

Breast Cancer Progression After Adjuvant Anthracyclines: Clinical Case #6 Discussion

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Breast Cancer Progression After Adjuvant Anthracyclines: A Summary of the Clinical Case (# 6): part I

Patient	59 year old, symptomatic metastases (lung + liver), elevation of liver function tests
Primary tumor :	HER-2 (IHC) : - ,ER : 40%, PR : 10%
Adjuvant therapy :	Adjuvant FEC x 6 → aromatase inhibitor

36 months after completion adj. FEC and during adj. AI → symptomatic disease progression

Clinical Case #6 (part I): Therapeutic Options

- **Second line HT**

- **Docetaxel 3 weekly**
- **Paclitaxel weekly**

- **Docetaxel + pegylated liposomal doxorubicin**
- **Docetaxel + capecitabine**
- **Paclitaxel + gemcitabine**

- **Chemotherapy + bevacizumab**
- **Clinical trial with docetaxel +/- sunitinib**



ELIGIBILITY

- histological confirmation
- postmenopausal status
- progression following AI
- ER+ and / or PgR+
- measurable disease
- performance status 0–2

Prior AI therapy

Fulvestrant
LD* + 250 mg
/ month
+ placebo for
exemestane
(n=330)

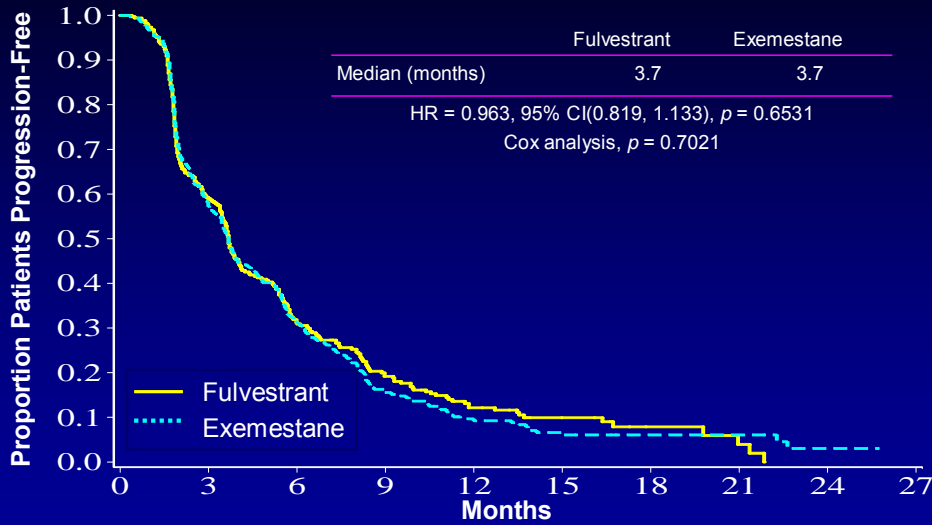
Exemestane
25 mg po od
+ placebo
for
fulvestrant
(n=330)

ENDPOINTS

- primary
 - ◆ TTP
- secondary
 - ◆ OR rate
 - ◆ duration of response
 - ◆ CB rate
 - ◆ survival
 - ◆ quality of life
 - ◆
 - ◆ pharmacokinetics
 - ◆ safety

*LD, loading dose (500 mg day 1 + 250 mg day 14)

TTP (ITT): Kaplan-Meier Plot



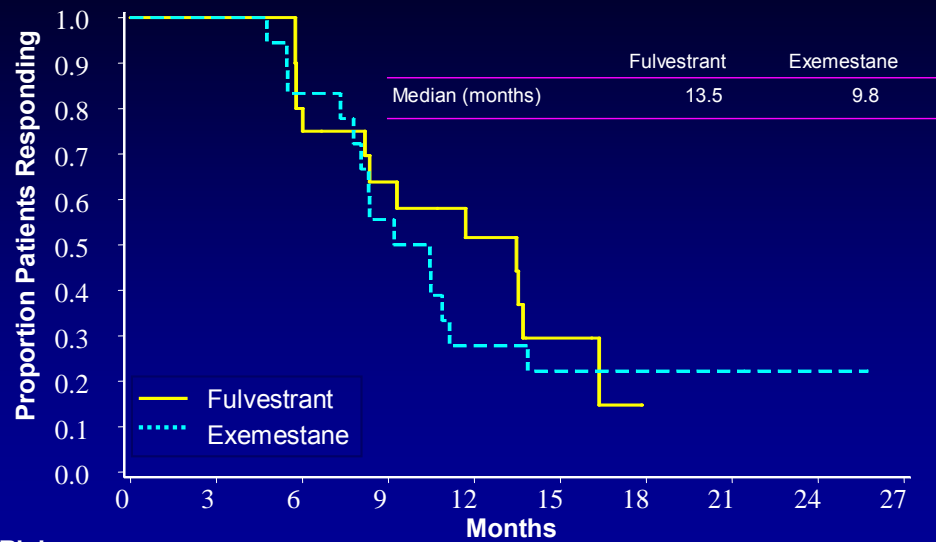
ROLE OF FASLODEX

At Risk:

	0	3	6	9	12	15	18	21	24	27
Fulvestrant	351	195	96	50	25	12	4	2		
Exemestane	342	190	98	41	21	12	8	6		

EFFECT TRIAL

DURATION OF RESPONSE (from randomisation)



At Risk:

	0	3	6	9	12	15	18	21	24	27
Fulvestrant	20	20	16	11	8	3	0	0		
Exemestane	18	18	15	10	5	4	3	3		

TAXANES

- Docetaxel 3 weekly > Paclitaxel 3 weekly
- Paclitaxel weekly (active and well tolerated)
- Nab-paclitaxel

Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil–Based Paclitaxel in Women With Metastatic Breast Cancer

	Nab Paclitaxel (260mg/m²)	Standard Paclitaxel (175mg/m²)	p
Response rate	33%	19%	0.001
Time to progression (median)	23 weeks	17 weeks	0.006
Overall survival (median)	65 weeks	56 weeks	0.374

30-min infusion; no premedication

Docetaxel +/- PLD in MBC Treated with Adjuvant Anthracycline: Results from a Randomized Phase 3 Study (n° of pts: 751)

	Docetaxel + PLD	Docetaxel	Pvalue
ORR (%)	35	26	0.0085
TTP (median in months)	9.8	7.0	0.000001

OS was similar

Both groups received a median of 6 cycles.

HFS + stomatitis occurred more often in PLD + D arm.

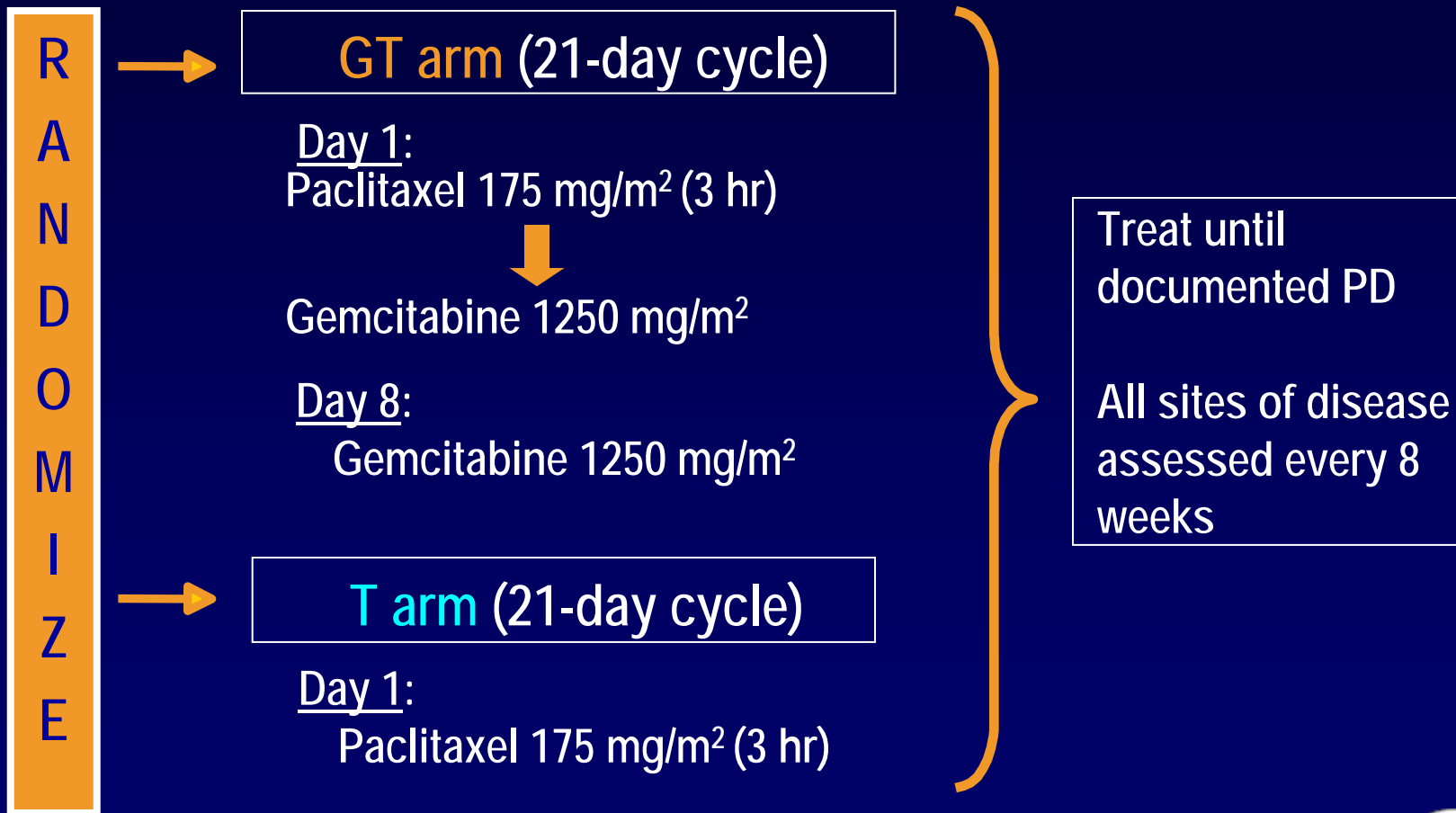
No increase in cardiac toxicity

PHASE III TRIAL DOCETAXEL VS DOCETAXEL + CAPECITABINE IN MBC PTS FAILING ANTHRACYCLINES

	Docetaxel	Capecitabine + docetaxel
n	256	255
L1/L2 (%)	31/53	35/48
Anthracyclines (%)	100	100
ORR (%)	30	42
TTP (months)	4.2	6.1
OS (months)	11.5	14.5



Paclitaxel + Gemcitabine : Phase III Trial Study Design (n=529)



Paclitaxel + Gemcitabine : Phase III Trial Planned Interim Analysis

Endpoint	GT	T	p-value
ORR (95% C.I.)	45.5% (38.5, 52.4)	25.5% (19.2, 31.8)	<0.00005
Median TTP (95% C.I.)	5.2 (4.2, 8.6)	2.9 (2.6, 3.7)	<0.0001
Median OS, mos (95% C.I.)	18.5 (16.5, 21.2)	15.8 (14.4, 17.4)	

ADVANCED BREAST CANCER: Comments on Taxane + antimetabolite studies

Subsequent Chemotherapy

PG vs. P

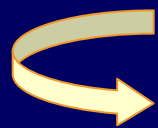
Docetaxel	10.5%	10.3%
Gemcitabine	3.8%	14.1%

T vs. TC

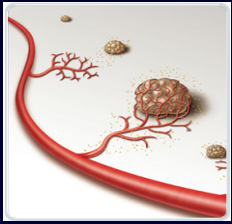
Capecitabine	17 %
Docetaxel	20 %

NO OR MINIMAL CROSSOVER

BENEFIT OF COMBINATION IS ONLY LEVEL-2 EVIDENCE-BASED

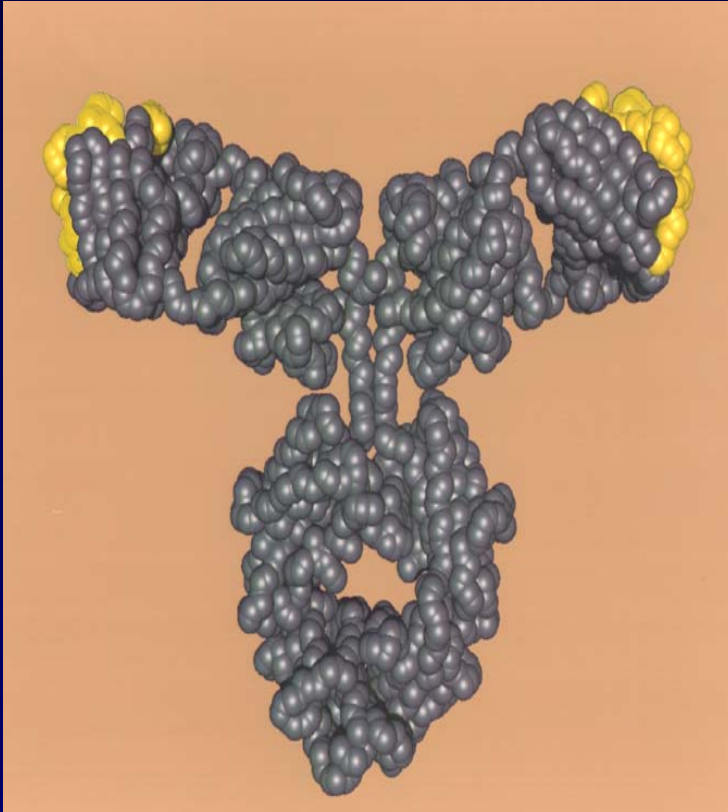


- Discuss with patients
- Consider combination in « high risk » symptomatic fit patients !!



Bevacizumab

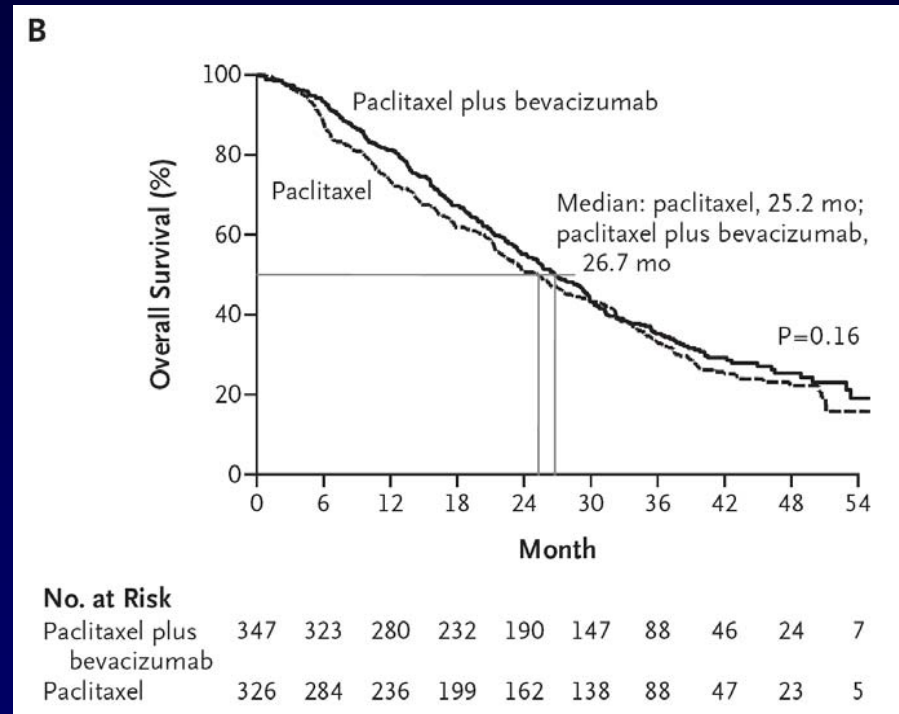
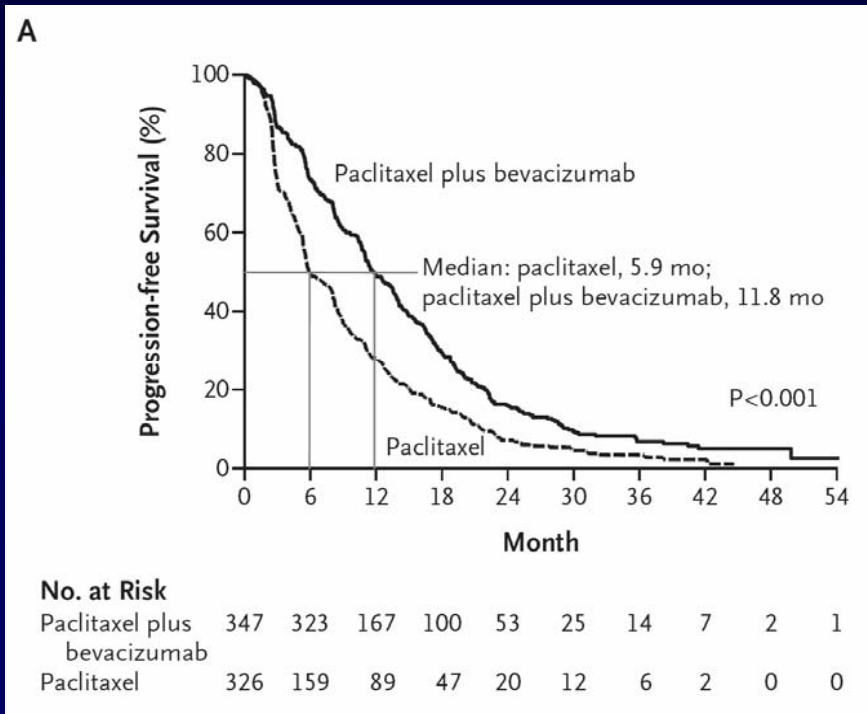
Recombinant Humanized Monoclonal Antibody to VEGF



- **Humanized** to avoid immunogenicity (93% human, 7% murine)
- Recognizes all isoforms of vascular endothelial growth factor
- Terminal half life 17-21 days

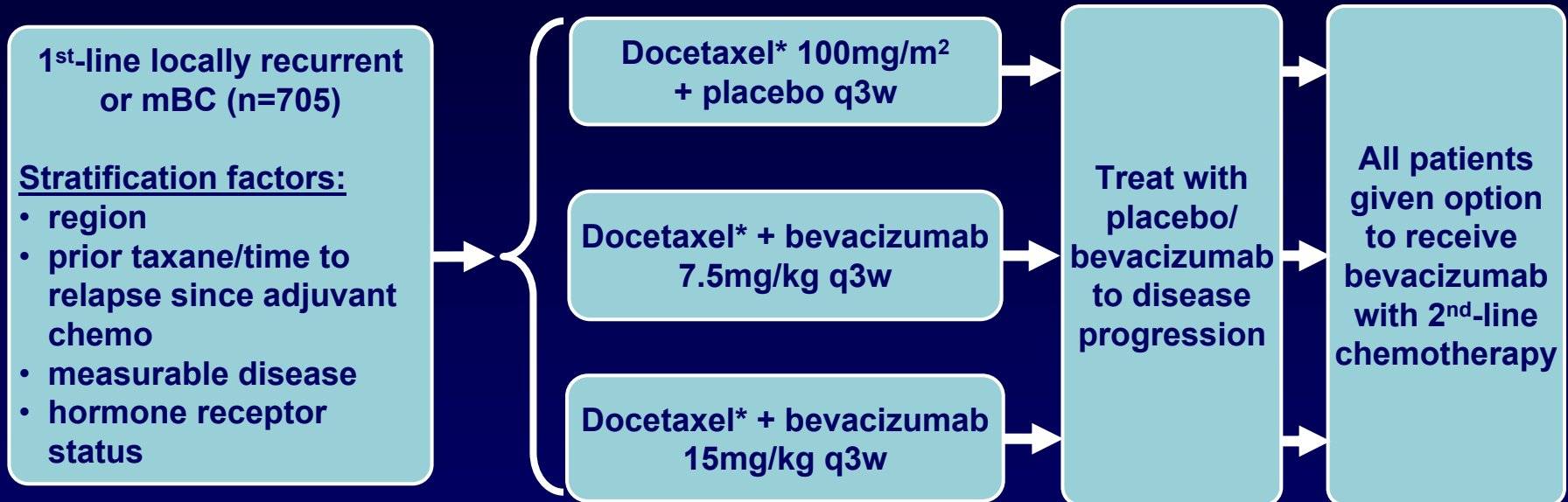
Paclitaxel +/- Bevacizumab in MBC

[Total No of patients = 722]



[ORR (eligible pts) : 37% vs 21%, P<0.001]

AVADO: Double-Blind, Placebo-Controlled Trial



- **Primary endpoint: progression-free survival**
- **Secondary endpoints: overall response rate, duration of response, time to treatment failure, overall survival, safety, quality of life**

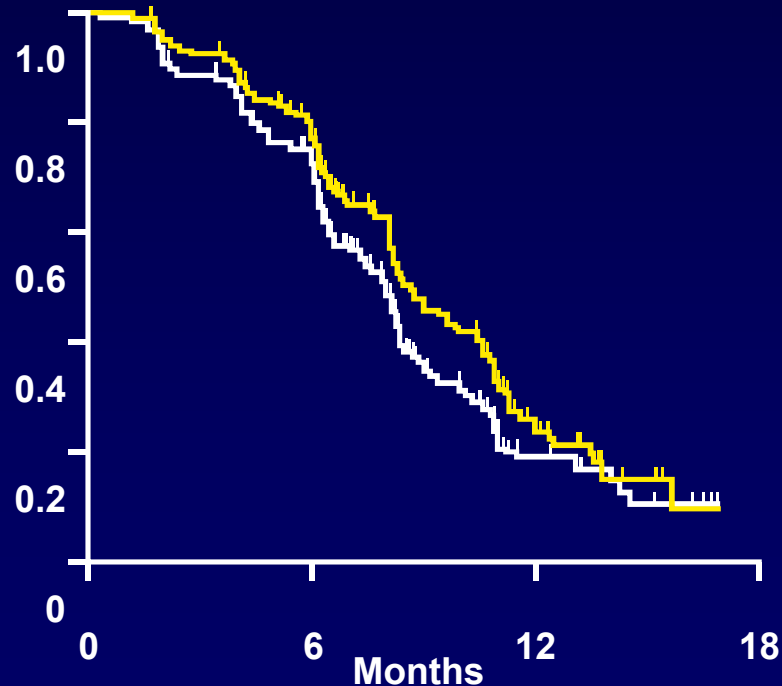
*Docetaxel was administered for a maximum of nine cycles, but earlier discontinuation was permitted

AVADO: Progression-free Survival (ITT population)

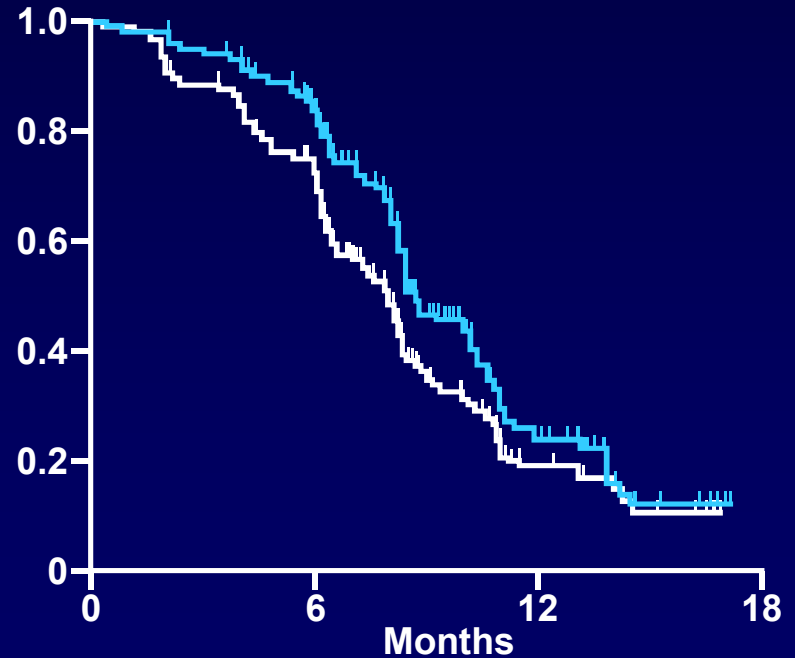
	Placebo + docetaxel (n=241)	Bev 7.5 [†] + docetaxel (n=248)
HR + 95% CI (unstratified)		0.79 (0.63–0.98) p=0.0318
HR + 95% CI (stratified*)		0.69 (0.54–0.89) p=0.0035
Median	8.0	8.7

	Placebo + docetaxel (n=241)	Bev 15 [†] + docetaxel (n=247)
HR + 95% CI (unstratified)		0.72 (0.57–0.90) p=0.0099
HR + 95% CI (stratified*)		0.61 (0.48–0.78) p<0.0001
Median	8.0	8.8

PFS estimate



PFS estimate



[†]mg/kg q3w; *Data censored for non-protocol therapy before PD

AVADO: Response (patients with measurable disease), %

	Placebo + docetaxel (n=207)	Bev 7.5 [†] + docetaxel (n=201)	Bev 15 [†] + docetaxel (n=206)
Overall response rate	44	55	63
p value (vs control)	–	0.0295	0.0001
Best response			
CR	1	3	1
PR	44	52	62
SD	39	35	25
PD	12	5	4

[†]mg/kg q3w



AVADO: Overall Survival* (ITT population)

	Placebo + docetaxel (n=241)	Bev 7.5 [†] + docetaxel (n=248)	Bev 15 [†] + docetaxel (n=247)
Deaths, n (%)	50 (21)	49 (20)	37 (15)
Median overall survival, months	NR	NR	NR
Hazard ratio (95% CI)	–	0.92 (0.62–1.37)	0.68 (0.45–1.04)
1-year survival, %	73	78	83
Patients still at risk, n	63	73	79

Cut-off for final survival analysis 24 months after last patient recruited (April 2009)

*Unstratified analysis; [†]mg/kg q3w; NR = not reached



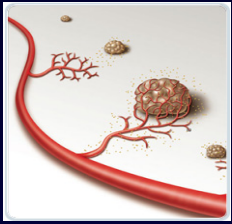
AVADO: Safety Summary

%	Placebo + docetaxel (n=233)	Bev 7.5 [†] + docetaxel (n=250)	Bev 15 [†] + docetaxel (n=247)
Any AE	99.6	100.0	99.6
Any grade ≥3 AE	67.0	74.8	74.1
AEs leading to death*	2.6	1.6	1.6
AEs leading to discontinuation [‡] of			
Docetaxel	24.0	20.8	24.3
Bevacizumab or placebo	11.2	8.0	11.7

[†]mg/kg q3w; *during study phase; [‡]not mutually exclusive

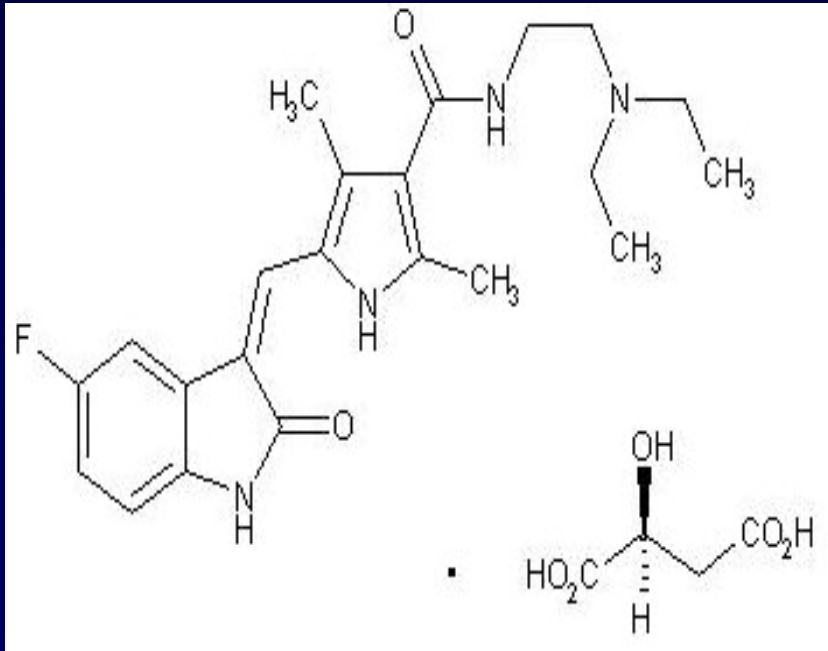


Unlike trastuzumab, to date, no predictive factors of response to bevacizumab, including VEGF expression, have been identified (role of VEGF polymorphism?)

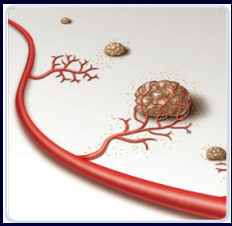


Sunitinib SU11248

Small molecule inhibitor



- Small molecule selective inhibitor of:
 - PDGFR
 - VEGFR2 (KDR)
 - KIT
 - FLT3



Sunitinib SU 11248

(Phase II Single Agent in Refractory MBC)

64 advanced breast cancer patients : 85% with visceral metastases

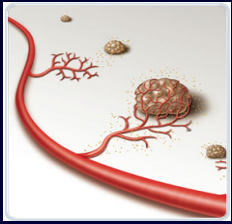
Sunitinib 50mg/day for 4 weeks then 2 weeks off, q6w

Toxicity: lower incidence of hypertension than bevacizumab
 higher incidence of bone marrow suppression
 (*G3 neutropenia 34%; G2/3 thrombocytopenia 19%*)

*One PR not yet confirmed.
13 patients too early for response
assessment.

	N=51
Partial Response*	7 (14%)
Stable Disease \geq 6 months	1 (2%)
Overall Clinical Benefit	8 (16%)





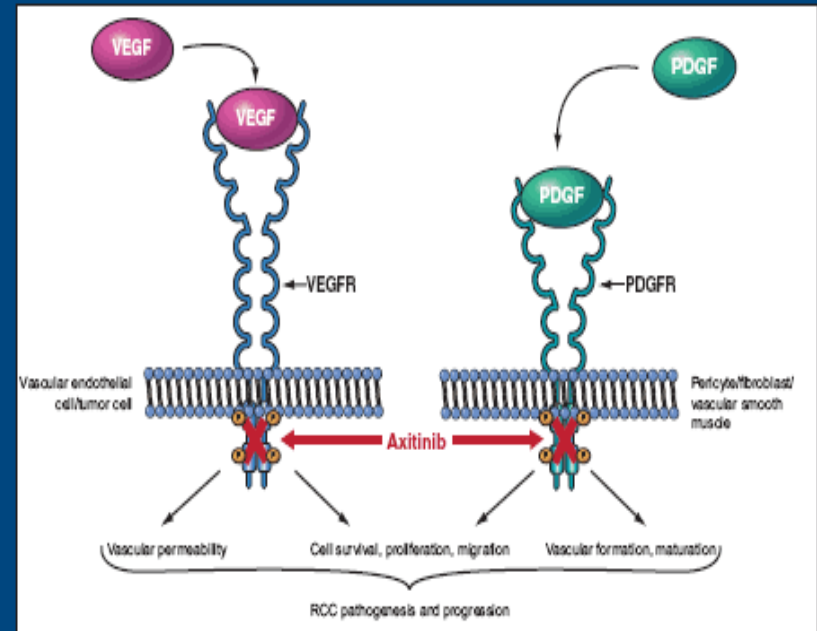
Axitinib

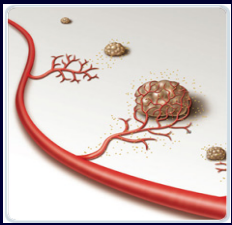
Oral tyrosine kinase inhibitor

Selective inhibitor of VEGFR 1, 2, 3

Activity in lung, thyroid and possibly pancreatic cancer

Axitinib

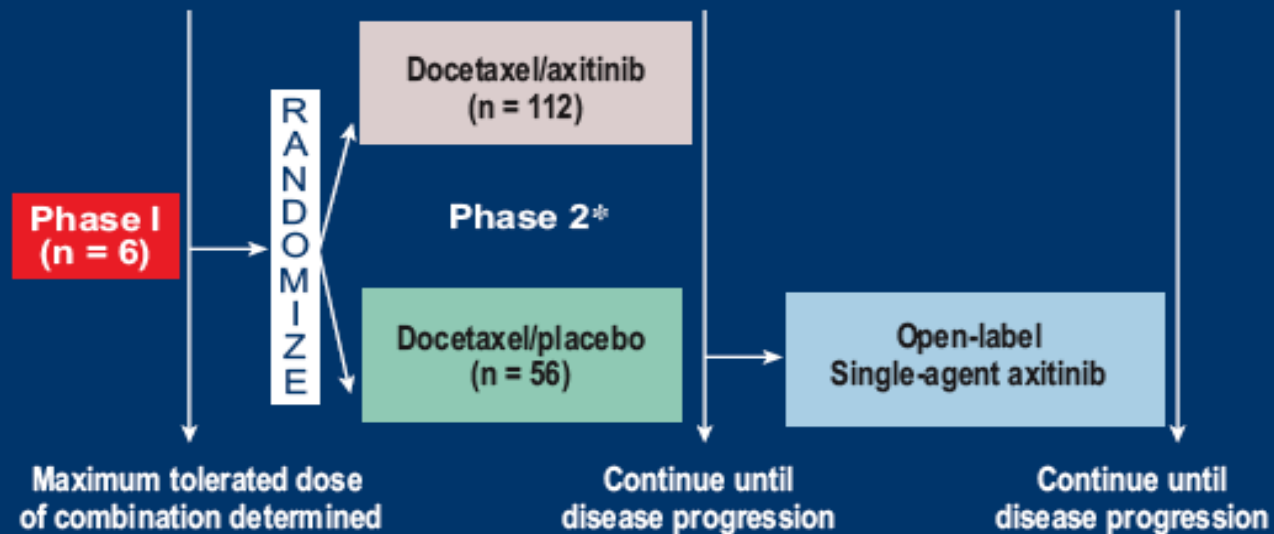




Docetaxel ± Axitinib :

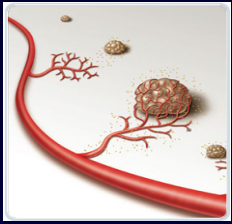
Phase II Study design in MBC

Phase I/II Trial of Axitinib/Docetaxel: Efficacy and Safety



* Double blinded





Docetaxel ± Axitinib :

A Phase II Study in 1st line MBC

Inclusion:

No prior chemo for MBC; 12 months from adjuvant chemotherapy

ECOG ≤ 2; No uncontrolled brain metastases

No prophylactic Growth Factor in cycle 1

Response:

	Ax + Doc	Plac + Doc
Median TTP	8.2m (<i>p</i> =0.052)	7m
ORR	40% (<i>p</i> =0.038)	23%

Non-Hematological Toxicities:

Diarrhea (60%); nausea (53%); alopecia (51%); fatigue (49%); stomatitis (44%); vomiting (40%)

Grade ³/₄ Toxicities:

Febrile Neutropenia (16 vs 7%)
Fatigue (13 vs 5%)
Stomatitis (13 vs 2%)
Diarrhea (11 vs 0%)
Hypertension (5 vs 2%)



Clinical Case # 6 (part I): Therapeutic Options

- **Second line HT**

- **Docetaxel 3 weekly**
- **Paclitaxel weekly**

- **Docetaxel + pegylated liposomal doxorubicin**
- **Docetaxel + capecitabine**
- **Paclitaxel + gemcitabine**

- **Chemotherapy + bevacizumab**
- **Clinical trial with docetaxel +/- sunitinib**

Breast Cancer Progression After Adjuvant A and Taxane for MBC (part II of clinical case # 6)

Patient	60 year old, symptomatic metastases (lungs, liver, bone), slight elevation of liver function tests
Primary tumor :	HER-2 (IHC) : - ,ER : 40%, PR : 10%
Prior therapy :	Adjuvant FEC x 6 → AI 36 months following adj. FEC and during AI → disease progression → taxane – based therapy

She did well for 12 months → symptomatic disease progression

Clinical case #6 (part II): Therapeutic Options

- Endocrine therapy

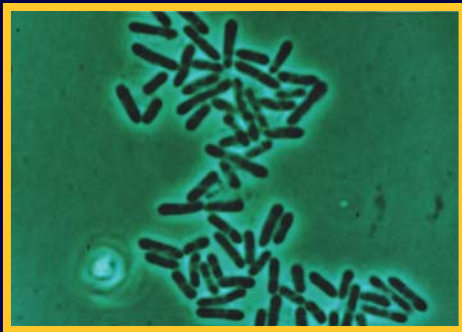
- Capecitabine
- Vinorelbine
- Pegylated liposomal doxorubicin

- Capecitabine + ixabepilone

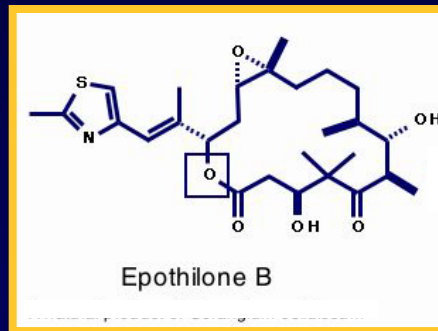
- Chemotherapy + bevacizumab
- Clinical trial with of chemotherapy + oral angiogenesis inhibitor

Epothilones: Ixabepilone

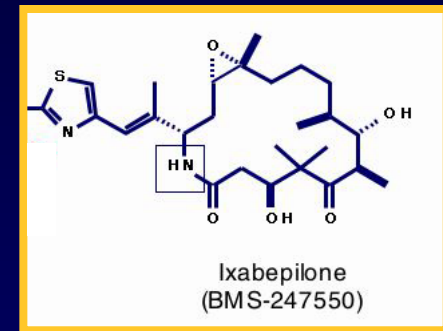
- **New anti-tubulin class - the natural epothilone and its analog**



S. cellulosum



Epothilone B

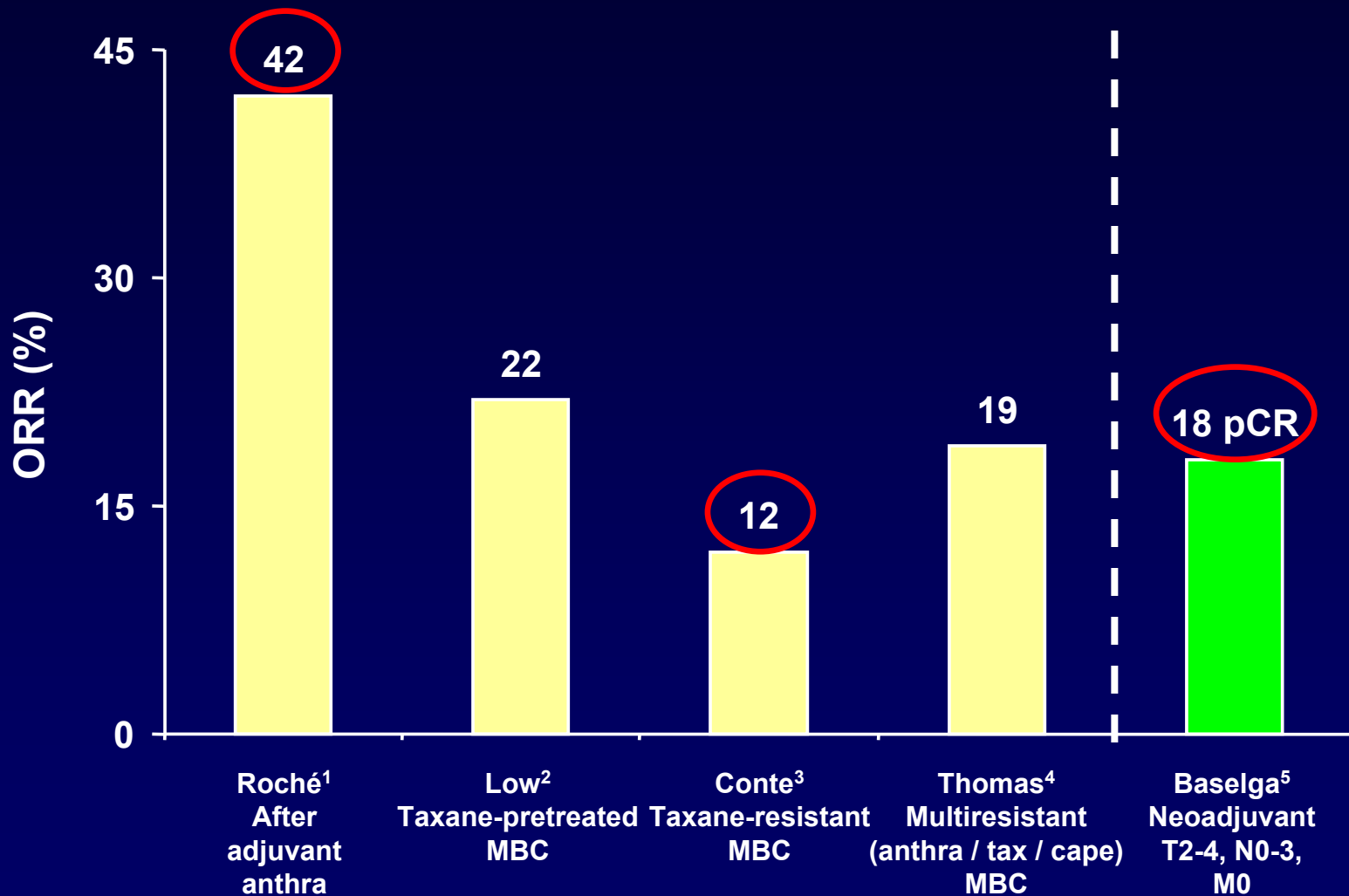


Ixabepilone
(BMS-247550)

Ixabepilone

- **Low susceptibility to tumor resistance mechanisms :**
 - MRP-1 and P-gp efflux pumps
 - β (III) tubulin overexpression
 - β tubulin mutations
- **Activity in multiple tumor models**
- **Demonstrated pre-clinical synergy with capecitabine**

Ixabepilone Phase II Data in Breast Cancer



1. Roché H et al. International Union Against Cancer World Cancer Congress, 8-12 July 2006; abstr 96-3. 2. Low et al. *J Clin Oncol* 2005;23:2726-34. 3. Conte P et al. *J Clin Oncol* 2006;24(18S):abstr 10505. 4. Thomas E et al. *J Clin Oncol* 2006;24(18S):abstr 660. 5. Baselga J et al *Breast Cancer Res Treat.* 2005;94(Suppl 1):S31:abstr 305.

Study Design of Randomized, Open-label, Phase III Trial in MBC

Metastatic or locally advanced breast cancer
RESISTANT
to anthracyclines
and taxanes

Ixabepilone
(40 mg/m² IV over 3 hr d1 q3wk)

+

Capecitabine
(**2000** mg/m²/day PO 2 divided doses
d1-d14 q3wk)

Capecitabine
(**2500** mg/m²/day PO 2 divided doses
d1-d14 q3wk)

Stratification

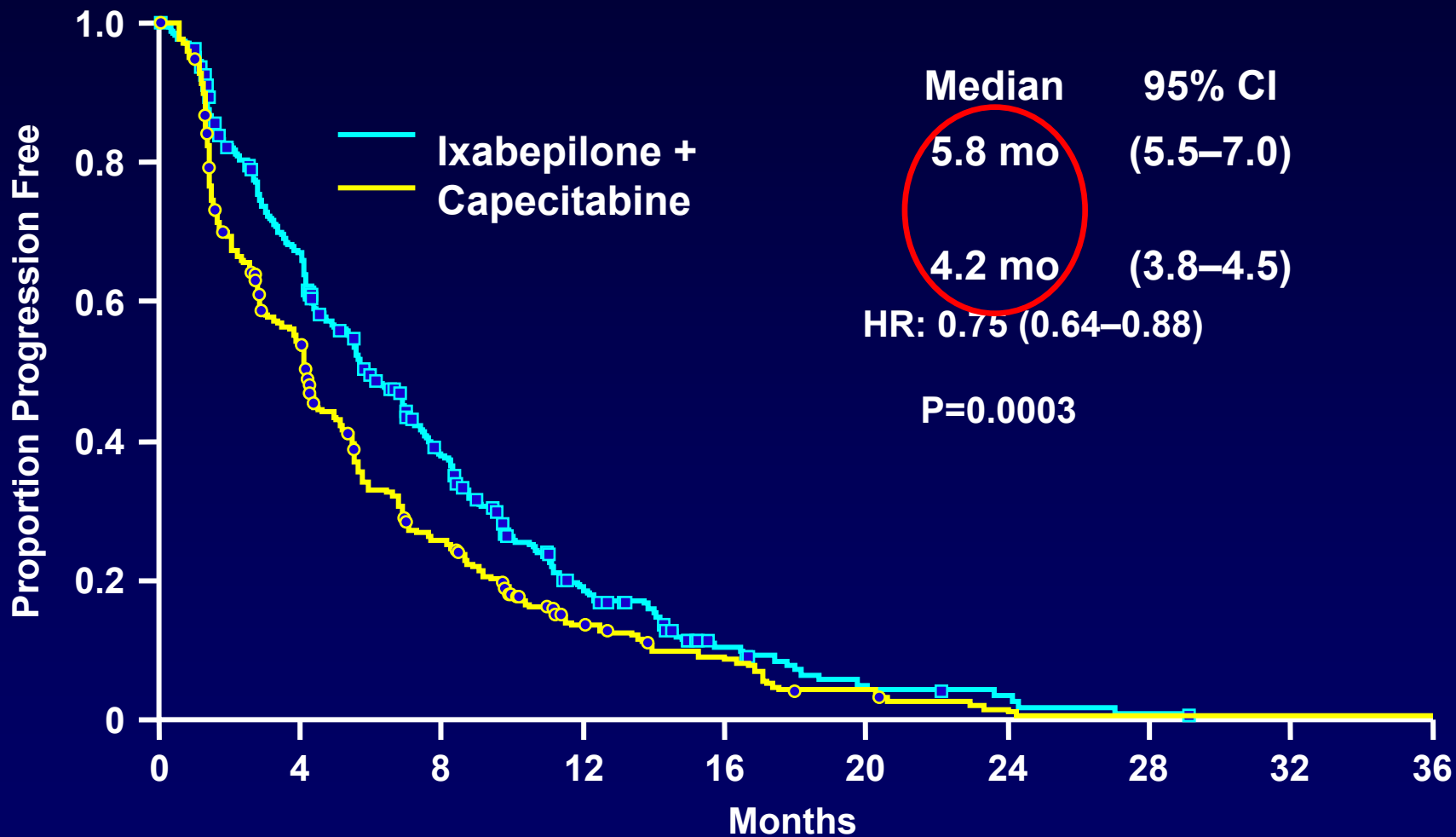
- Visceral metastases
- Prior chemotherapy for MBC
- Anthracycline resistance
- Study site

Response Rate

% Response	Investigator		IRR	
	Ixabepilone + Capecitabine N=375	Capecitabine N=377	Ixabepilone + Capecitabine N=375	Capecitabine N=377
ORR (CR + PR)	42	23	35	14
	P<0.0001		P<0.0001	
Stable disease	36	38	41	46
Progressive disease	14	29	15	27
Unable to determine	8	10	9	12



Progression-free Survival by Independent Radiologic Review



Grade 3/4 Hematologic Toxicities

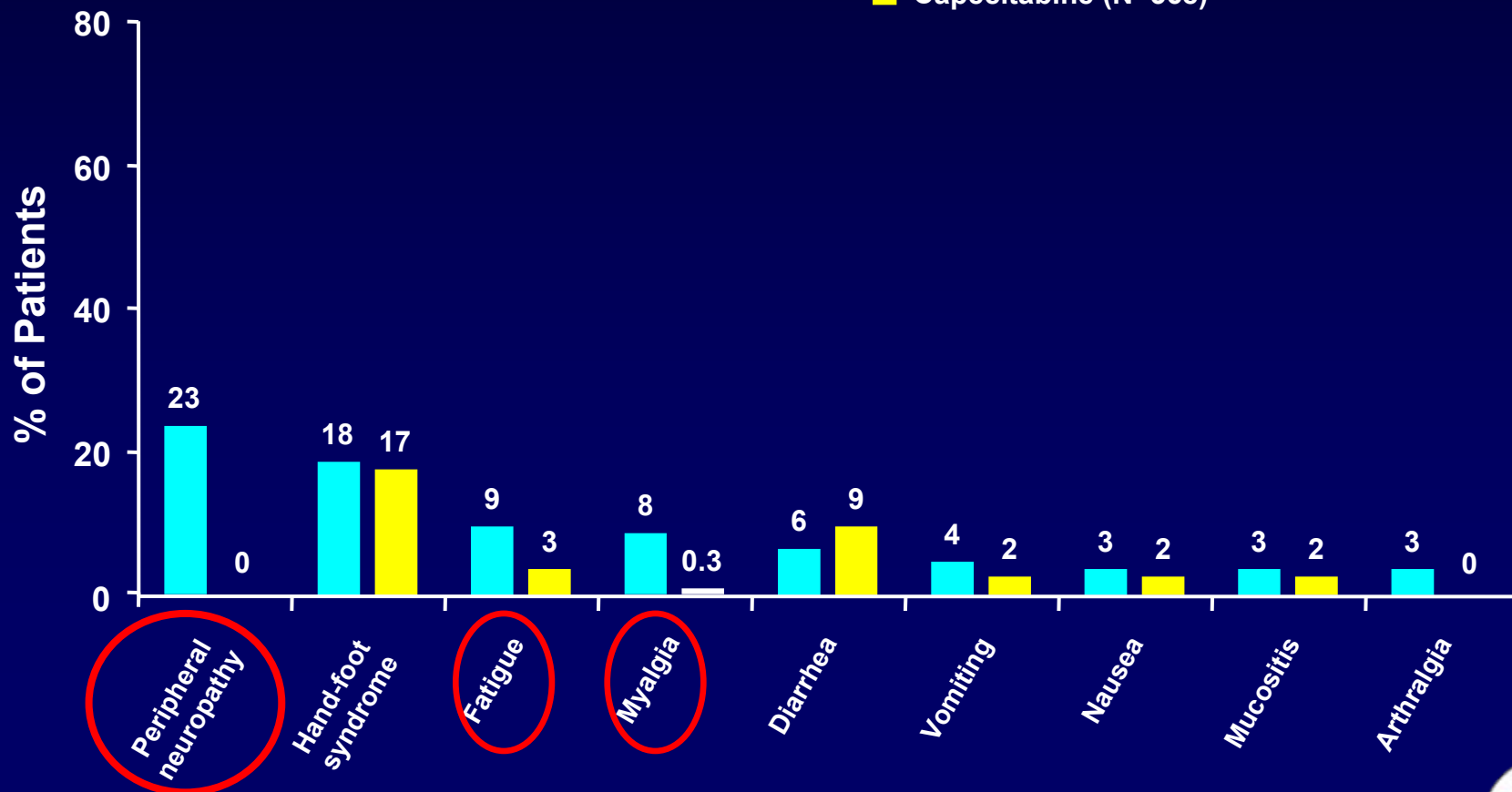
(%)*	Ixabepilone + Capecitabine N=369	Capecitabine N=368	P-value
Leukopenia	57	6	<0.0001
Anemia	10	4	0.005
Neutropenia	68	11	<0.0001
Thrombocytopena	8	4	0.011
Febrile neutropenia	4	<1	0.001

*By worst CTCAE v.3 grade

Grade 3/4 Non-hematologic Toxicities

■ Ixabepilone + Capecitabine (N=369)

■ Capecitabine (N=368)



Capecitabine +/- Ixabepilone in symptomatic patients with MBC previously treated with anthracycline and taxane in two large phase III study

	C + Ixa (n =268)	C (n = 257)	P value
ORR (%)	35	19	
PFS median (mo)	4.6	3.1	0.002
OS, median (mo)	12.3	9.5	0.0015

Antiangiogenic Agents

Bevacizumab in Metastatic Breast Cancer

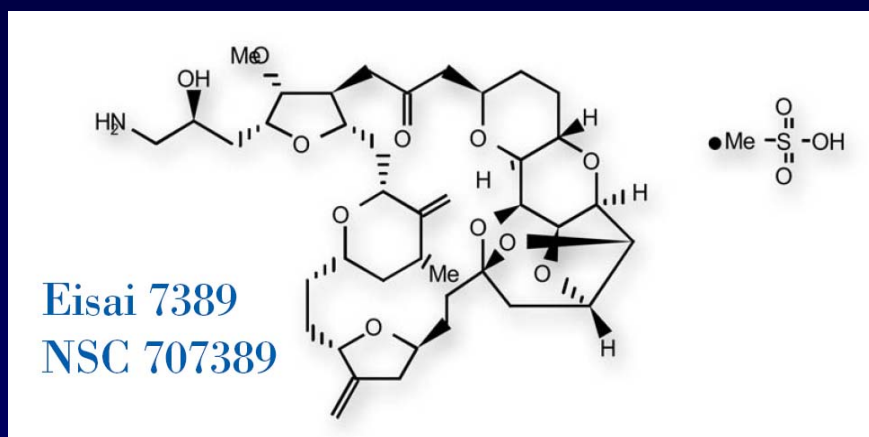
Author	N of pts	Treatment	RR (%)	PFS (mo)	OS (mo)
→ Miller (2005)	462 (pretreated)	Capecitabine ± Bevacizumab	20 vs. 9 (p=0.001)	5 vs 4 (p=0.98)	15 vs.15 (p=nr)
Miller (2005)	715 (1st line)	Weekly paclitaxel ± Bevacizumab	29 vs. 14 (p<0.0001)	11 vs 6 (p<0.001)	HR 0.67 (p=0.01)

Differences in Study Populations Could (partially) Explain the Different Results

	Paclitaxel trial	Capecitabine trial
Prior chemo for MBC	0%	85%
Prior chemo	64%	100%
Prior A + T	minority	100%
HER-2+	hardly any	25%
Prior trastuzumab	hardly any	23%

IMPORTANCE OF GIVING THE BIOLOGICAL AGENT EARLY

E7389 (Eribulin mesylate): Halichondrin B analog



- E7389, analog of halichondrin B, has broad anti-proliferative activity and a unique profile of tubulin interaction

E7389 (Eribulin mesylate), a novel anti-tubulin, in patients with refractory breast cancer

- 88 patients with **MBC** (≥ 2 prior chemotherapy regimens, included an anthracycline and a taxane)
- At the end of cycle four there were 10 (15 %) confirmed partial responses (PRs) out of 66 evaluable pts in group 1 (days 1, 8, and 15), and 1 confirmed PR (5.6 %) out of 18 evaluable pts in group 2 (days 1 and 8)
- Among 73 patients with safety data available, two pts had Grade 3 febrile neutropenia, and 31 had Grade 3 or 4 **neutropenia**

**Phase II study of eribulin mesylate (E7389) in pts with
MBC previously treated with anthracycline, taxane, and
capecitabine therapy
(N° of eligible patients : 269)**

Response rate (independent review)	: 9.3 %
Response rate (investigator)	: 14 %
Response rate (ER+ and/or PgR+)	: 11.5 %
Response rate (ER-, PgR-, HER2-)	: 2 %
Neutropenia gr 3/4	: 54 %
Febrile neutropenia	: 5.5 %
Peripheral neuropathy gr 3	: 5.5 %

Median of 4 prior chemotherapies

E7389 : 1.4 mg/m² IV d 1+8

Two pivotal phase III trials are currently ongoing



Clinical case # 6 (part II): Therapeutic options

- Endocrine therapy

- Capecitabine
- Vinorelbine
- Pegylated liposomal doxorubicin

- Capecitabine + ixabepilone

- Chemotherapy + bevacizumab
- Clinical trial with of chemotherapy + oral angiogenesis inhibitor

Thank you
