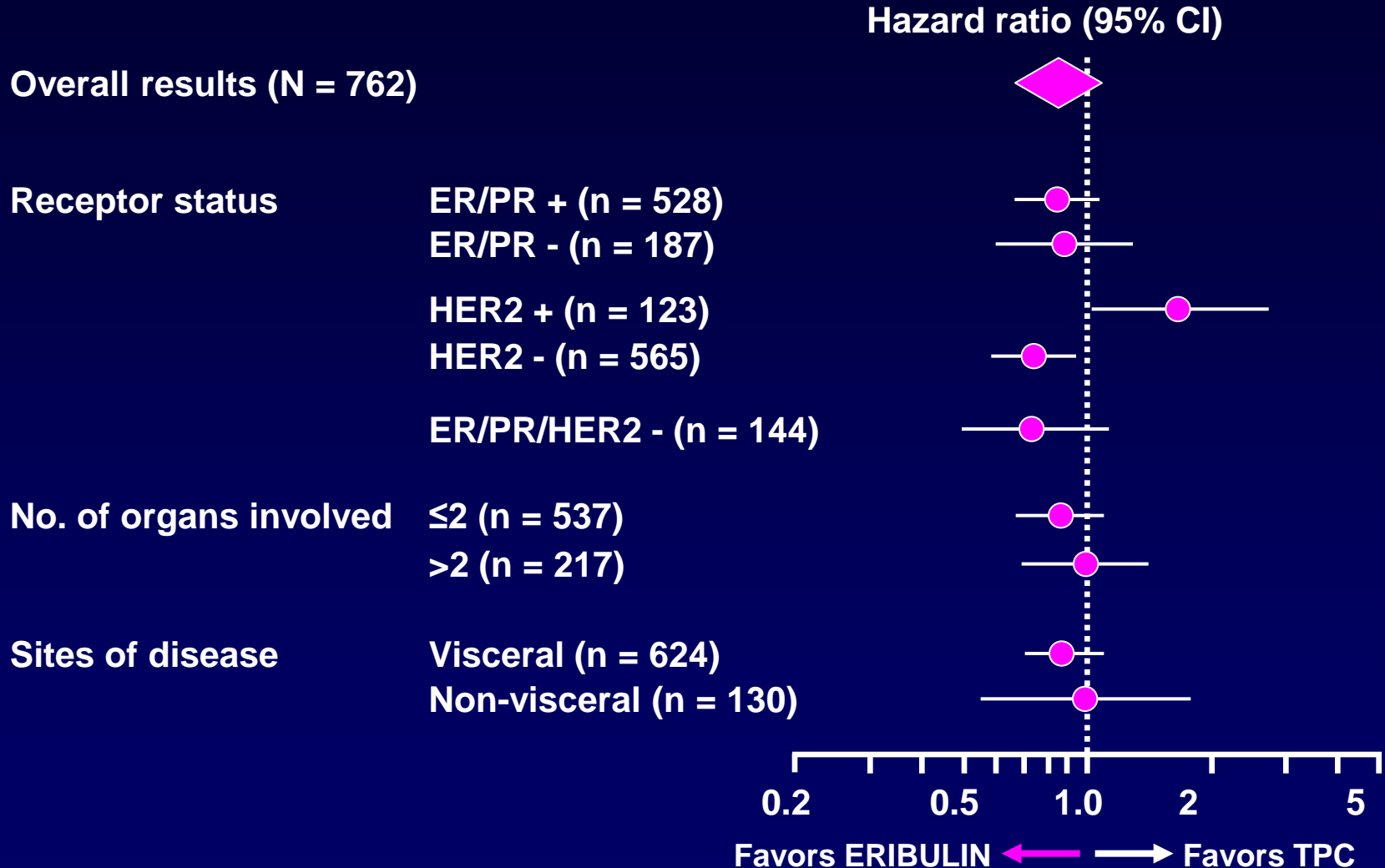
EMBRACE: Overall Survival Subsets



ITT population;

Based upon a stratified Cox analysis including geographic region, HER-2/*neu* status, and prior capecitabine therapy as strata
Twelves C, et al. *Ann Oncol.* 2010;21(suppl 8): Abstract 2750.

EMBRACE: Progression-Free Survival Subsets



ITT population;

Based upon a stratified Cox analysis including geographic region, HER-2/*neu* status, and prior capecitabine therapy as strata

Twelves C, et al. *Ann Oncol.* 2010;21(suppl 8): Abstract 2750.

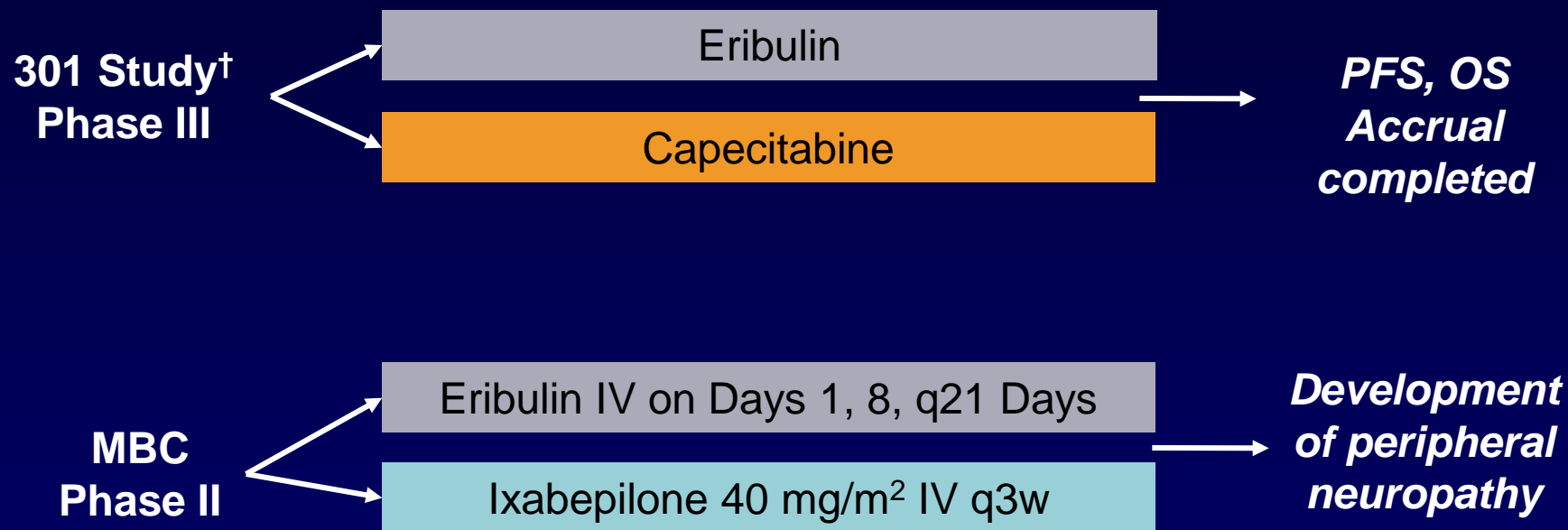
Grade 3 and 4 AEs*

	Grade 3		Grade 4	
	Eribulin (n = 503)	TPC (n = 247)	Eribulin (n = 503)	TPC (n = 247)
Hematologic events, %				
Neutropenia	21.1	14.2	24.1	6.9
Leukopenia	11.7	4.9	2.2	0.8
Anemia	1.8	3.2	0.2	0.4
Febrile neutropenia	3.0	0.8	1.2	0.4
Nonhematologic events, %				
Asthenia/fatigue	8.2	10.1	0.6	0
Peripheral neuropathy[†]	7.8	2.0	0.4	0
Nausea	1.2	2.4	0	0
Dyspnea	3.6	2.4	0	0.4
Mucosal inflammation	1.4	2.0	0	0
Hand-foot syndrome	0.4	3.6	0	0

*≥2% incidence

[†]Neuropathy peripheral, neuropathy, paresthesia, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy

Ongoing Clinical Trials of Eribulin in Metastatic Breast Cancer



[†]Second-line breast cancer treatment.

MY OPINION (Part I)

What would you recommend for this woman after surgery for local recurrence?

- 1. Observation**
- 2. Radiotherapy to chest wall with electron beam**
- 3. Endocrine therapy with AI**
- 4. Chemotherapy followed by endocrine therapy with AI**

MY OPINION (Part II)

Patient received endocrine therapy with an AI and was fine for 8 months when she developed cough and loss of appetite. Current evaluation confirms multiple metastases in both lungs and 2 liver metastases up to 1.5 cm in size. Her ECOG PS is 1, laboratory exams are within normal limits, LVEF by MUGA 58%.

Which of the following systemic therapy options would you choose for this patient at the time of progression?

1. Third-line endocrine therapy
2. Taxane monotherapy
3. Capecitabine
4. Pegylated liposomal doxorubicin
5. Combination therapy (eg, capecitabine or gemcitabine + docetaxel, vinorelbine/capecitabine)
6. Chemotherapy + bevacizumab
7. Clinical trial of chemotherapy + other targeted therapy

MY OPINION (Part III)

Patient was treated with capecitabine monotherapy. Following initial clinical stabilization of disease, after 4 months, further progression was confirmed in lung and liver. Patient ECOG PS is 1, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are 10% above upper limits of normal, other lab exams are normal. She is very concerned regarding her rapid progression.

What would be your treatment choice now?

1. Pegylated liposomal doxorubicin
2. Vinorelbine
3. Eribulin compassionate use if available
4. *Nab*-paclitaxel
5. Combination chemotherapy (eg, cyclophosphamide, methotrexate, 5-fluorouracil [CMF])
6. Chemotherapy + bevacizumab