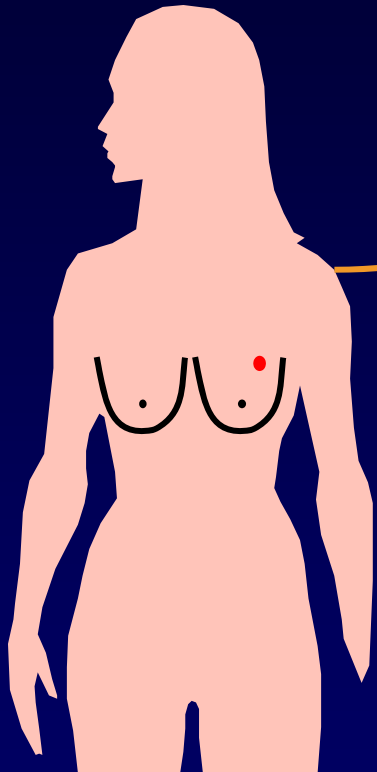


**Case #6:
Metastatic Breast Cancer
Following Anthracycline and
Taxane**

Bella Kaufman, MD
Sheba Medical Center
Tel Hashomer, Israel



62 years old, hypertension
T2N1
IDC, G III, ER\PR weakly +,
HER2 -

FEC -100 x 3 >> Doc x 3>>AI

Vomited 3 times on day 1.

Delayed vomiting – 2 days

Nausea - 4 days

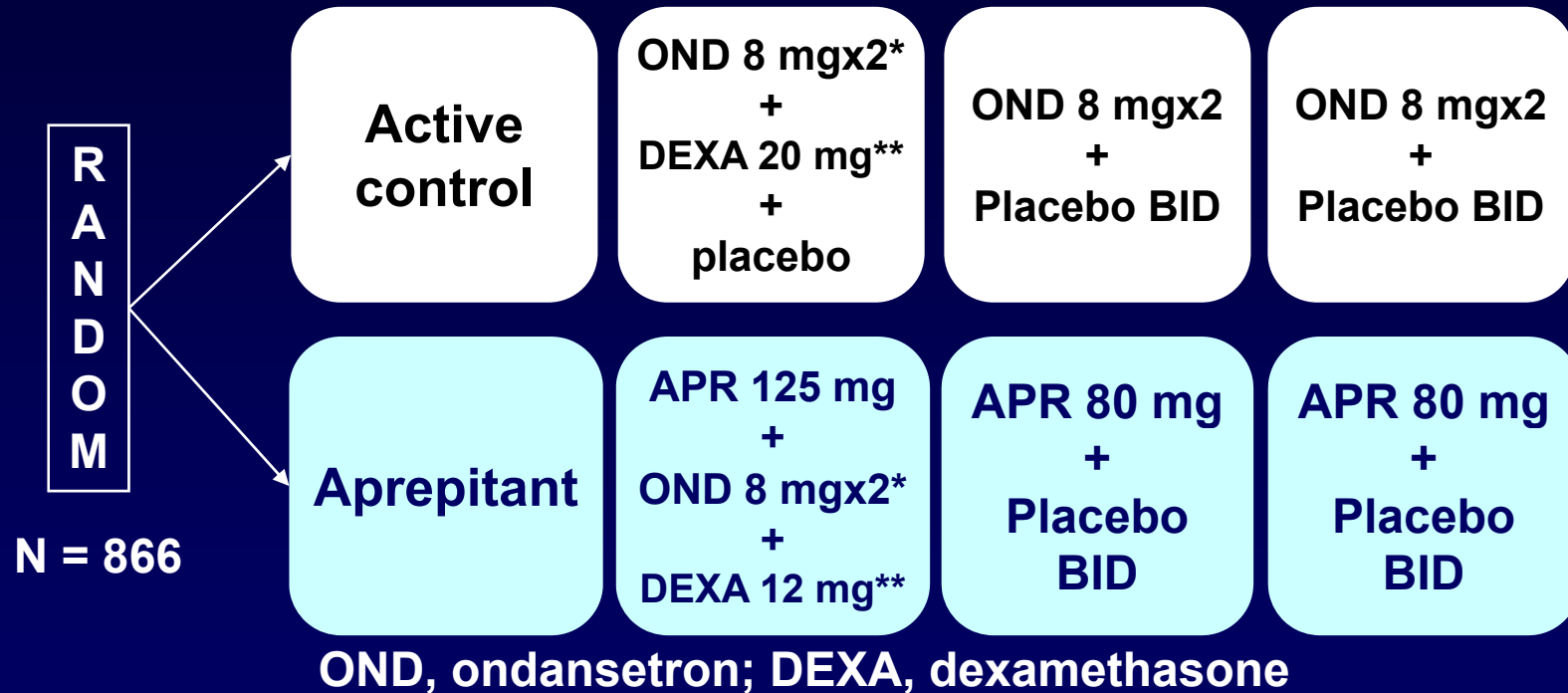
- **Acute (post-treatment)**
 - Occurs within first 24 hours after administration of cancer chemotherapy
- **Delayed**
 - CINV that begins after first 24 hours
- **Breakthrough**
 - CINV that occurs despite prophylaxis and requires rescue

Moderate Emetic Risk (MER) in Breast Cancer Treatment with Anthracyclines

- Until recently, the standard antiemetic therapy for chemotherapy with MER = 5-HT₃ receptor antagonist (dolasetron, granisetron, ondansetron, palonosetron, ramosetron, and tropisetron) + dexamethasone
- Palonosetron: > ondansetron and > dolasetron (trials designed to show noninferiority rather than superiority)
- Both ASCO and MASCC guidelines do not recommend one 5-HT₃ agent over another

Aprepitant (Neurokinin-1 Receptor Antagonist) in Breast Cancer Patients Treated with Moderately Emetogenic CT

- Anthracycline-cyclophosphamide–based CT



- Primary endpoint: Complete response (no emetic episodes and no rescue medication) days 1-5

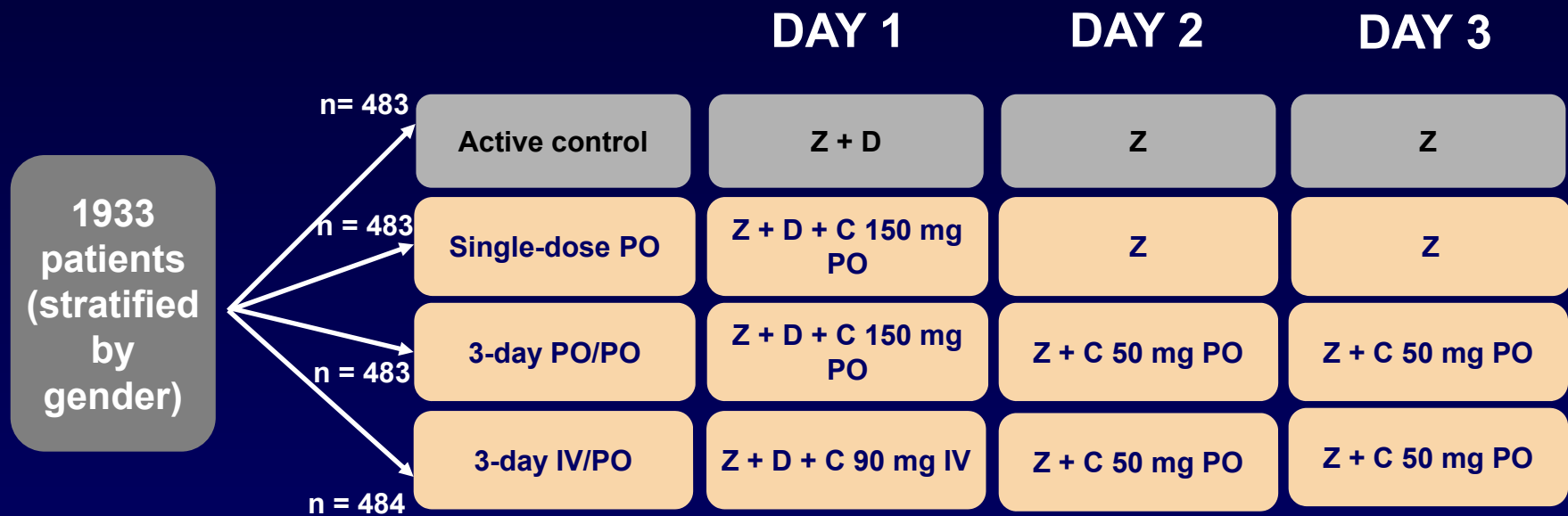
*First dose 30-60 minutes prior to chemotherapy.
Second dose 8 hours after the first dose.

**Given 30 minutes prior to chemotherapy.

Results

- Overall complete response (0-120 h) was greater with the aprepitant regimen than with the control regimen (50.8% vs 42.5%; $P = .015$)
 - Acute phase (0-24 h): CR 76% vs 69%; $P = .034$
 - Delayed phase (24-120 h): CR 55% vs 49%; $P = .064$
- More patients in the aprepitant group reported minimal or no impact of chemotherapy-induced nausea and vomiting on daily life (63.5% vs 55.6%, $P = .019$)

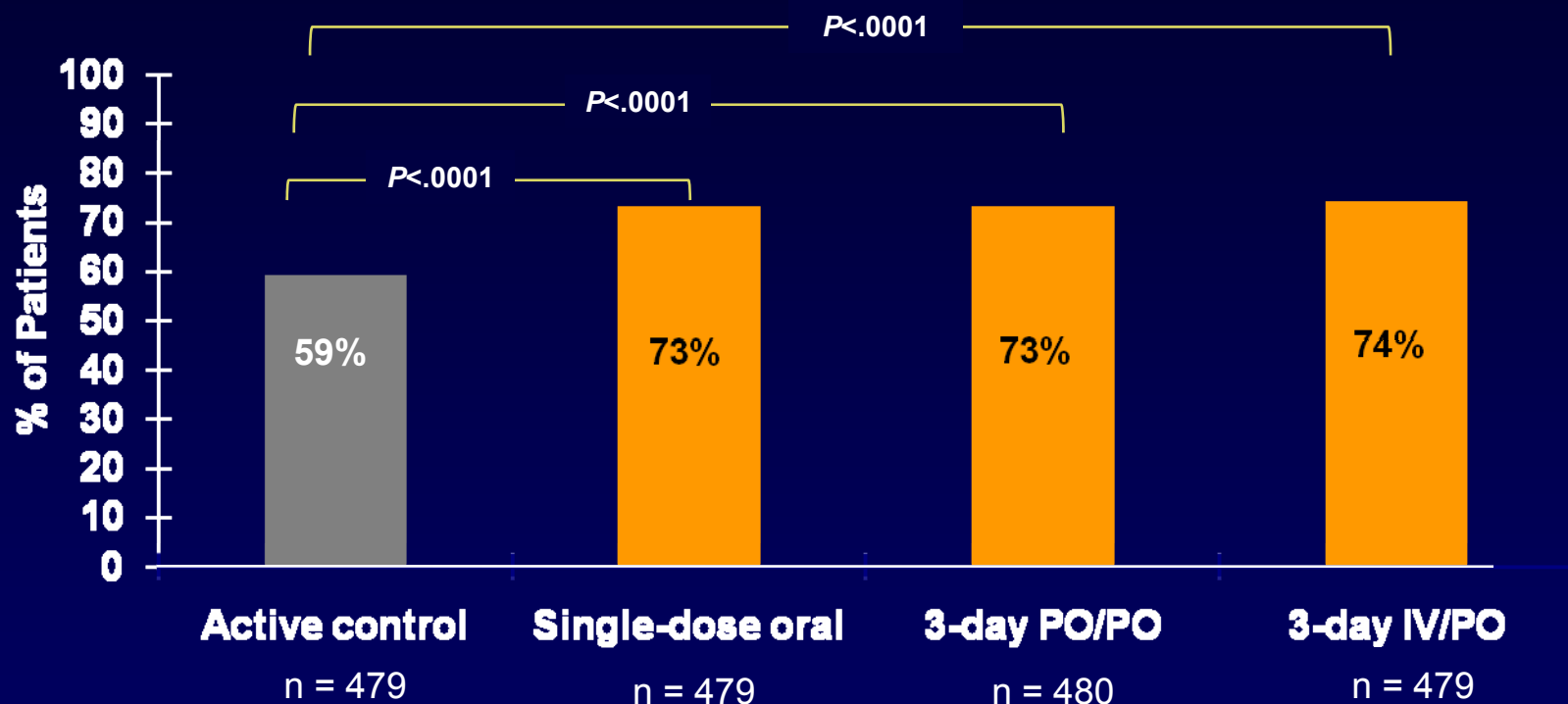
Phase III Trial of NK1 Receptor Antagonist Casopitant: Single Oral and 3-Day Oral and 3-Day IV/Oral Dosing Regimens for CINV in Patients Receiving MEC



Z: ondansetron 8 mg BID ; D: dexamethasone 8 mg IV; C: casopitant

Primary endpoint **complete response:** No vomiting/retching and no rescue medication over the first 120 hours following initiation of the first cycle of an anthracycline and cyclophosphamide (AC) containing MEC regimen

Overall CR in Cycle 1 (0-120 h)



- Complete response rates for all three casopitant regimens tested were significantly greater than active control ($P < .0001$)
- The efficacy of all three casopitant regimens was maintained in subsequent cycles

American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006

Mark G. Kris, Paul J. Hesketh, Mark R. Somerfield, Petra Feyer, Rebecca Clark-Snow, James M. Koeller, Gary R. Morrow, Lawrence W. Chinnery, Maurice J. Chesney, Richard J. Gralla, and Steven M. Grunberg

A B S T R A C T

Purpose

To update the 1999 American Society of Clinical Oncology guideline for antiemetics in oncology.

Update Methodology

The Update Committee conducted a literature search of the English literature from 1999 to February 2006.

February

reviews

The 3-drug combination of a 5-HT₃ receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving an anthracycline and cyclophosphamide.

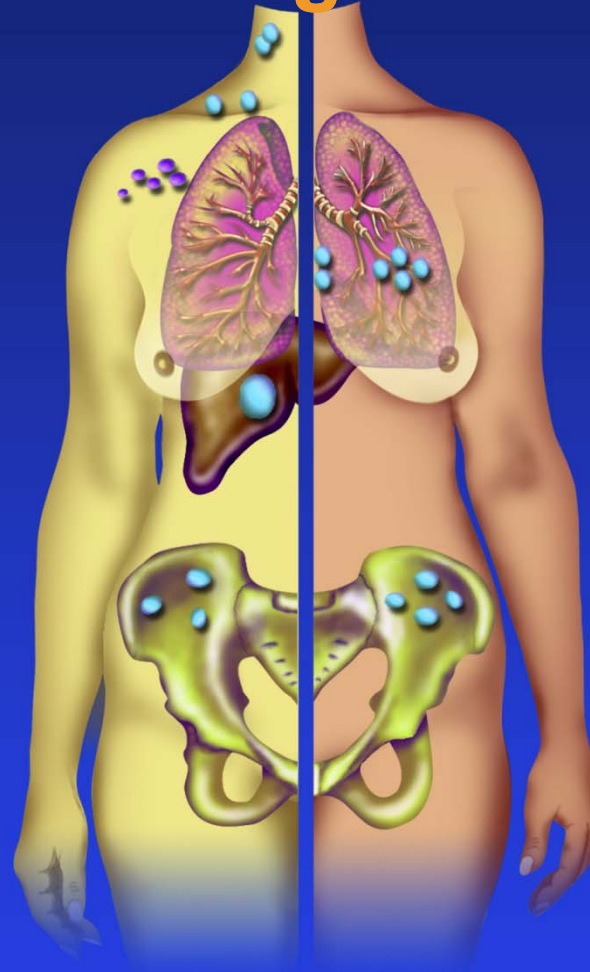
agonist,

risk. For

whom

agents of lower therapeutic index are appropriate first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT₃ serotonin receptor antagonists, neurokinin-1 receptor antagonists, and dexamethasone. The three-drug combination of a 5-HT₃ receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving an anthracycline and cyclophosphamide. For patients receiving other chemotherapy of moderate emetic risk, the Update Committee continues to recommend the two-drug combination of a 5-HT₃ receptor serotonin antagonist and dexamethasone. In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended for the prevention of delayed emesis. The Update Committee no longer recommends the combination of a 5-HT₃ serotonin receptor antagonist and dexamethasone for the prevention of delayed emesis after chemotherapeutic agents of high emetic risk.

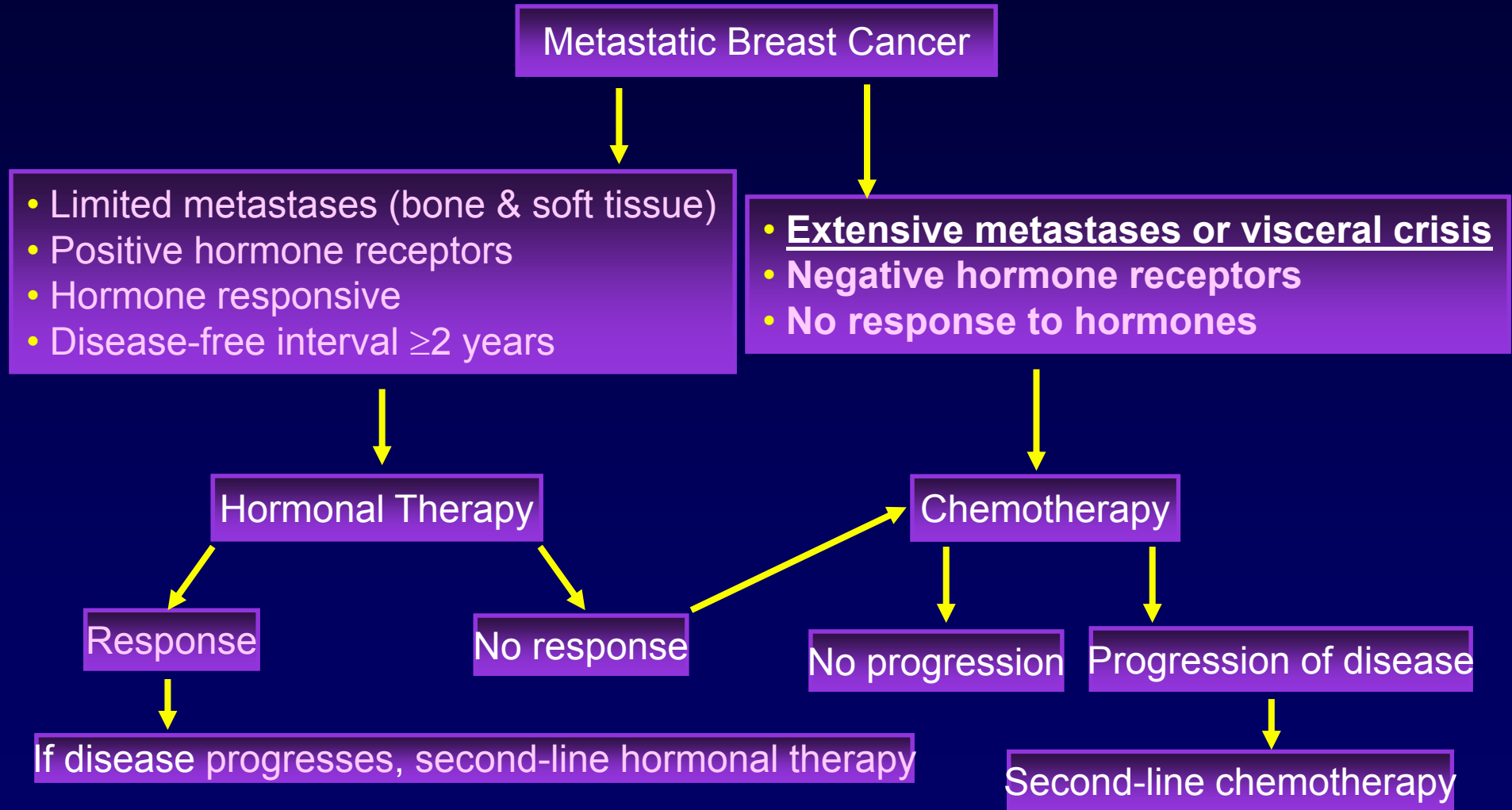
BREAST CANCER Stage IV



Two years later :

- Shortness of breath
- Cough
- Lung metastases
- R pleural effusion
- ECOG performance – 1
- Laboratory –WNL
- LVEF - 55%
- Controlled hypertension

Systemic Treatment Approach for Metastatic Breast Cancer



Chemotherapy for MBC

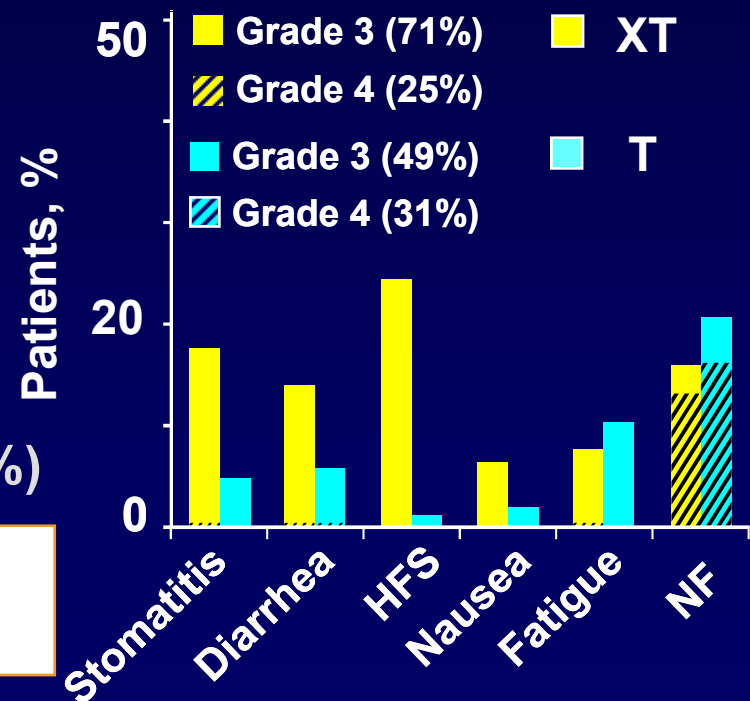
- **Sequential single agents preferred for most patients**
 - Variety of options—no single ‘gold standard’
 - Limits toxicity
 - Supported by clinical trial data
- **Combinations appropriate for rapidly progressive symptomatic disease**
 - Reduction in symptoms outweighs potential toxicity
 - May not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

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)
- G3-4 nonhematologic toxicity low in both arms



GT: High therapeutic index

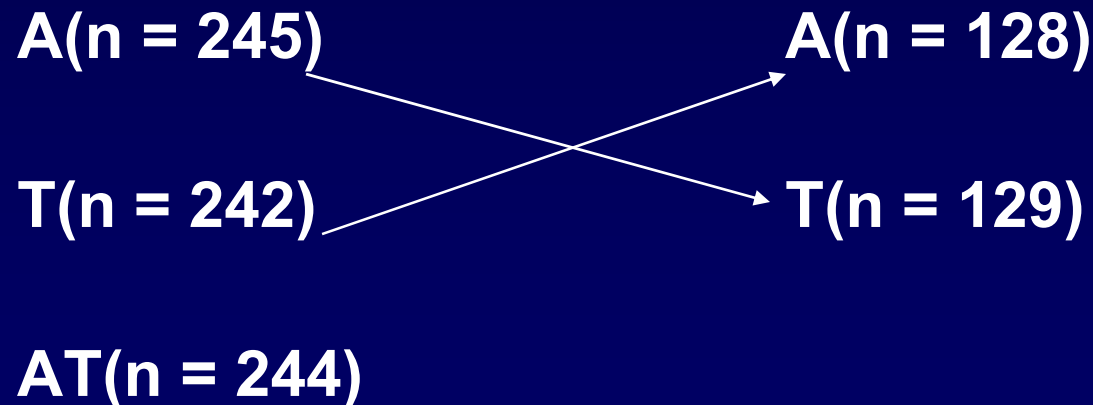
E1193: Combination vs Sequential

AB vs A → B vs B → A

A 60 mg/m²

T 175 mg/m² over 24 hours

AT 50 mg/m² → 3 hours → 150 mg/m² over 24 hours



E1193: Combination vs Sequential

AB vs A → B vs B → A

	RR, %	TTF, months	OS, months
A	36	6	19.1
T	34	6.3	22.5
AT	47*	8.2*	22.4
*P	A = .017 T = .006	A = .002 T = .057	

QOL using FACT-B — no significant difference

Crossover Results

A → T	22	4.5	14.9
T → A	20	4.2	12.7

NCCN Guidelines

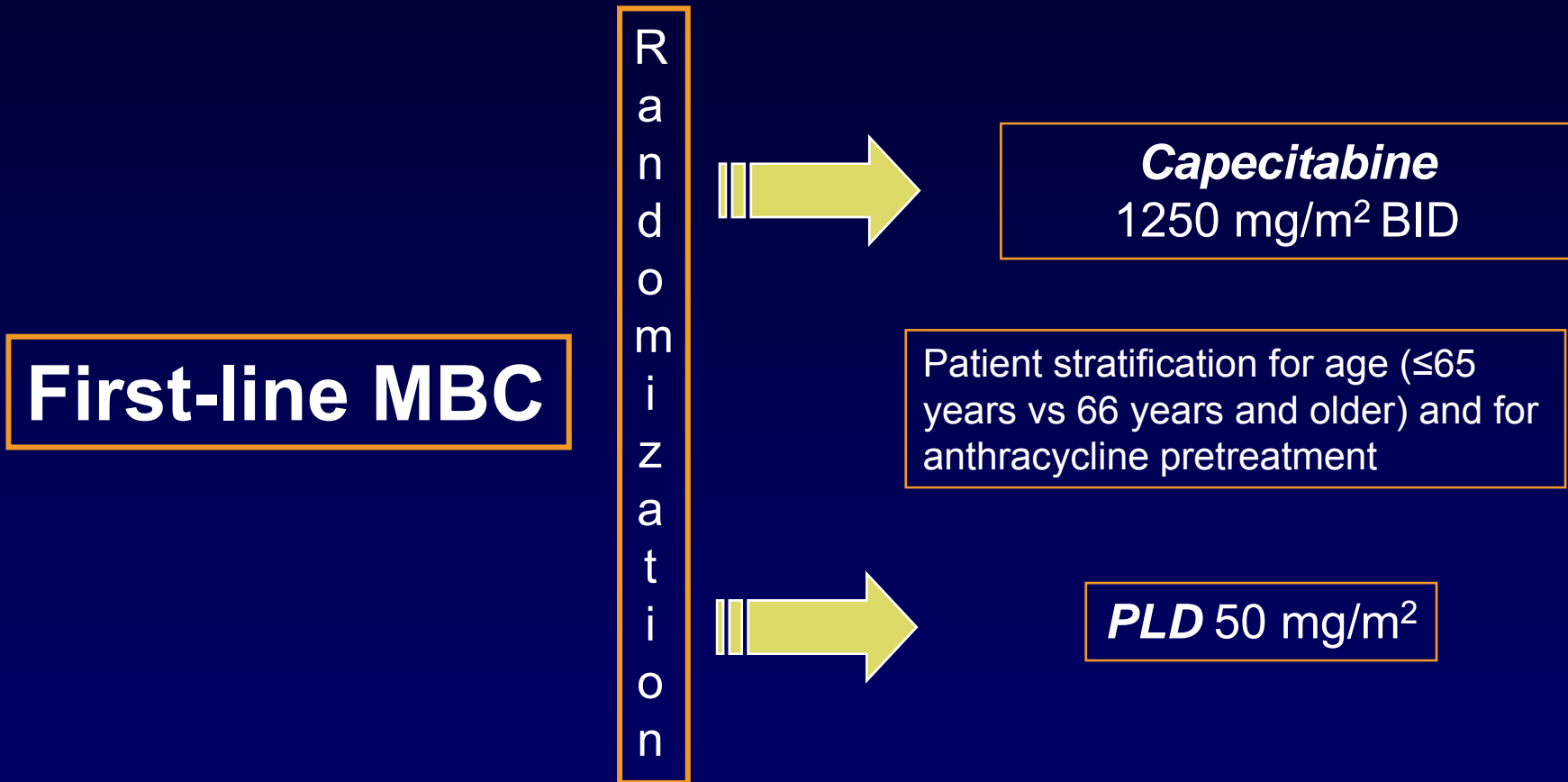
- **There is no compelling evidence that combination regimens are superior to sequential single agents**

Single-Agent Chemotherapy

- Since disease free interval = 2 years
rechallenge of agents used in the adjuvant
setting valuable alternative to the use of
noncross-resistant agents
 - Options:
 - Capecitabine
 - PLD
 - Taxane
- } No alopecia

- **NCCN believes that the best management of any cancer patient is in a clinical trial**
- **Participation in a clinical trials is especially encouraged**

PELICAN Trial: PLD vs Capecitabine Study Design



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

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

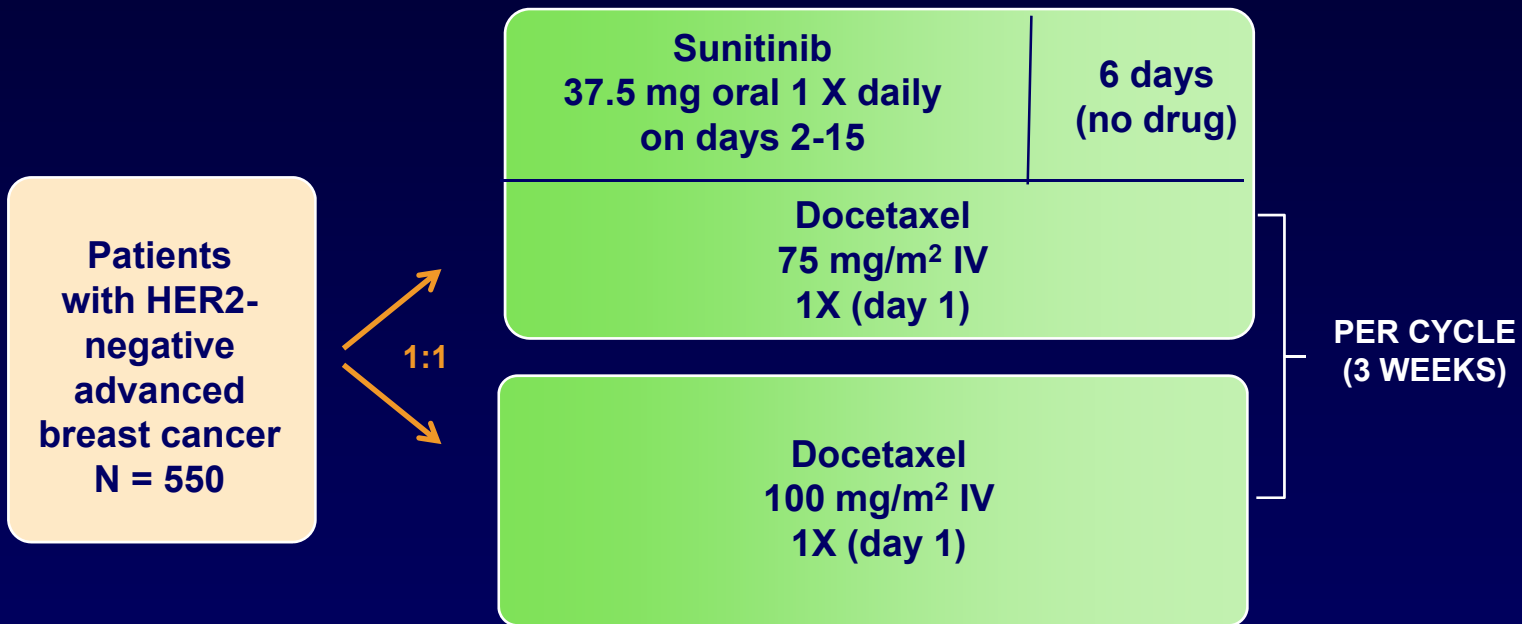
	E2100 ¹		AVADO ²		RIBBON-1: Capecitabine ³		RIBBON-1: A/T ³	
Placebo (PI) controlled	No		Yes		Yes		Yes	
Chemotherapy	Weekly paclitaxel (P)		q 3 wk docetaxel (D)		Capecitabine (C)		q 3 wk docetaxel/nabPAC/FAC/EC/FEC	
Dose of bevacizumab (B)	10 mg/kg q 2 wk		7.5 or 15 mg/kg q 3 wk		15 mg/kg q 3 wk		15 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%	49%	55%/63%	24%	35%	38%	51%
PFS, months	5.9	11.8	8.0	8.7/8.8	5.7	8.6	8.0	9.2
HR	0.60 P<.0001		0.79 (7.5 mg) P = .0318 0.72 (15 mg) P = .0099		0.69 P = .0002		0.64 P<.0001	
OS, months	25.2	26.7	NR	NR	21.2	29	23.8	25.2
HR	0.88 P = .16		0.92 (7.5 mg) 0.86 (15 mg)		0.85 P = .27		1.03 P = .83	

1. Miller K, et al. *N Eng J Med.* 2007;357(26):2666-2676. 2. Miles D, et al. *J Clin Oncol.* 2008;26:(May 20 Suppl): Abstract LBA1011. 3. Robert NJ, et al. *J Clin Oncol.* 2009;27(15S): Abstract 1005.

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

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

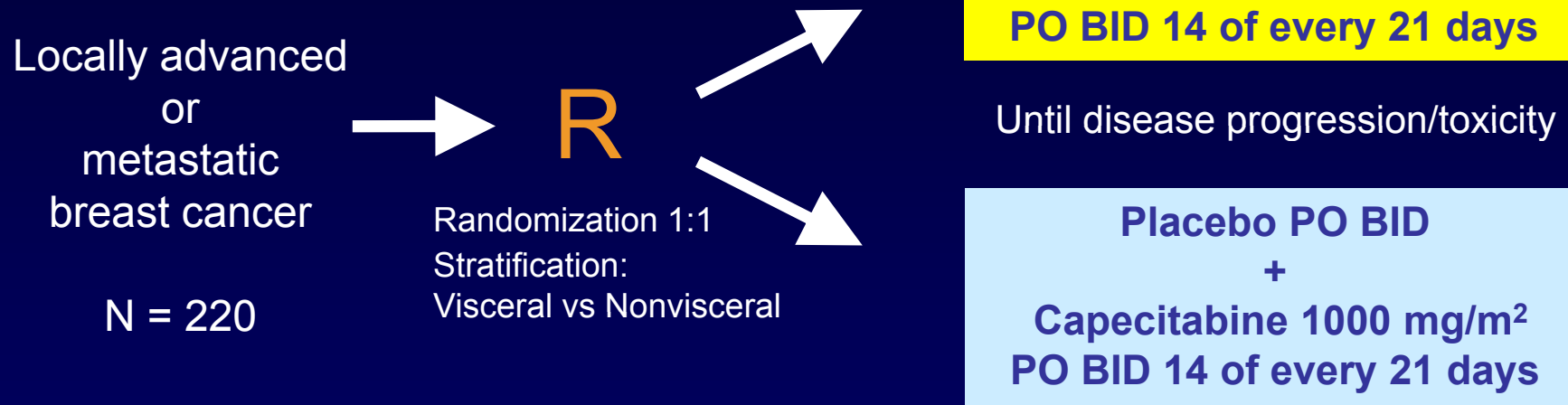


Trial design	Endpoints	Study sites	Indication
Multinational, multi-center, randomized, open label	Primary: PFS Secondary: ORR, DR, safety, QoL, pharm-economics	Global	First-line

Accrual completed

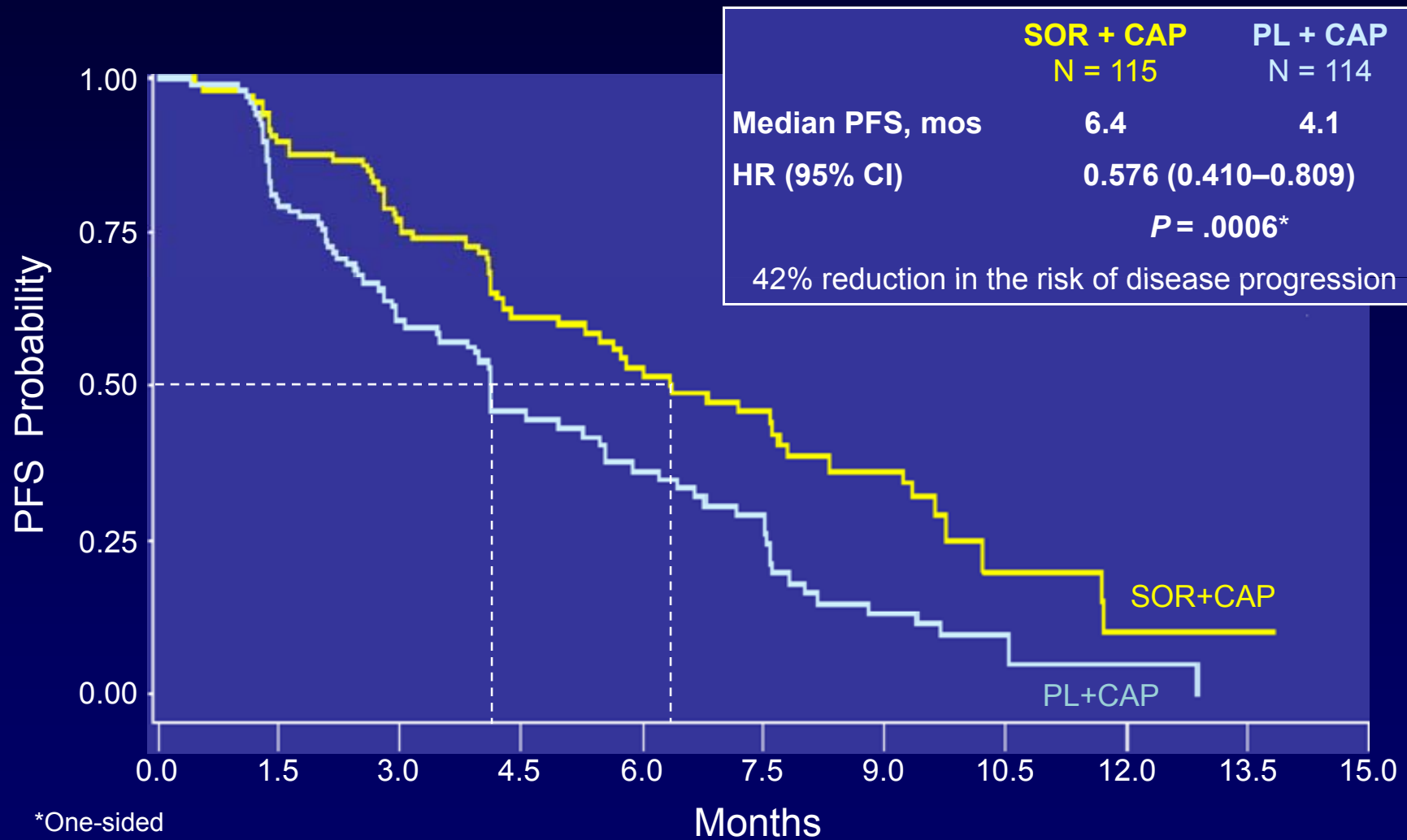
SOLTI-0701: Study Design

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



Patient was treated with paclitaxel, after initial stabilization for 3 months further progression was confirmed.

Capecitabine in Taxane-Pretreated MBC: Consistent Efficacy Data

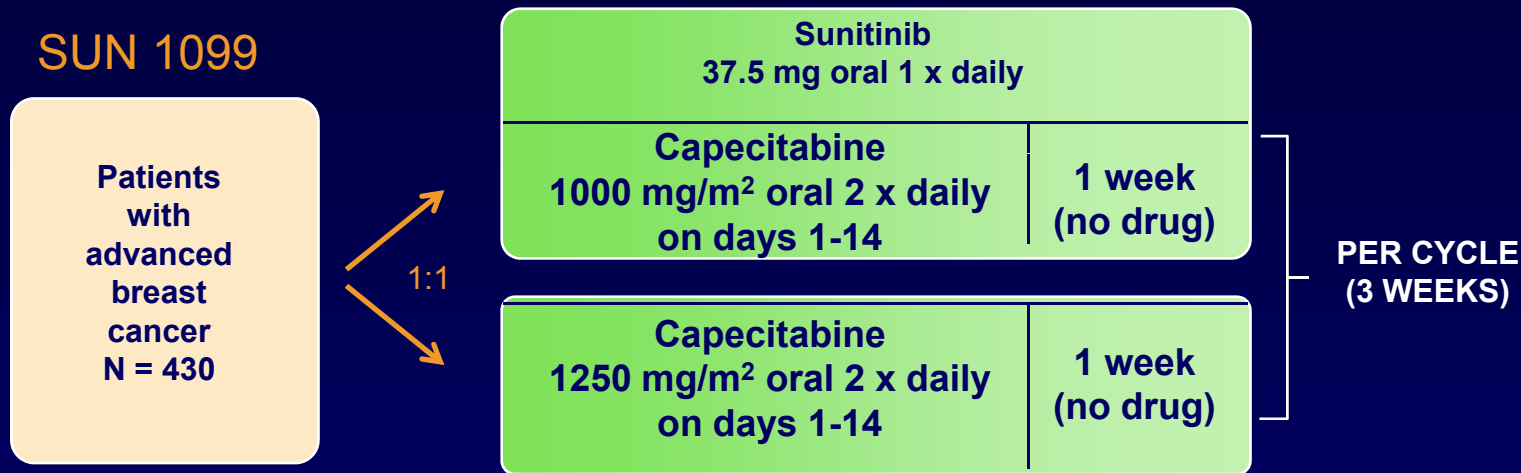
No.	CR+PR, %	ORR+SD, %	Median TTP, months	Median OS, months
163	20 ¹	63	3.0	11.6
75	26 ²	57	3.2	12.2
136	15 ³	62	3.3	10.4
126	28 ⁴	63	4.6	15.2
230	19 ⁵	NA	4.2	NA

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.

Chemotherapy + Bevacizumab

- No evidence of efficacy in >first-line
- Capecitabine + bevacizumab vs capecitabine in patients pretreated with anthracycline and taxane: ↑ RR but no advantage in TTP¹
- Capecitabine + bevacizumab first-line: TTP 8.6 months vs 5.7 months (single-agent capecitabine)²

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

- **NCCN believes that the best management of any cancer patient is in a clinical trial.**
- **Participation in a clinical trials is especially encouraged.**