

**Case # 6:
Management of Metastatic Breast
Cancer with Disease Progression
Following Treatment with an
Anthracycline and Taxane**

**Laura Biganzoli, MD
“Sandro Pitigliani” Medical Oncology Unit
Hospital of Prato, Prato
Istituto Toscano Tumory
Italy**

Part I

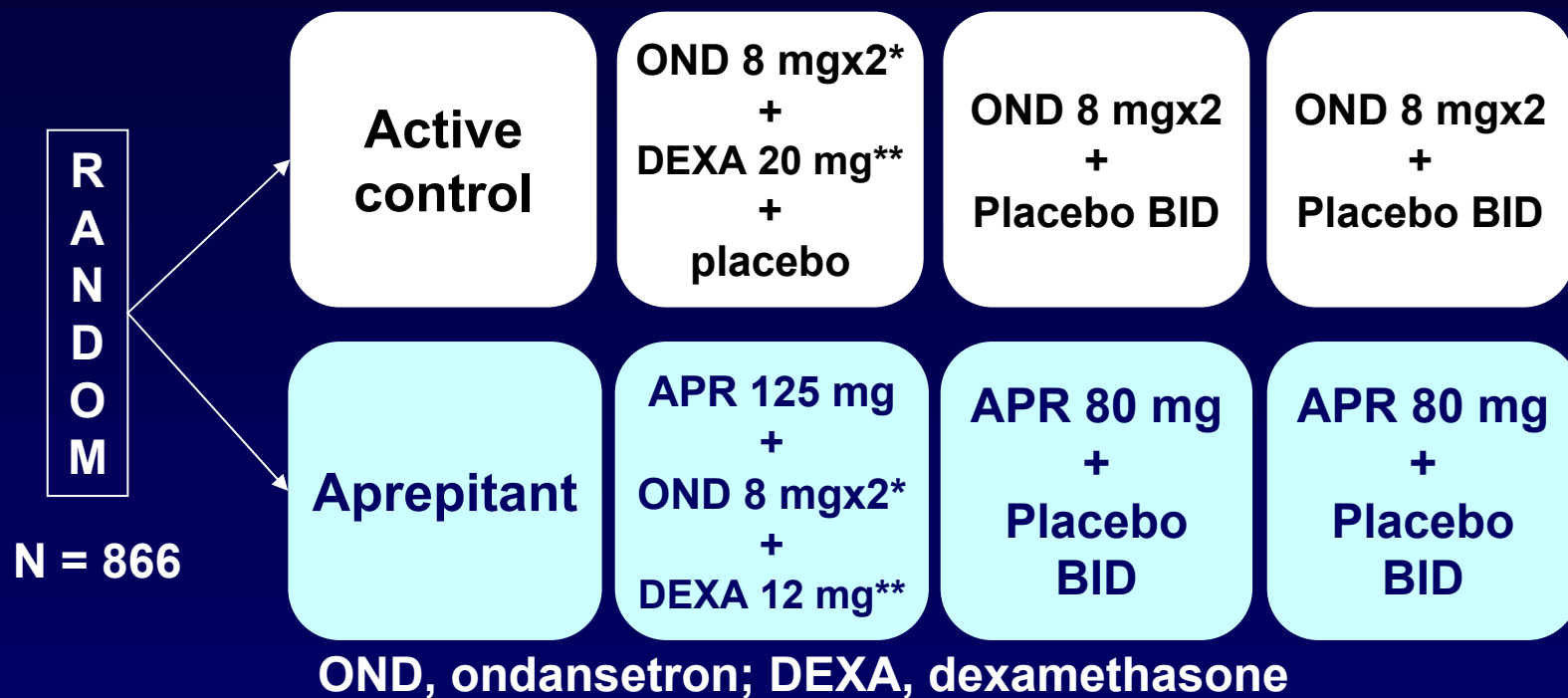
- **During the first cycle of FEC-100, the patient vomited 3 times on the day of chemotherapy administration and experienced delayed vomiting/retching for 2 days and nausea for 4 days. Antiemetic prophylaxis given for the first cycle was granisetron (Kytril®) and dexamethasone on day 1 followed by dexamethasone alone on days 2-4. How would you modify the antiemetic regimen for the second cycle?**
- 1. Palonosetron (Aloxi®) + dexamethasone**
 - 2. 5HT3 + dexamethasone + casopitant (Zunrisa™)**
 - 3. 5HT3 + dexamethasone + aprepitant (Emend®)**
 - 4. I would not modify the antiemetic regimen**

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%, $P = .019$)**

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

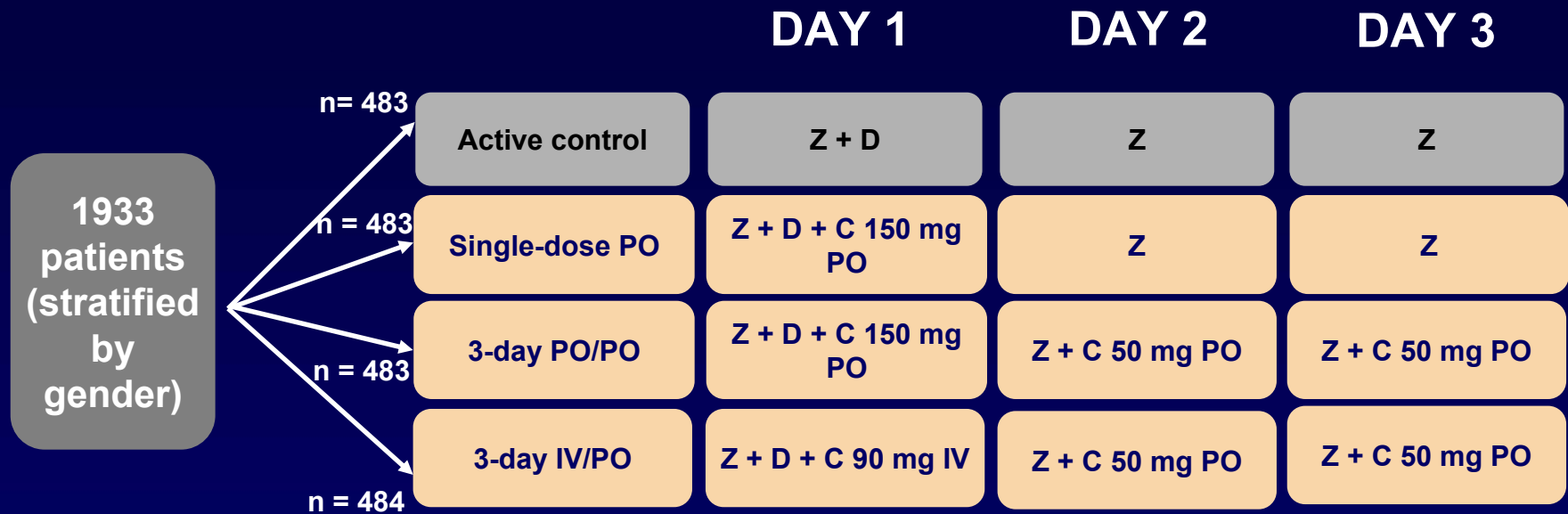
To update the 1999 American Society of Clinical Oncology guideline for antiemetics in oncology.

Update Methodology

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

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.

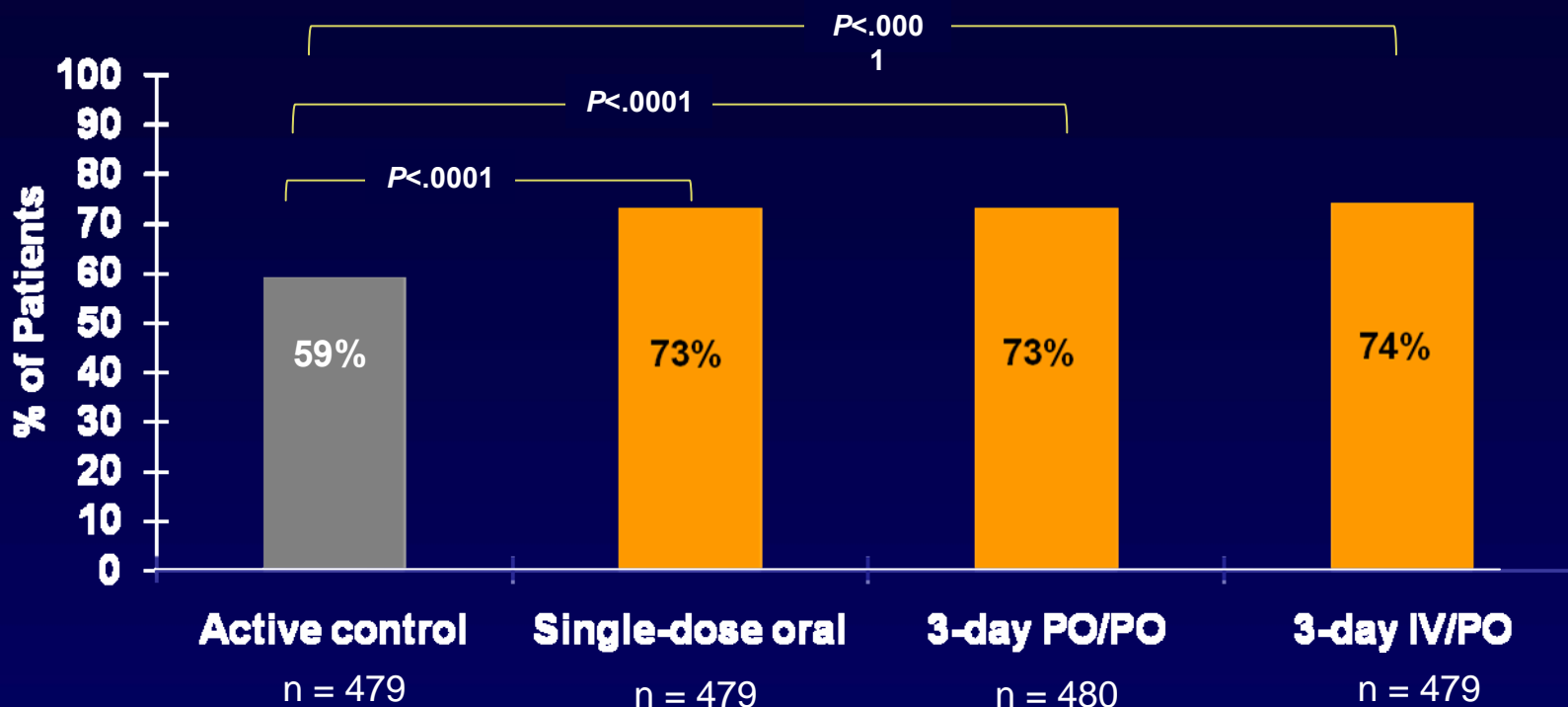
Phase III Trial of NK1 Receptor Antagonist Casopitant: Single Oral and 3-Day Oral and 3-Day IV/Oral Dosing Regimens for CINV in Patients Receiving MEC



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

Part I: My Proposal

- **5HT3 + dexamethasone + NK1 receptor antagonist**

Clinical Course

- **The patient did well for 2 years after completion of adjuvant chemotherapy, when she developed shortness of breath and cough. With further evaluation, lung metastases and right pleural effusion were found. After pleural drainage shortness of breath improved.**
 - **ECOG performance is 1**
 - **Laboratory: within normal limits**
 - **LVEF by MUGA = 55% (normal)**
 - **Hypertension x 2 years well controlled by ACE inhibitor**

Part II

- Which of the following systemic therapy options would you choose for this patient at the time of progressive disease (PD)?
 1. Second-line endocrine therapy
 2. Taxane monotherapy
 3. Capecitabine (Xeloda[®])
 4. Pegylated liposomal doxorubicin (PLD, Caelyx[®])
 5. Combination therapy with capecitabine and docetaxel
 6. Gemcitabine (Gemzar[®]) and paclitaxel
 7. Chemotherapy + bevacizumab (Avastin[®])
 8. Clinical trial of docetaxel + sunitinib (Sutent[®]) versus docetaxel

Option 1: Endocrine Therapy

- **No endocrine therapy because of PD on adjuvant AI and symptomatic patient**
- **Consider endocrine therapy as maintenance therapy after chemotherapy**

Choosing the Right Chemotherapy Regimen for Advanced Breast Cancer

“Friendly”

Agent/Regimen

**Slowly-progressing
disease**

**Any site provided limited
visceral involvement**

Asymptomatic patient

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

“Aggressive” Regimen


**Rapidly progressing/life-
threatening disease**

**Massive visceral
involvement**

Symptomatic patient

Fit

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**

PELICAN Trial: PLD vs Capecitabine Study Design

First-line MBC

R
a
n
d
o
m
i
z
a
t
i
o
n



Capecitabine
1250 mg/m² BID

Patient stratification for age (≤ 65 yrs vs 66 yrs and older) and for anthracycline pretreatment



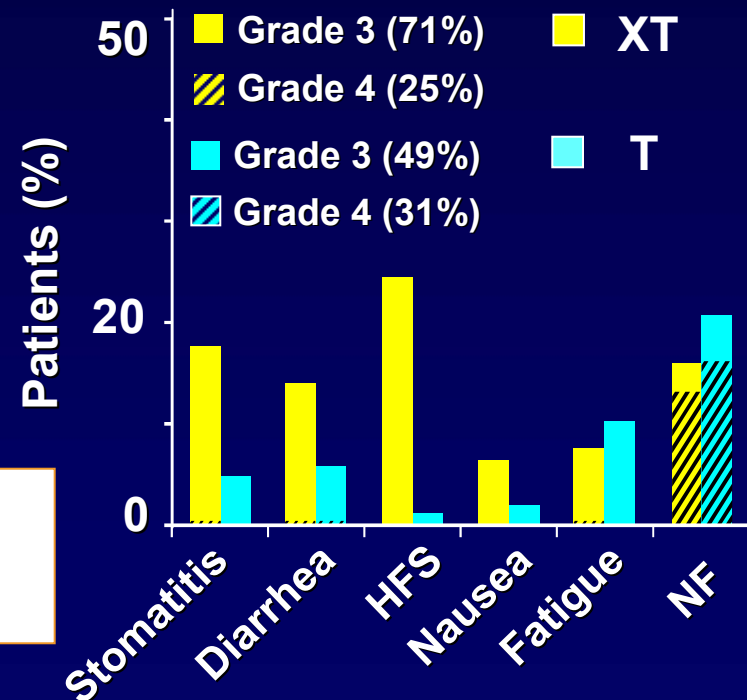
PLD 50 mg/m²

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 (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
(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



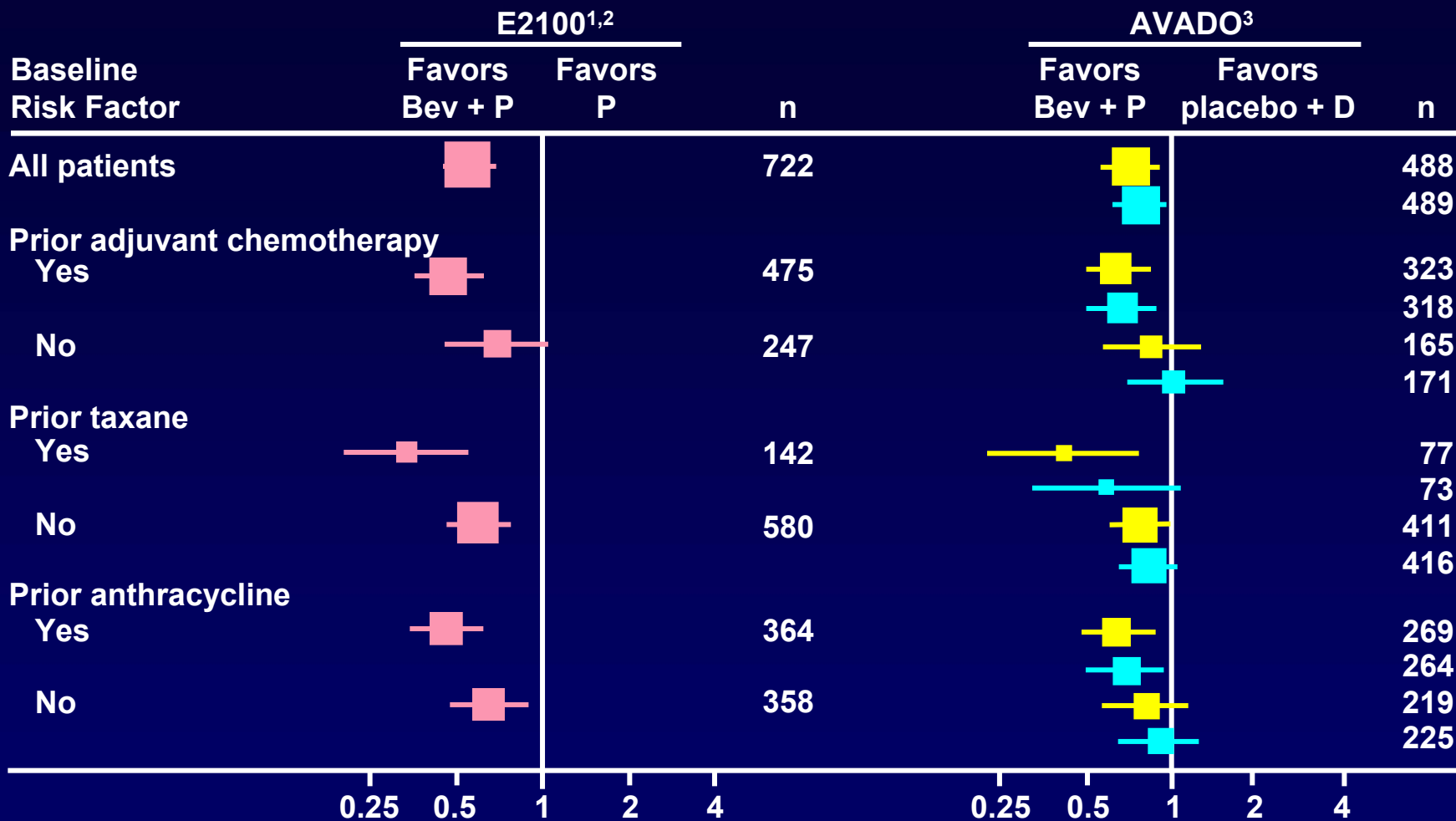
GT: high therapeutic index

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	80	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.

Bevacizumab + Taxane Is Active Even in Taxane Pretreated Patients



■ Bev 15mg/kg q3w + D
 ■ Bev 7.5mg/kg q3w + D
 ■ Bev 10mg/kg q2w + P

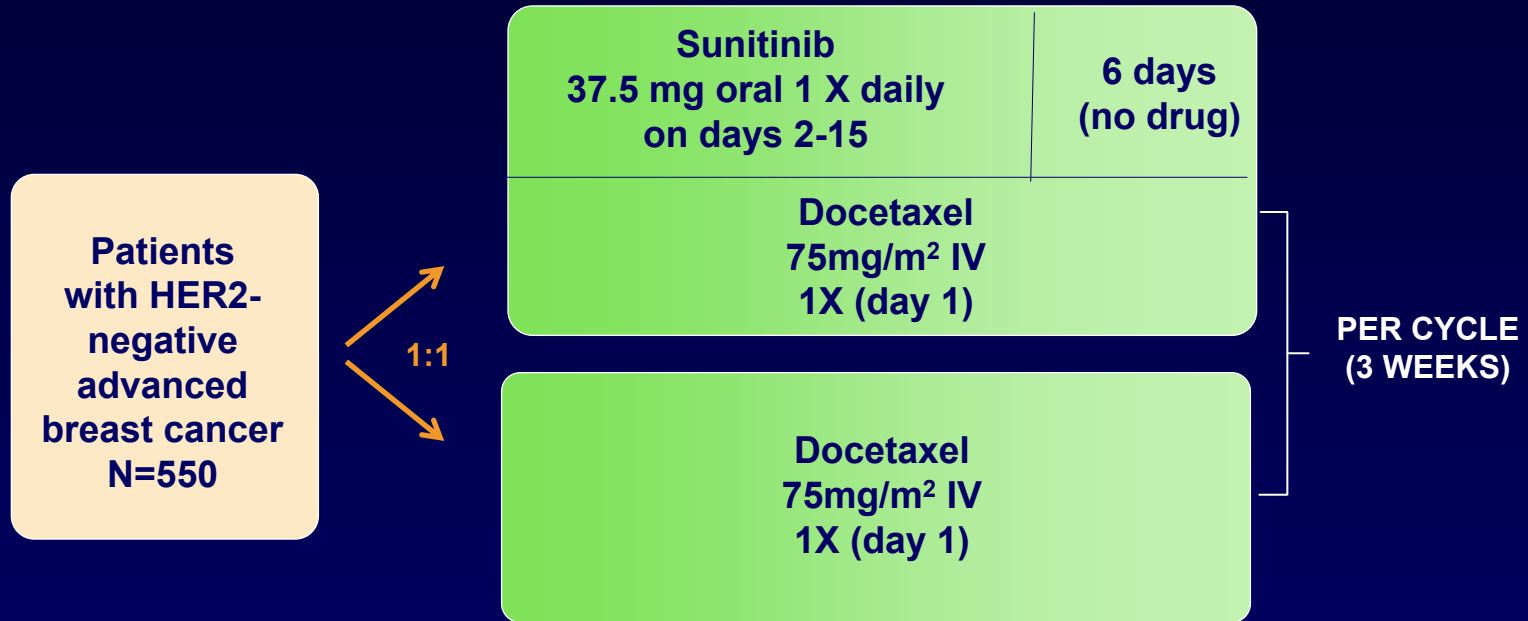
Andreas Schneeweiss ESMO 2008 presentation

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.

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 1st-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	1 st line

Part II: My Preferred Options

- 1. Clinical trial of docetaxel vs docetaxel plus sunitinib malate**
- 2. Single agent taxane or friendly polychemotherapy, ie. gemcitabine + paclitaxel, or taxane + bevacizumab**

Part III

- **Patient was treated with paclitaxel monotherapy weekly. After initial clinical stabilization of disease after 3 months of this therapy, further progression was confirmed in lung and right supraclavicular node. Patient performance status is 1, but she is very concerned regarding her fast progression. What would be your treatment choice now?**
 - 1. Capecitabine**
 - 2. PLD**
 - 3. Vinorelbine**
 - 4. Combination chemotherapy (eg, CMF)**
 - 5. Chemotherapy + bevacizumab**
 - 6. Clinical trial of sunitinib + capecitabine versus capecitabine**

Single-Agent Chemotherapy

1. Capecitabine

2. PLD

3. Vinorelbine

limited data in taxane
pretreated patients

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):S190 (Abst 693). 2. Blum JL et al. *Cancer* 2001;92:1759–68. 3. Reichardt P et al. *Ann Oncol* (in press). 4. Updated from Fumoleau P et al. *Proc Am Soc Clin Oncol* 2002;20:62a (Abst 247). 5. Maung K. *Clin Breast Cancer* 2003;3:375–7.

CMF

- **Classical oral CMF > CMF q 21¹**
- **CMF 1, 8 q 28 obsolete regimen in the metastatic setting**
 - **Four cycles of IV CMF administered after doxorubicin x 4 were able to increase tumor response in 64% of evaluable cases²**

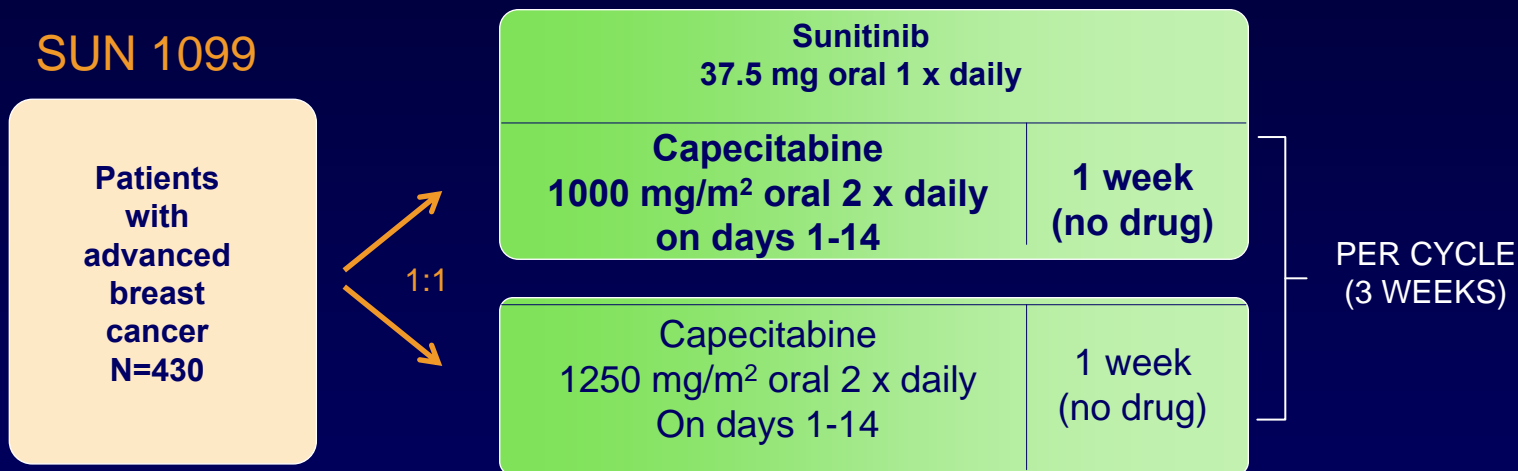
Chemotherapy + Bevacizumab

- **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 mos (single agent capecitabine)²**

Part III: My Preferred Option

- **Clinical trial of sunitinib + capecitabine versus capecitabine**

SUN 1099



Trial design	Endpoints	Study sites	Indication
Multinational, multi-center, randomized, open label	Primary: PFS Secondary: ORR, OS, QoL, safety, pharm-economics	US, EU, Canada	2 nd line