CURRICULUM VITAE

dr. Cosphiadi Irawan SpPD KHOM FINASIM

Education : : S1, FKUI 1985, S2, PPDS1 Dept.of Internal Medicine Medical Faculty University of Indonesia (FKUI) /

Ciptomangunkusumo Hospital (RSCM) 1995, Consultant Hematology-Medical Oncol. 2006

Course:

Stem Cell-Cryopreservation Toranomon Hosp. Tokyo 2005

Malignantcy on Lymphoid-LM, Dana Farber Boston, 2007

Course SC Processing BM /PBSC Queen Mary Hospital Hkg

Occupation :

Supervisor of education S1 Darmais Cancer Hospital up to 2009

Member of education program: S1 & National Board Collegium Sp1 Dept of Int Med.

Staff Div Hematology-Medical Oncol. FKUI RSCM/ RSKD

Member of Stem Cell research FKUI-RSCM

SYSTEMIC THERAPY IN RECURRENCE / METASTATIC BREAST CANCER : HORMONAL , CHEMO AND BIOLOGICAL THERAPY

COSPHIADI IRAWAN
Div. Hematology-Medical Oncology
Ciptomangunkusumo General Hospital
Medical Faculty University of Indonesia

METASTATIC BREAST CANCER (MBC) :

- It is incurable disease, BUT it can be effectively managed with appropriate treatment strategies

- By knowing patients characteristic ; predictive & prognosis factors

- GOAL OF TREATMENT : control the tumor, relief symptoms, maintain and improved quality of life and prolongation of survival

- Dr Schilsky (ASCO 2009) : Our focus has always been, and must remain, treating the patient, not the disease. We must each acquire the skills and make the commitment to do so in an optimal way.

(Cont.) :

- WESTERN COUNTRY :
- Early – localized stage : 60 % (- 20 to 30 % → recurrent and metastatic disease-)

- Regional stage 30 % (- spread to the regional lymph nodes or beyond primary site-)
- Less than 10 % were in metastatic stage [1]

- Our data in Darmais and Cipto Mangunkusumo hospital, showed that on between 1998 -2002 / 2001- 2005 around 60 -70 % patients were come with locally advance and advance stage. [2]

1. Adam B. Commun Oncol. 2010 ; 7: 115 - 123
2. Cosphiadi et al. Acta Med Indones J Intern Med.(40).2008: 178 - 180

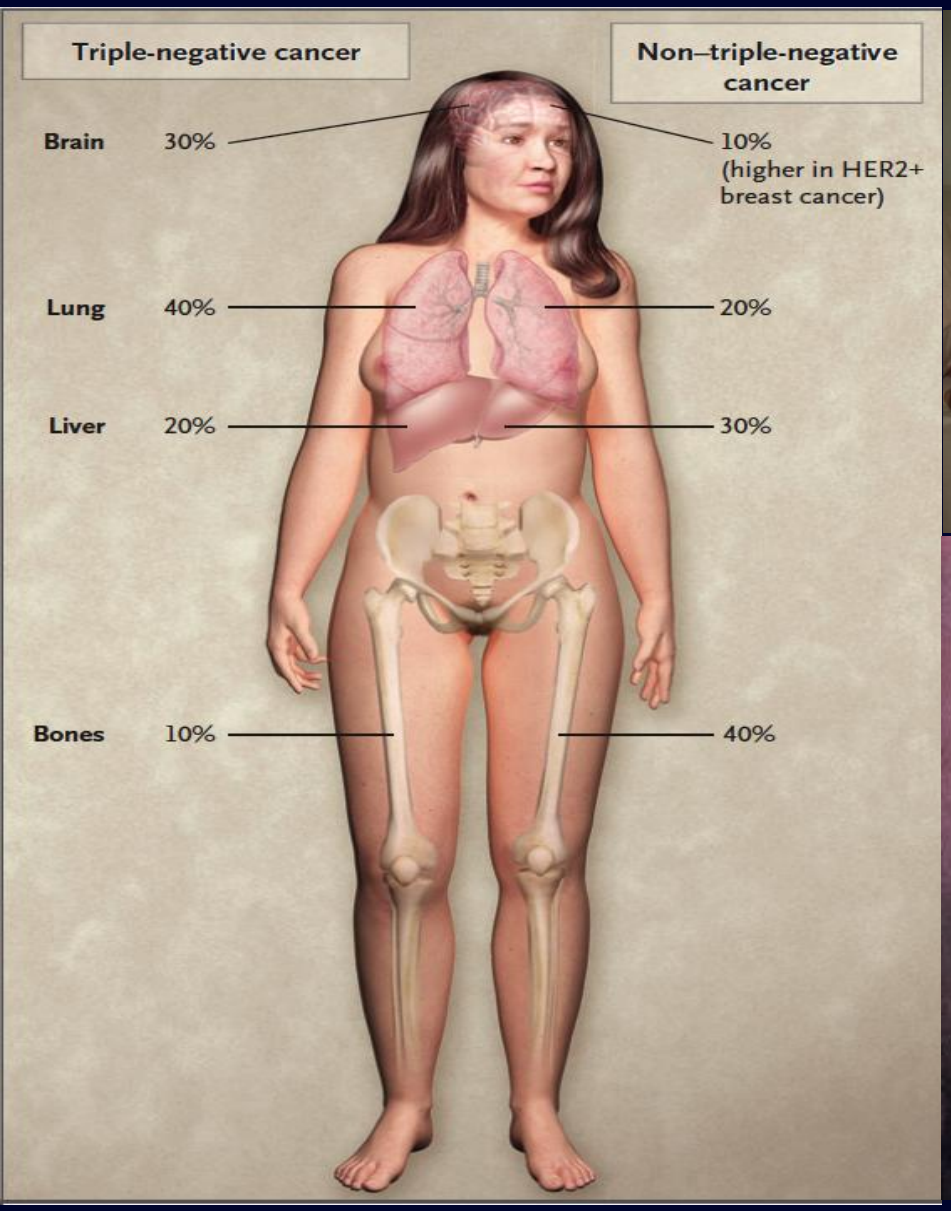
(Cont.)

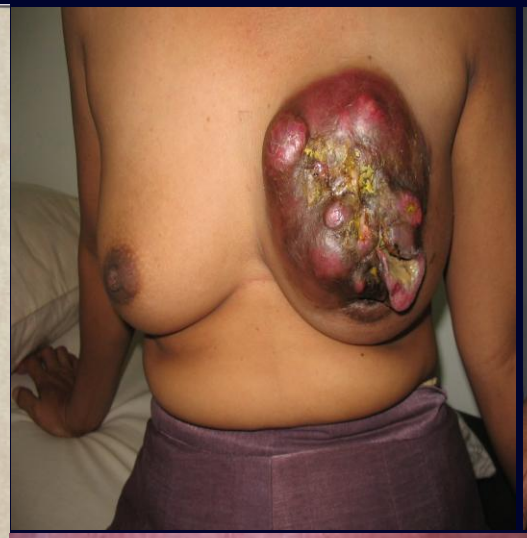
- MD Anderson : (1973 - 1982)
- experience 1581 patient treated with doxorubicin & alkylating 1st line setting :
- 16,6 % CR AND 3,1 % maintain CR up to 5 year

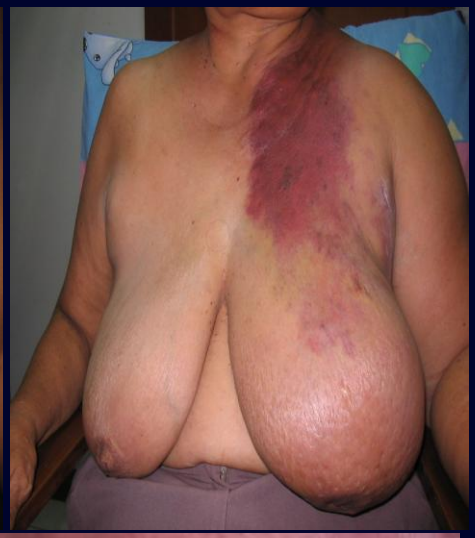
- Long term disease control were more likely to be premenopausal, young , excellent performance & low tumor burden → SUGEST IMPORTANT ROLE of chemotherapy in MBC

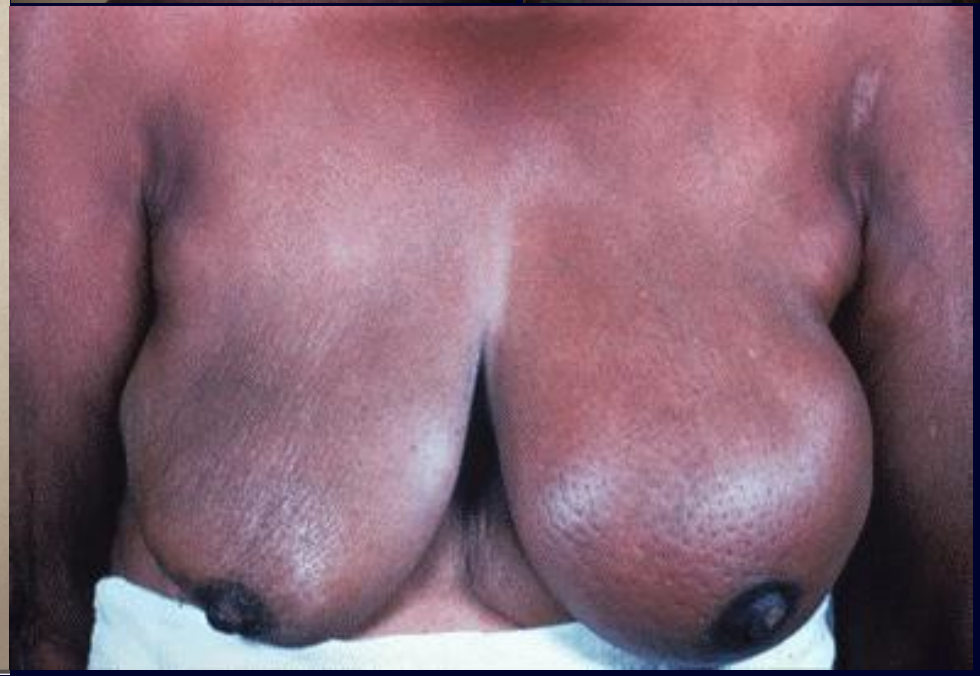
Melinda L,Clinical Breast Cancer, (9) 2009 : S66-72

METASTATIC BREAST CANCER







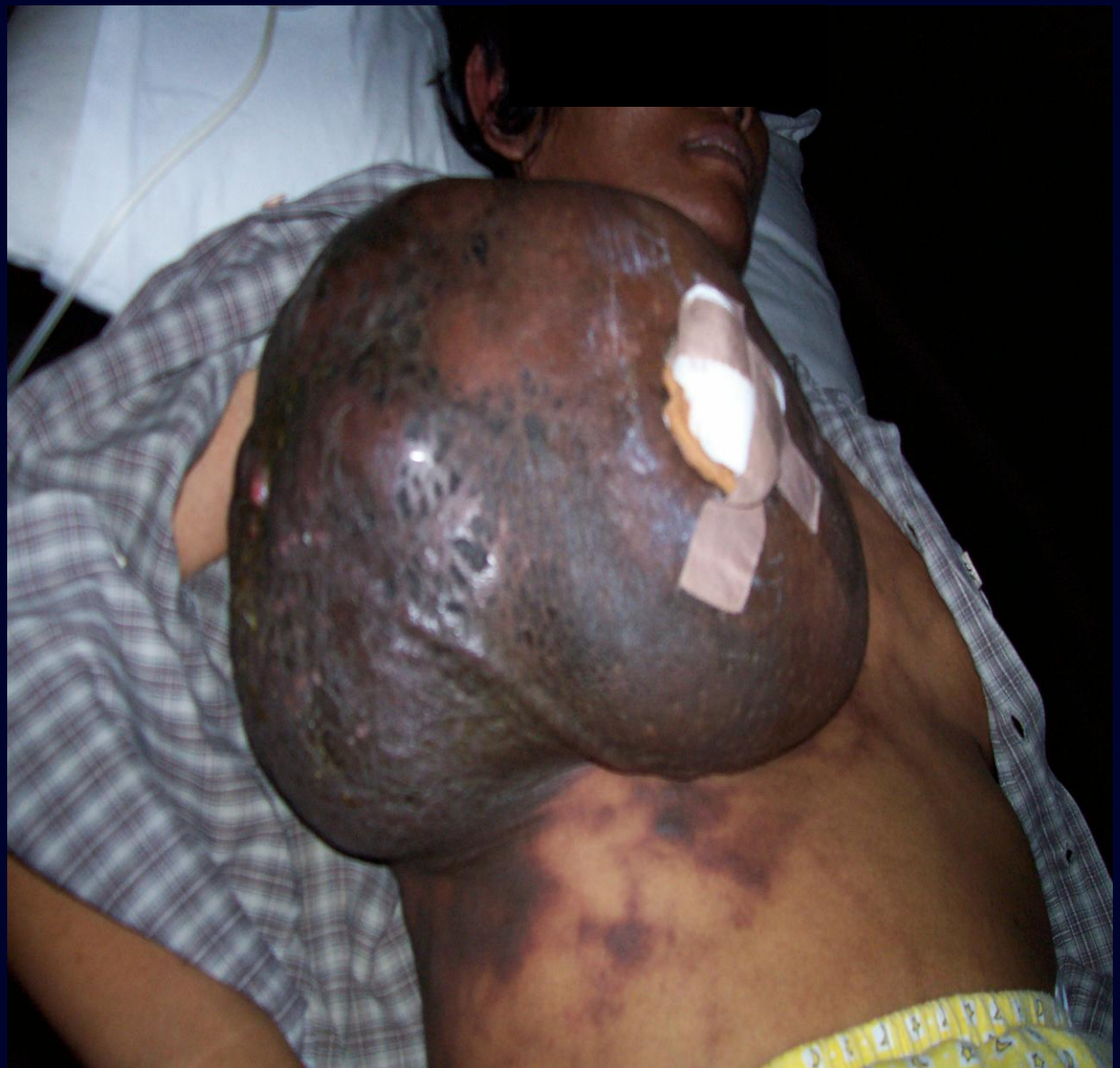


PROGNOSTIC FACTOR IN MBC :

Prognostic factor	Favorable	Unfavorable
Performance status	Good	Poor
Sites of disease	Bone, soft tissue	Viscera, CNS
No. of sites of disease	Few	Multiple
Hormone receptor status	Positive	Negative
Her-2/*neu* status	Negative	Positive (significance less clear in Her-2/*neu* inhibitors era)
Disease-free interval	>2 years	<2 years
Prior adjuvant therapy	No	Yes
Prior therapy for MBC	No	Yes

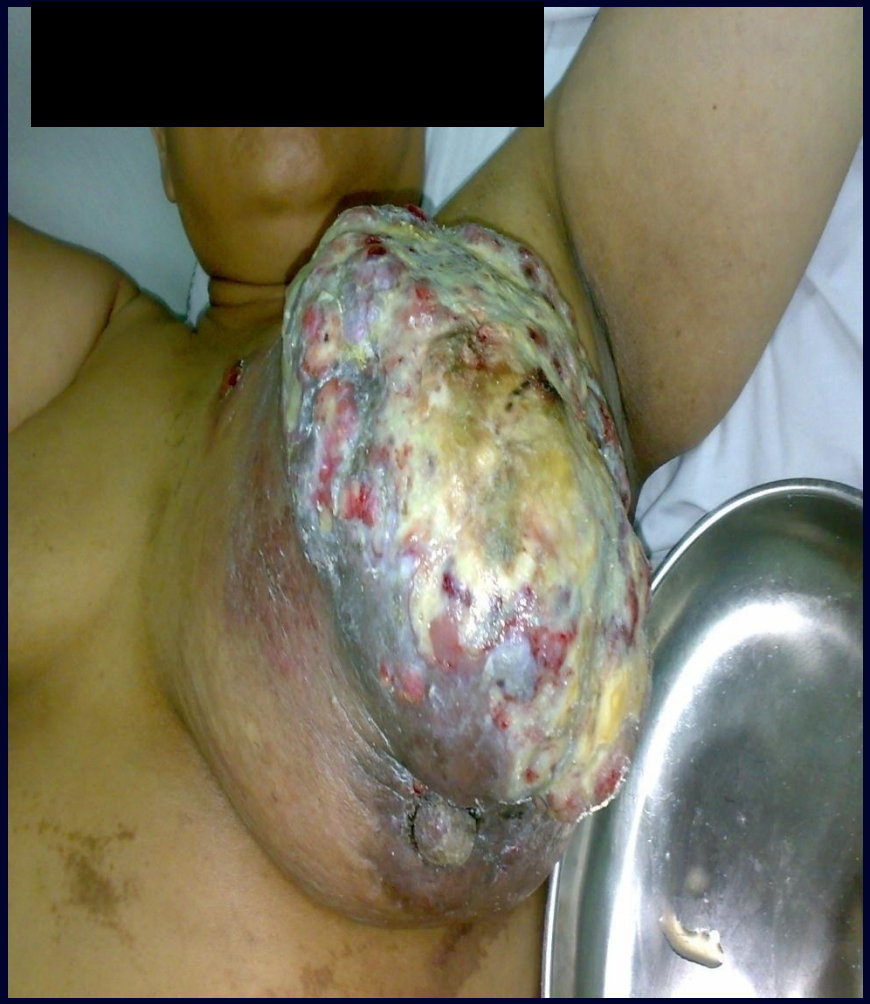
Baslija S, et al.Annals of Oncology 20: 1771–1785, 2009

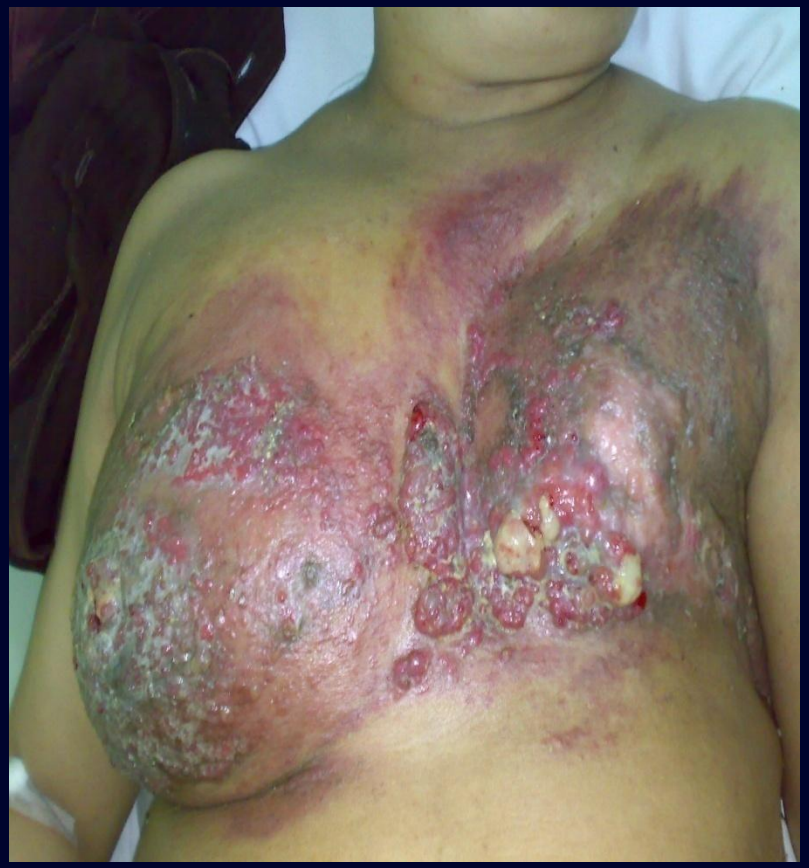
MBC :



- 42 yr; LUMP since 1,5 yr
- Ductal Invasif Stg IV
- Grade 2
- HER-2/neu +
- ER – PR +

TWO OF OUR PATIENTS WHO COME FOR THE FIRST TIME IN DARMAIS NATIONAL CANCER CENTER





HORMONAL THERAPY : Tamoxifen (TAM) :

.AJUVANT :

- Primary tumor RELAPS , : 47% ; 2p<0,00001
- Mortality: 26%, 2p < 0,00001

- SHOWED treatment benefit with 5 year of therapy
  - Adverse event :

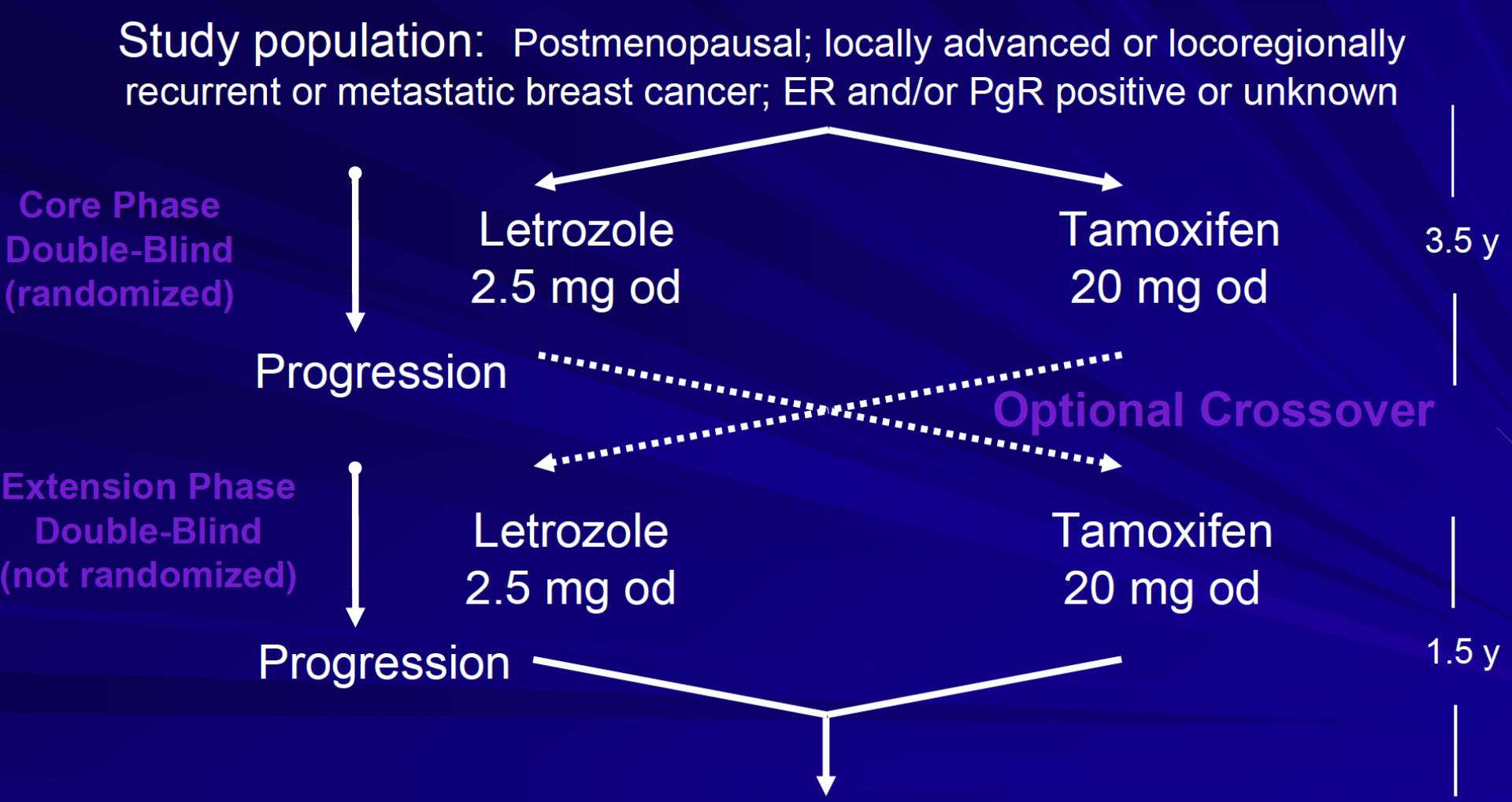
    thromboemboli events: RR 7,0

    endometrial cancer: RR 7,5; 2/1000 related deaths x 5yr

. MBC , showed RR up to 40 %

Lohrisch C, Piccart M Educational Book of the 25th ESMO congres, 2000: 13 -23

Protocol 025 Study Design: Letrozole vs. Tamoxifen as First-Line Therapy



Mouridsen et al. *J Clin Oncol.* 2001;19: 2596.

Letrozole Significantly Better Than Tamoxifen in TTP and TTF (Update September 2001*)

	Letrozole n=453	Tamoxifen n=454	Hazard Ratio (95% CI)	*P* Value
Progression	79%	85%	0.72	
TTP (median)	9.4 mo	6.0 mo	(0.62–0.83)	<0.0001
Failure	89%	94%	0.73	
TTF (median)	9.0 mo	5.7 mo	(0.64–0.84)	<0.0001

*Median duration of follow-up was 32 months.

Trial Design: Two Large, Randomised Trials

N America (JM Nabholtz) and Europe (J Bonneterre)

Postmenopausal women with advanced breast cancer eligible for endocrine therapy as first-line treatment (ER+ and/or PR+ or unknown)

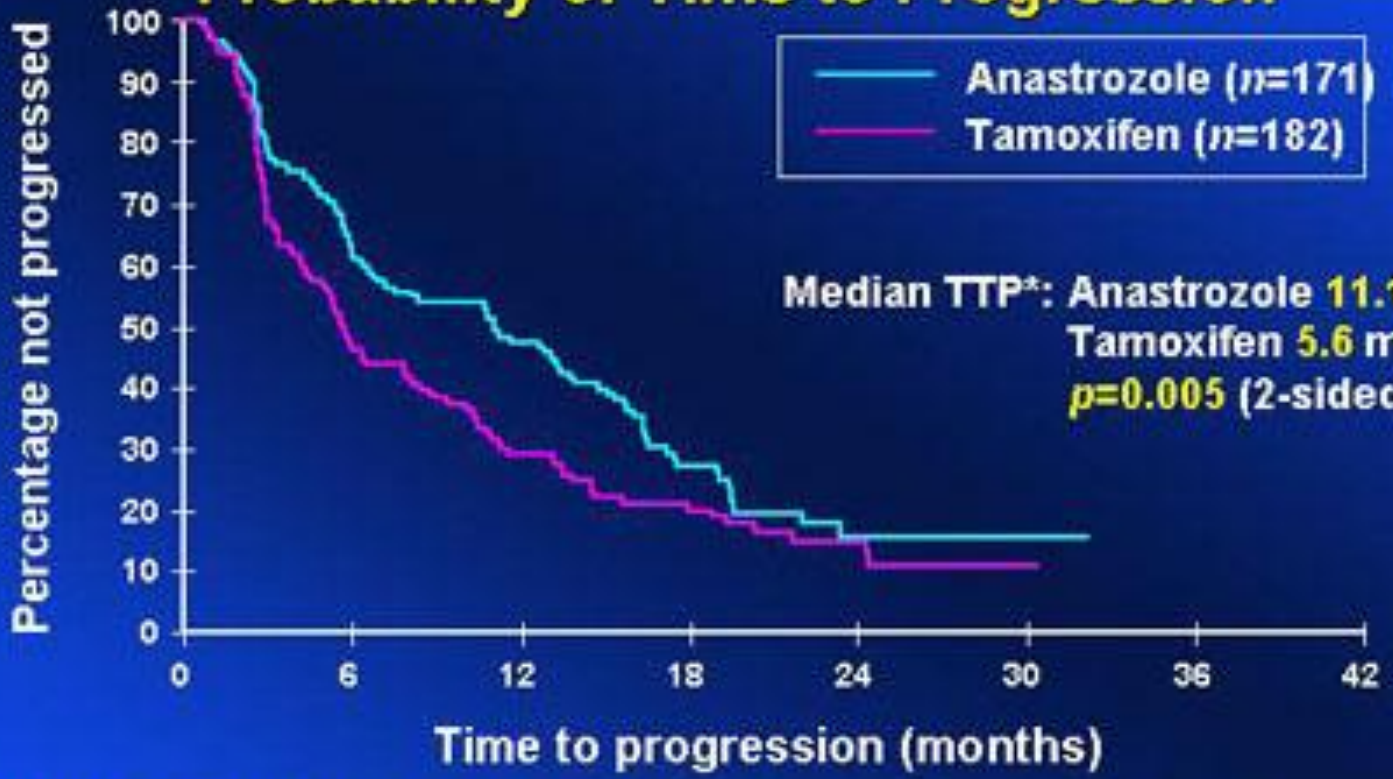
Randomised 1:1 (double-blind, double dummy)

Anastrozole 1mg daily plus tamoxifen placebo daily

Tamoxifen 20mg daily plus Anastrozole placebo daily

- **Primary objectives:**
  - Time to progression (TTP)
  - Objective response (OR)
  - Tolerability
- **Secondary objectives:**
  - Time to treatment failure (TTF)
  - TTP in responding patients
  - Survival

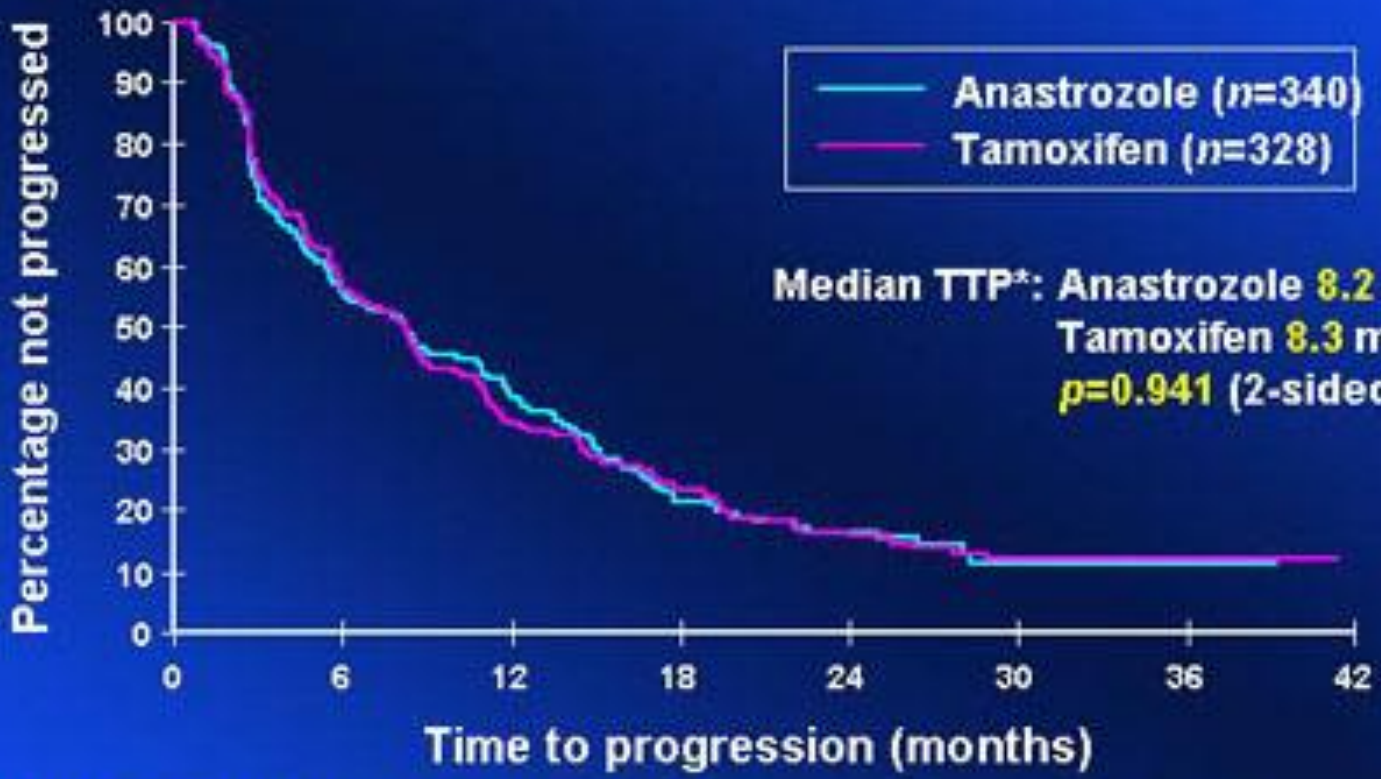
Trial JM Nabholtz : Kaplan-Meier Curve of Probability of Time to Progression



Median TTP*: Anastrozole 11.1 months
Tamoxifen 5.6 months
p=0.005 (2-sided)

* Hazard ratio (tam : 'Arimidex') 1.44, lower CL 1.16. Study 'powered' for equivalence. Median follow-up of 18 months. 71% progressed

Trial J Bonneterre : Kaplan-Meier Curve of Probability of Time to Progression



Median TTP*: Anastrozole 8.2 months
Tamoxifen 8.3 months
p=0.941 (2-sided)

* Hazard ratio (tam : 'Arimidex') 0.99, lower CL 0.86. Study 'powered' for equivalence. Median follow-up of 19 months. 74% progressed

Aromatase inhibitors (AI) in the metastatic setting.

- AI established as similar or superior to tamoxifen for metastatic disease in the early 1990's.

Author	Comparators	N	Response (%)	Clinical Benefit (%)[a]	Median Time to Progression (Mo)
Nabholtz et al.	Anastrozole	171	21	59[b]	11.1[b]
	Tamoxifen	182	17	46	5.6
Bonneterre et al.	Anastrozole	340	33	56	8.2
	Tamoxifen	328	33	56	8.3
Mouridsen et al	Letrozole	453	30[b]	49[b]	9.4[b]
	Tamoxifen	454	20[b]	38	6.0
Paridaens et al.	Exemestane	182	46[b]	66[b]	9.9[b]
	Tamoxifen	189	31	49	5.8

[a]Defined as total % patients responding or achieving stable disease for at least 6 months.
[b]Significant difference vs. tamoxifen[AU:5]

2nd and 3rd line in metastatic disease

- Switching class of AI or switching to direct ER inhibitor continues to produce clinical response.

Endocrine Drug	Author	Treatment Setting	Prior Endocrine Therapies	N	Clinical Benefit (%)
Exemestane	Lonning et al.	3rd to 4th line	Nonsteroidal AIs	241	24
	Fernie et al.	2nd line	Nonsteroidal AIs	96	39
	Bertelli et al.	2nd line	Non-steroidal AIs	11	65
Fulvestrant	Perey et al.	3rd line	Tam, nonsteroidal AIs	32	34
	Petruzelka et al.	2nd to 5th line	Tam, nonsteroidal AIs	44	52
	Franco et al.	3rd to 5th line	Tam, AIs, progestins, Exemestane	42	19
	Steger et al.	2nd to 5th line	Tam, AIs, progestins, Exemestane	111	42

Hormonal Therapy
Metastatic Breast Cancer

Conclusion 1

Post menopausal 1st line Treatment :

AROMATASE INHIBITORS ARE AN ALTERNATIVE TO TAM.

(ec : Letrozole showed superior than TAM; Anastrozole the same or as good as TAM)

Conclusion 2

When the cancer is tamoxifen-resistant / failure, the best second-line is a 3rd generation of aromatase inhibitor or fulvestran

Conclusion 3

Following failure of non steroidal AI; steroidal AI, TAM , fulvestran can be considered

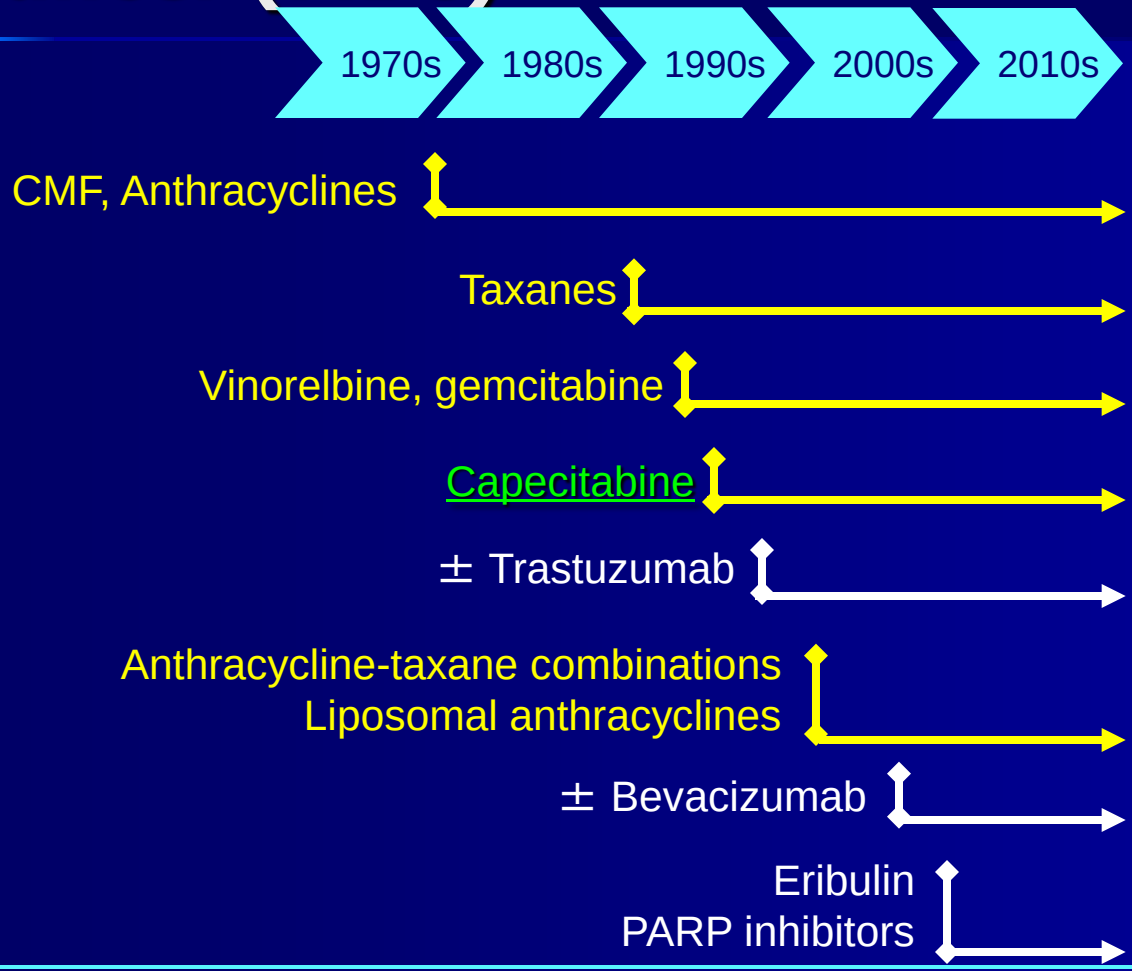
Beslija et al. Annals of Oncology 20: 1771–1785, 2009

Hormonal Therapy in HER2+ MBC

Regimen	ORR, %	PFS, Mos
Trastuzumab (N = 79)[1]	26	3.5-3.8
Anastrozole + trastuzumab (N = 103)[2]	20	4.8
Anastrozole (N = 104)[2]	7	2.4
Lapatinib + letrozole (N = 642)[3]	28	8.2
Letrozole (N = 644)[3]	15	3.0
Lapatinib (N = 138)[4]	24	NA

1. Vogel C, et al. J Clin Oncol. 2002;20:719-726.
2. Mackey JR, et al. SABCS 2006. Abstract 3.
3. Johnston S, et al. J Clin Oncol. 2009;27:5538-5546.
4. Gomez HL, et al. J Clin Oncol. 2008;26:2999-3005.

The evolution of first-line chemotherapy for metastatic breast cancer (MBC)



TREATMENT DURATION : in 1st line best marginal is longer CT→ reduced risk of death

Beslija et al. Annals of Oncology 20: 1771–1785, 2009

Table 1. Efficacy of capecitabine in patients with metastatic breast cancer

Author	*n* Pts.	Dose (mg/m^2)[a]	Response rate
O'Shaughnesy [54]	62*	2,510	25%
O'Reilly [55]	22**	2,510	35%
Blum [53]	135***	2,510	20%

[a]Total dose = given in two divided daily doses for 14 days followed by 7 days off.

*First-line

**Anthracycline-resistant

***Anthracycline/paclitaxel-resistant

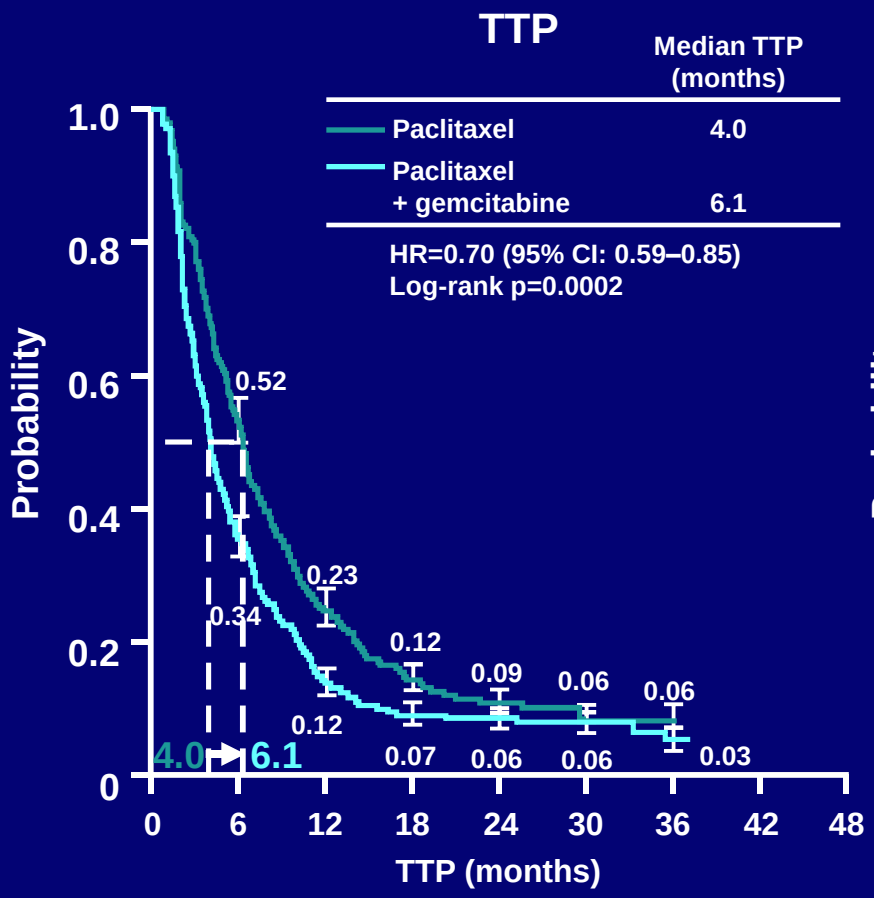
Single-agent vs Combination Trials

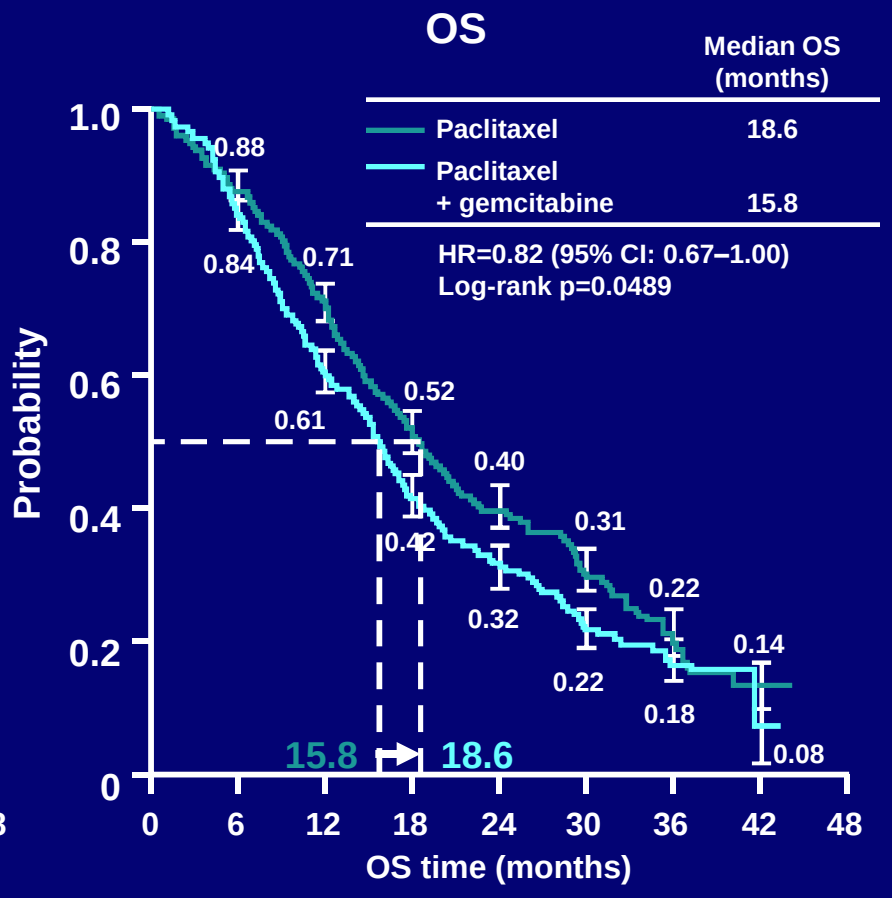
Clinical Trial	Median TTP (months)	Overall Survival (months)	Grade IV Neutropenia (%)
Albain et al (N=529)			
Pac	3.98	15.8	7
Pac + Gem	6.14	18.6	17
	p = .0002	p = .0489	
O'Shaughnessy et al (N=511)			
Docetaxel (Doc)	4.2	11.5	11
Doc + Cap	6.1	14.5	12
	p= .0001	p= .0126	

Albain KS et al. *J Clin Oncol*. 2008 ; 26 : 3950 -7 .
O'Shaughnessy J et al. *J Clin Oncol*. 2002;20(12):2812-2823.

Addition of gemcitabine to first-line paclitaxel significantly improved TTP and OS

Phase III, randomised, open-label, multicentre study of paclitaxel ± gemcitabine in anthracycline-pretreated patients with advanced BC

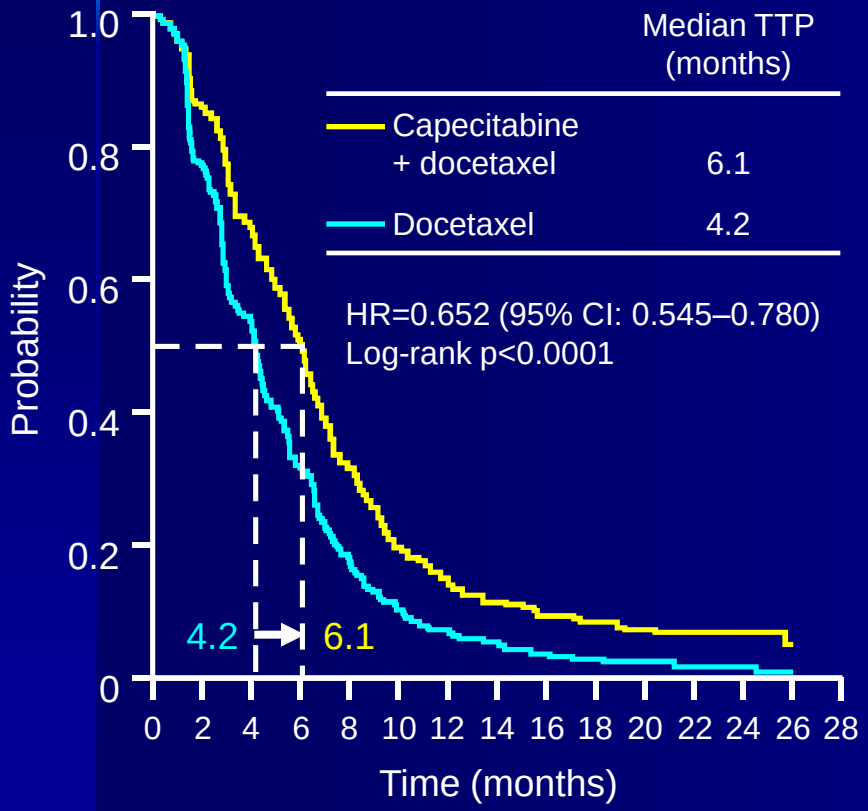


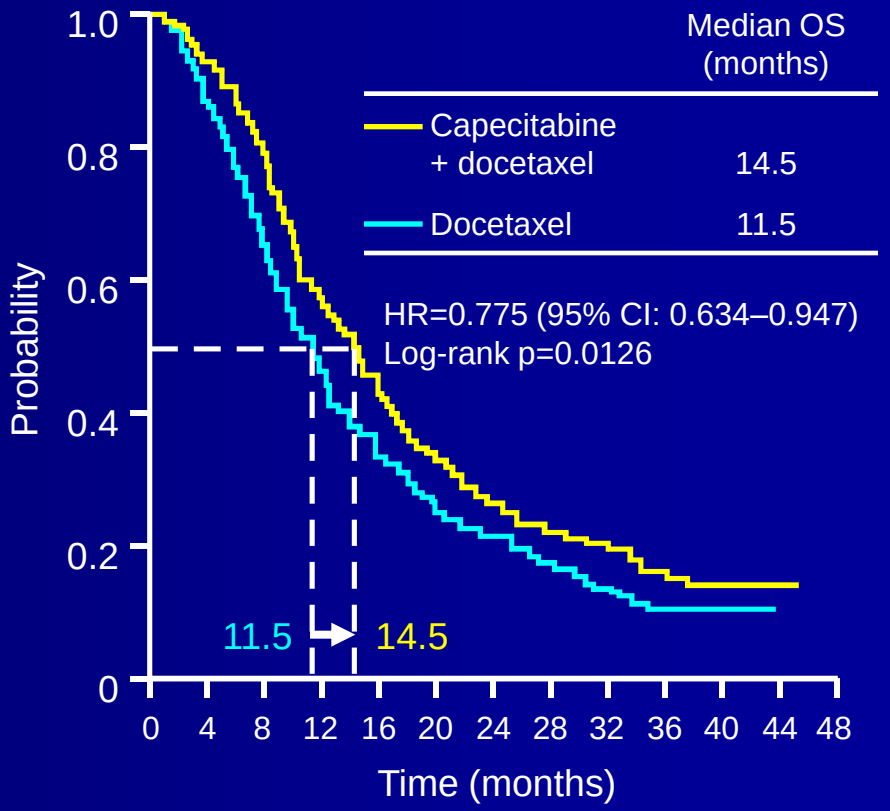


Albain, et al. JCO 2008

Capecitabine + docetaxel: increased TTP and OS compared with standard taxane therapy

Phase III, randomised, open-label, multicentre study of docetaxel ± capecitabine in anthracycline-pretreated patients with advanced BC





Minimum follow-up = 27 months
Note: extended follow-up was not preplanned

O'Shaughnessy, et al. JCO 2002

ECOG: E1193 Phase III Trial

Results: Efficacy and Tolerability ; N = 739 MBC

Outcome	Dox	Pac	Dox + Pac	*P* Value
Response rate (%)	36	34	47	0.007* 0.004†
Median survival (mo's)	18.9	22.2	22.0	NS
TTP (mo)	6.0	6.3	8.2	0.0022* 0.0567†
Gr III/IV leukopenia (%)	47	60	55	—
Gr III/IV infection (%)	4.1	8.3	12.7	—
Gr III/IV neurologic complications (%)	1.6	3.7	10.7	—

*Dox vs Dox + Pac; †Pac vs Dox + Pac.

*Sledge GW et al. J Clin Oncol. 2003;21(4):588-592.

[Intervention Review]
Single agent versus combination chemotherapy for MBC

Carrick S, et al. Cochrane Database Syst Review . 2005

- **Main results**
- Forty three eligible trials (48 comparisons) were identified. N: 9742 women, 55% of whom were receiving 1st line th. for MBC → OS was a statistically significant in favour of the combination (HR 0.88, 95% CI 0.83-0.93, p<0.00001).

Results were very similar when trials of first-line treatment were **single agent versus combination chemotherapy for MBC**

(cont.) :

- Analyses where the single agent was also included in the combination regimen:

  Survival : Favour combination regimens vs single agent taxane (HR 0.82; 95% CI 0.75-0.89, p<0.00001), but not vs anthracycline (HR 0.94.86-1.02, p=0.15).

- **TTP & RR** : Favour combination regimens (HR 0.78, 95%CI 0.74 - 0.82, p<0.00001) and response (RR 1.29, 95% CI 1.14 -1.45, p<0.0001) respectively ; although heterogeneity was statistically significant in both instances
- Effect on WBC, ↗ alopecia, nausea, vomiting :HIGHER in combination

Authors' conclusions

- Combination chemotherapy show a statistically significant advantage for survival, RR & TTP ; but they also produce more toxicity. Whether combination regimens are more effective than single agents given sequentially…. ?

Biological & Targeted Therapy Increases Benefits for patients with MBC

HER2-negative MBC

- E2100/AVADO: significant benefit of bevacizumab-taxane vs taxane[1,2]
- RIBBON-1: significantly greater PFS and ORR with first-line capecitabine-bevacizumab vs capecitabine-placebo[3]
- SOLTI-0701: significantly prolonged PFS with capecitabine-sorafenib vs capecitabine in pretreated MBC (HR 0.58; p=0.0006)[4]
  - 45% grade 3 HFS with capecitabine-sorafenib
- RIBBON-2: significant PFS benefit with second-line bevacizumab-CTX vs CTX[5]

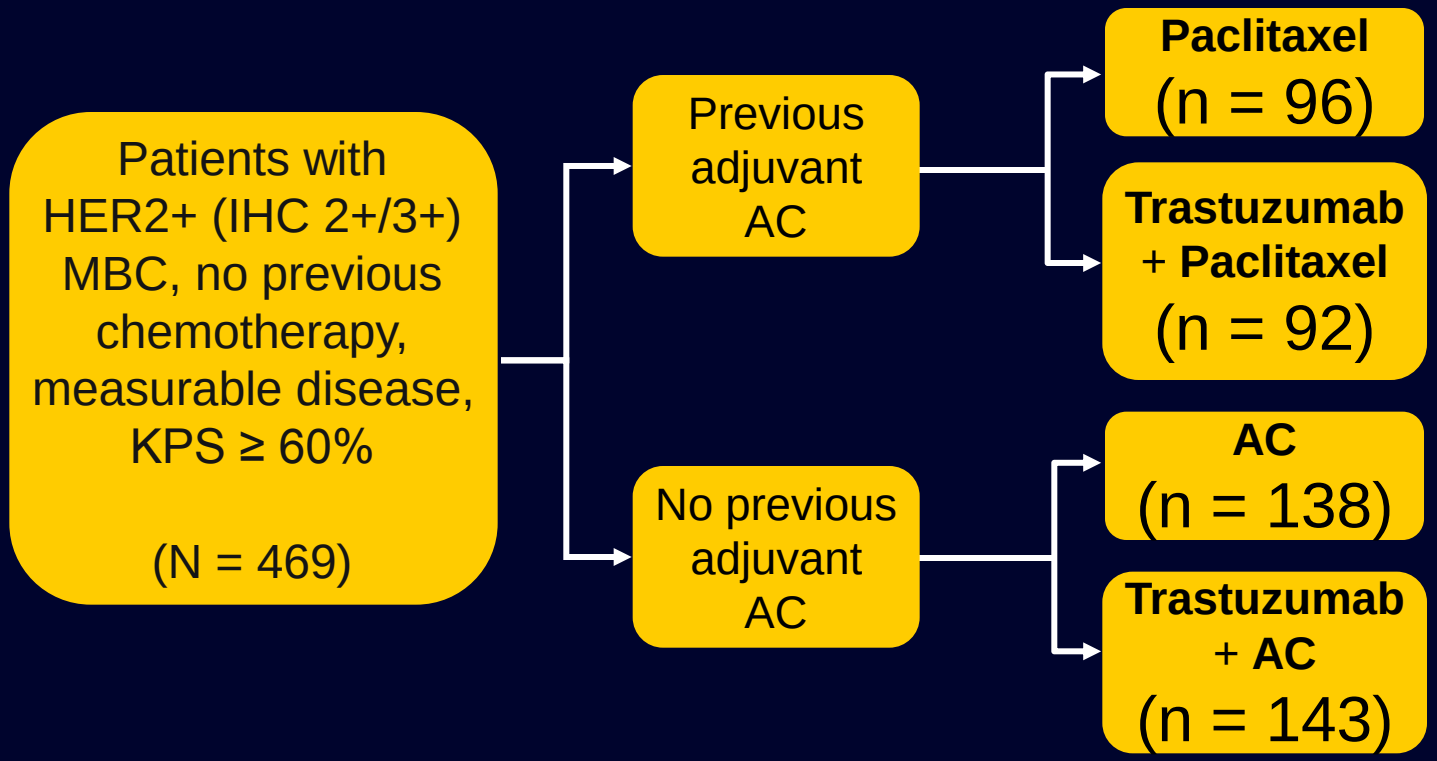
HER2-positive MBC

- CHAT: significantly increased TTP (p=0.03) and PFS (p=0.04) with first-line trastuzumab-docetaxel-capecitabine vs trastuzumab-docetaxel[6]
- Ongoing evaluation of first-line capecitabine-trastuzumab in MBC

[1]Klencke et al. 2008; [2]Pivot et al. 2009
[3]Robert N, et al. SABCS 2009; [4]Baselga J, et al. SABCS 2009
[5]Brufsky A, et al. SABCS 2009; [6]Wardley AM, et al. J Clin Oncol 2009

CTX = chemotherapy

Trastuzumab Combinations as First-line Therapy for MBC: Pivotal Phase III Trial



Slamon DJ, et al. N Engl J Med. 2001;344:783-792.

Trastuzumab in MBC: The Pivotal Trial

Treatment	Objective Response Rate, %	Median TTP, Mos	Median OS, Mos
Chemo	32	4.6	20.3
Chemo + Trastuzumab	50	7.4	25.1

P < .001 for all 3 comparisons. 1

Excess cardiotoxicity NHYA class III/IV heart failure : 16 % in Tz / anthr. VS 2 % in Tz/ paclitaxel

Paclitaxel, carboplatin / Tz : ↗ PFS 10,7 vs 7,1 mos HR 0,66; p= 0,03. but NOT OS 2
Additional carboplatin to docetaxel / Tz : DOES NOT improved ORR, TTP , OS 3

1. Slamon DJ, et al. N Engl J Med.2001;344:783-792 2. Robert N et al . J Clin Oncol 2006; 27 : 86 - 92

3. Valero V, et al. J Clin Oncol. 2011;29:149-156.

Trastuzumab in Recommended First-line Combinations for HER2+ MBC

- **HER2+ disease *without* previous trastuzumab: trastuzumab plus**
  - **Paclitaxel ± carboplatin**
  - **Docetaxel**
  - **Vinorelbine**
  - **Capecitabine**
- **HER2+ disease *with* previous trastuzumab: trastuzumab plus**
  - Other first-line agents
  - Capecitabine
  - Lapatinib (without cytotoxic therapy) or combine with capecitabine

NCCN. Clinical practice guidelines in oncology: breast cancer. v2.2011
Melinda L,Clinical Breast Cancer, (9) 2009 : S66-72

NCCN Guidelines™ Version 2.2011 Updates (MBC)

- Continuation of Her-2 blockade for patients with Her-2 MBC which progresses on 1st line trastuzumab-containing regimen.

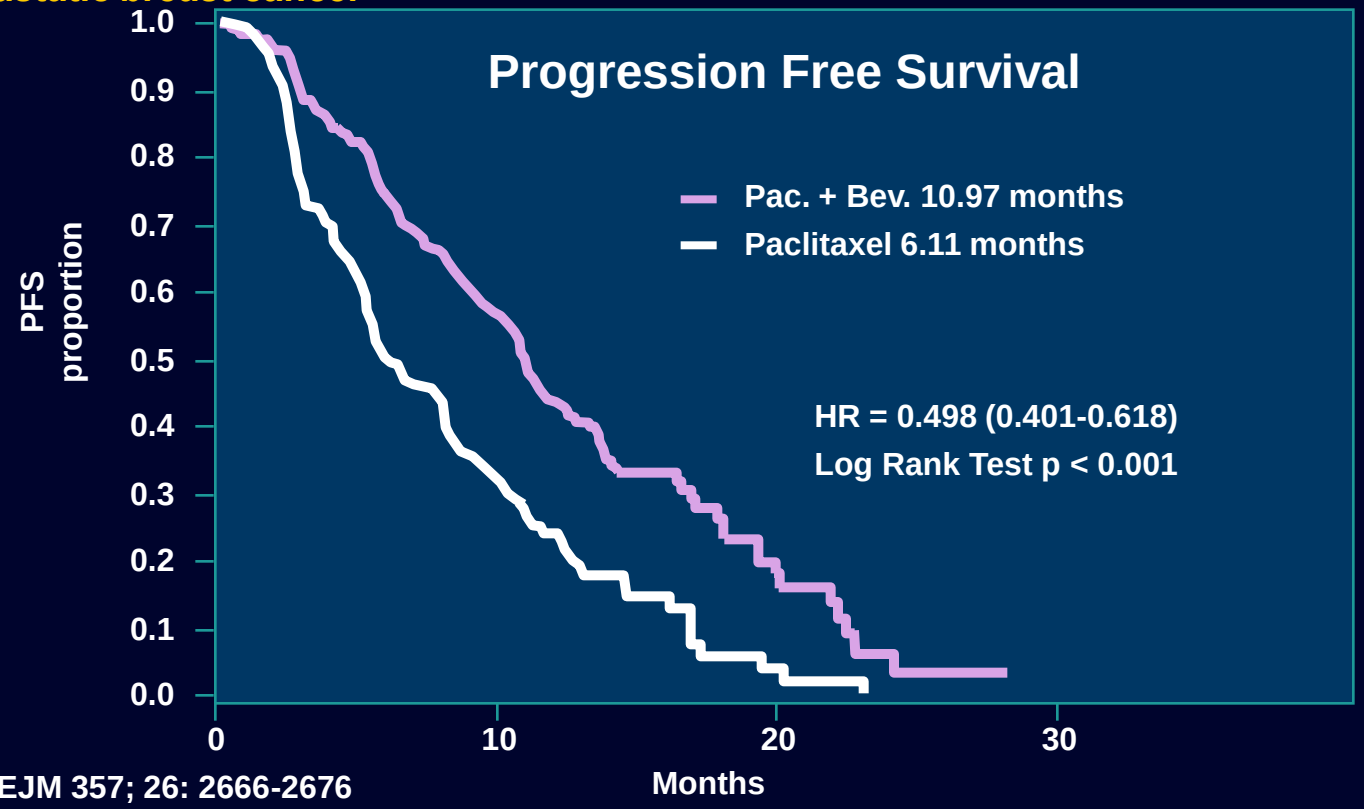
- The regimen of capecitabine plus lapatinib is also an option for patients with Her-2 positive disease following progression on a trastuzumab containing regimen.

Bevacizumab is approved in 1st line MBC

Marketing Authorization for Europe obtained on 29 March 2007 (based on E2100 study)

Recent, unprecedented, FDA decision for Fast Track Approval

"Avastin in combination with paclitaxel is indicated for first-line treatment of patients with metastatic breast cancer"



Miller et al. NEJM 357; 26: 2666-2676

Docetaxel + Avastin in First-Line MBC: AVADO

N = 736
HER2-negative

- Docetaxel 100 mg/m² (q 3 wk up to 9 cycles) + placebo
- Docetaxel 100 mg/m² (q 3 wk up to 9 cycles) + bevacizumab 7.5 mg/kg
- Docetaxel 100 mg/m² (q 3 wk up to 9 cycles) + bevacizumab 15 mg/kg

Primary objective: PFS

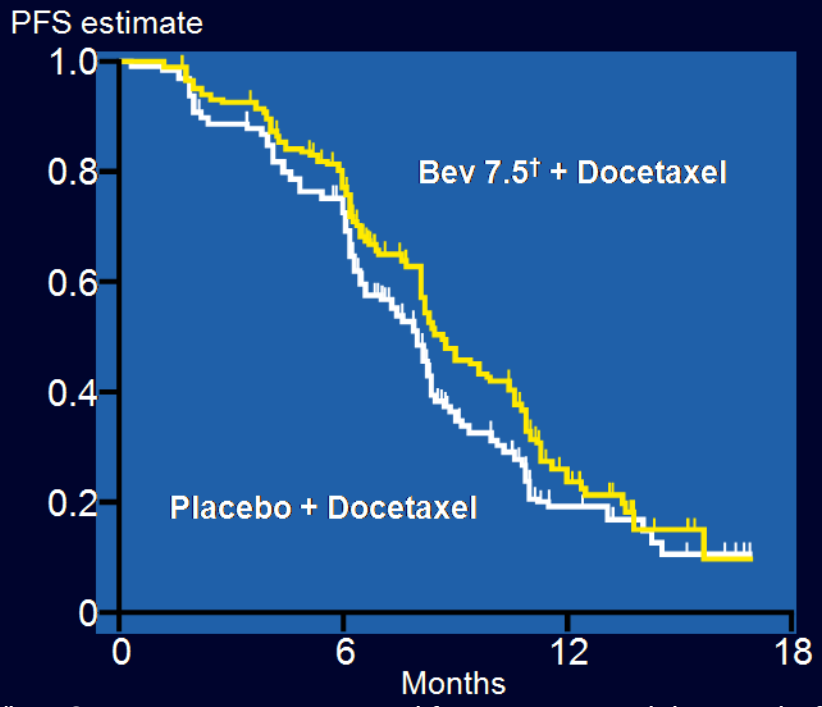
Median follow-up: 10.2 months

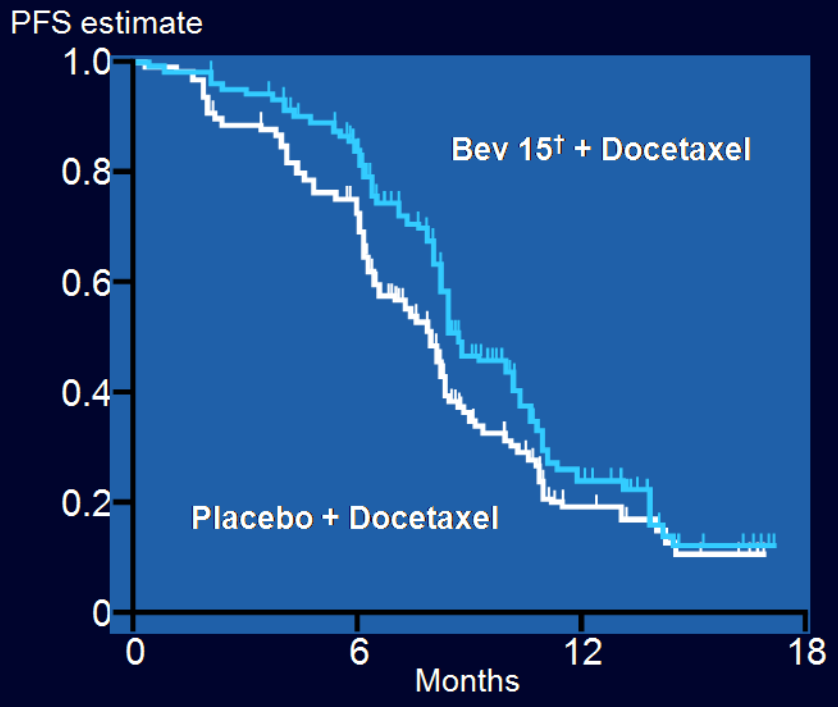
Miles et al. ASCO 2008. Abstract LBA1011.

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=.0318
HR + 95% CI (stratified*)		0.69 (0.54–0.89) p=.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=.0099
HR + 95% CI (stratified*)		0.61 (0.48–0.78) p<.0001
Median	8.0	8.8





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

Miles et al. ASCO 2008. Abstract LBA1011.

AVADO: Overall Survival (ITT Population)

Data not yet mature

	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	**–**	**0.92**	**0.68**
(95% CI)		**(0.62–1.37)**	**(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 q 3 wk; NR = not reached.

Miles et al. ASCO 2008. Abstract LBA1011.

Table 2

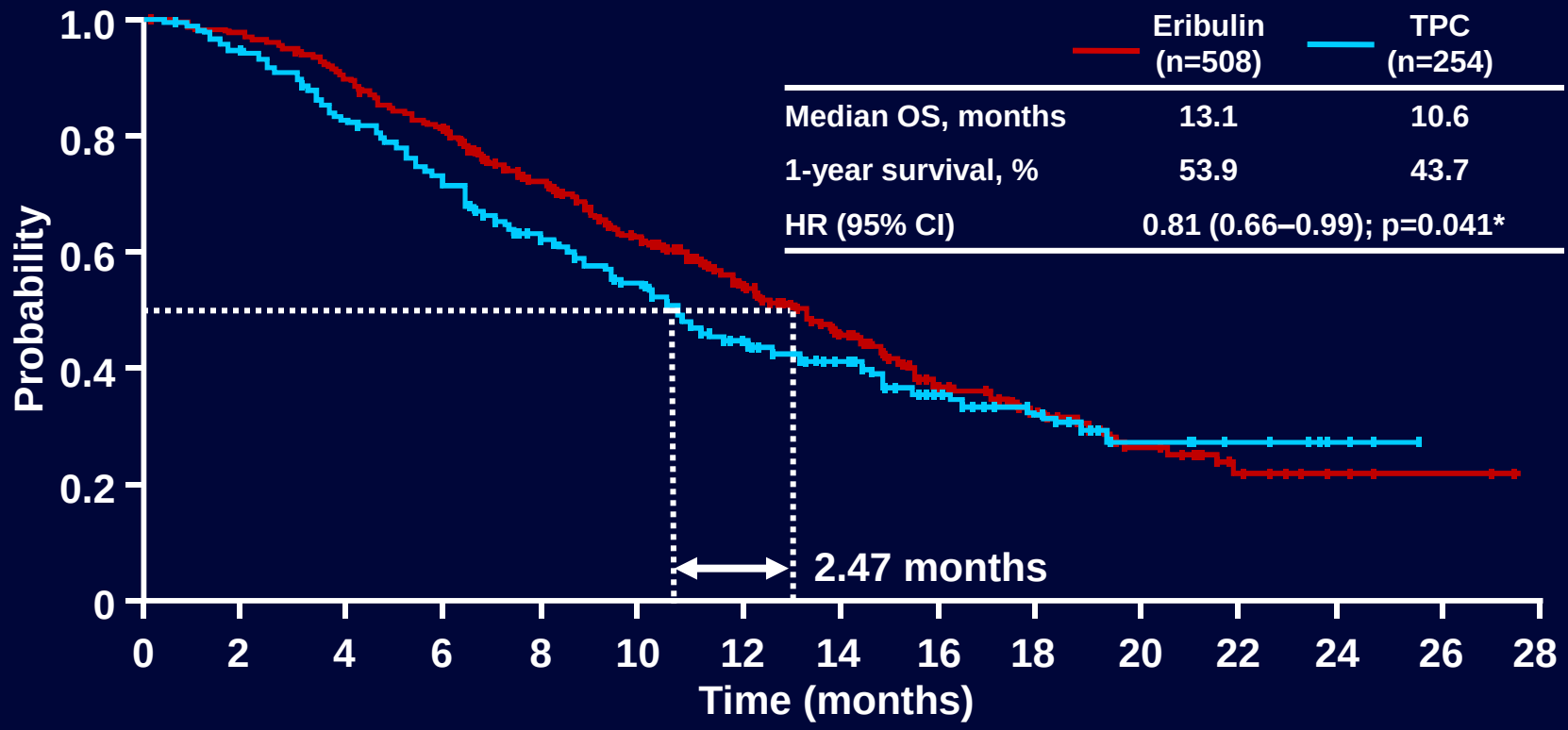
Therapeutic Strategies in Triple-Negative Breast Cancer

Treatment Approach	Status
Anthracyclines	Proven efficacy[46,47]
Taxanes	Proven efficacy[45]
Platinum agents	Active, comparison to other cytotoxics unclear[51]
Bevacizumab	Suggested in subset analyses of unselected phase III trial, E2100[60]
Sunitinib	Suggested by subset analyses of unselected phase II trial[62]
EGFR inhibition	Preclinical data, modest activity with chemotherapy in phase II studies[52,55]
PARP inhibition	Preclinical data, in investigation

EGFR = epidermal growth factor receptor; PARP = poly ADP-ribose polymerase.

Eribulin significantly improved OS vs Treatment by choice (single agent) : EMBRACE

Phase III trial of eribulin compared with TPC in patients with heavily pretreated (incl. : anthra. & taxane) locally recurrent or mBC



- Eribulin approved by FDA and EMEA: 1,4 mg/m2 IV (D1,8 / 21 days)

*Stratified log-rank test
TPC = treatment of physician's choice

Cortes, et al. Lancet 2011

Printed by Arya Wibitomo on 3/9/2011 11:18:04 PM. For personal use only. Not approved for distribution. Copyright © 2011 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

PREFERRED SINGLE AGENTS

Anthracyclines
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

OTHER SINGLE AGENTS
- Cyclophosphamide
- Mitoxantrone
- Cisplatin
- Etoposide (po) (category 2B)
- Vinblastine
- Fluorouracil CI
- Ixabepilone

PREFERRED AGENTS WITH BEVACIZUMAB[2]
- Paclitaxel

PREFERRED CHEMOTHERAPY COMBINATIONS
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

OTHER COMBINATIONS
- Ixabepilone + capecitabine (category 2B)

PREFERRED FIRST-LINE AGENTS FOR HER2-POSITIVE DISEASE

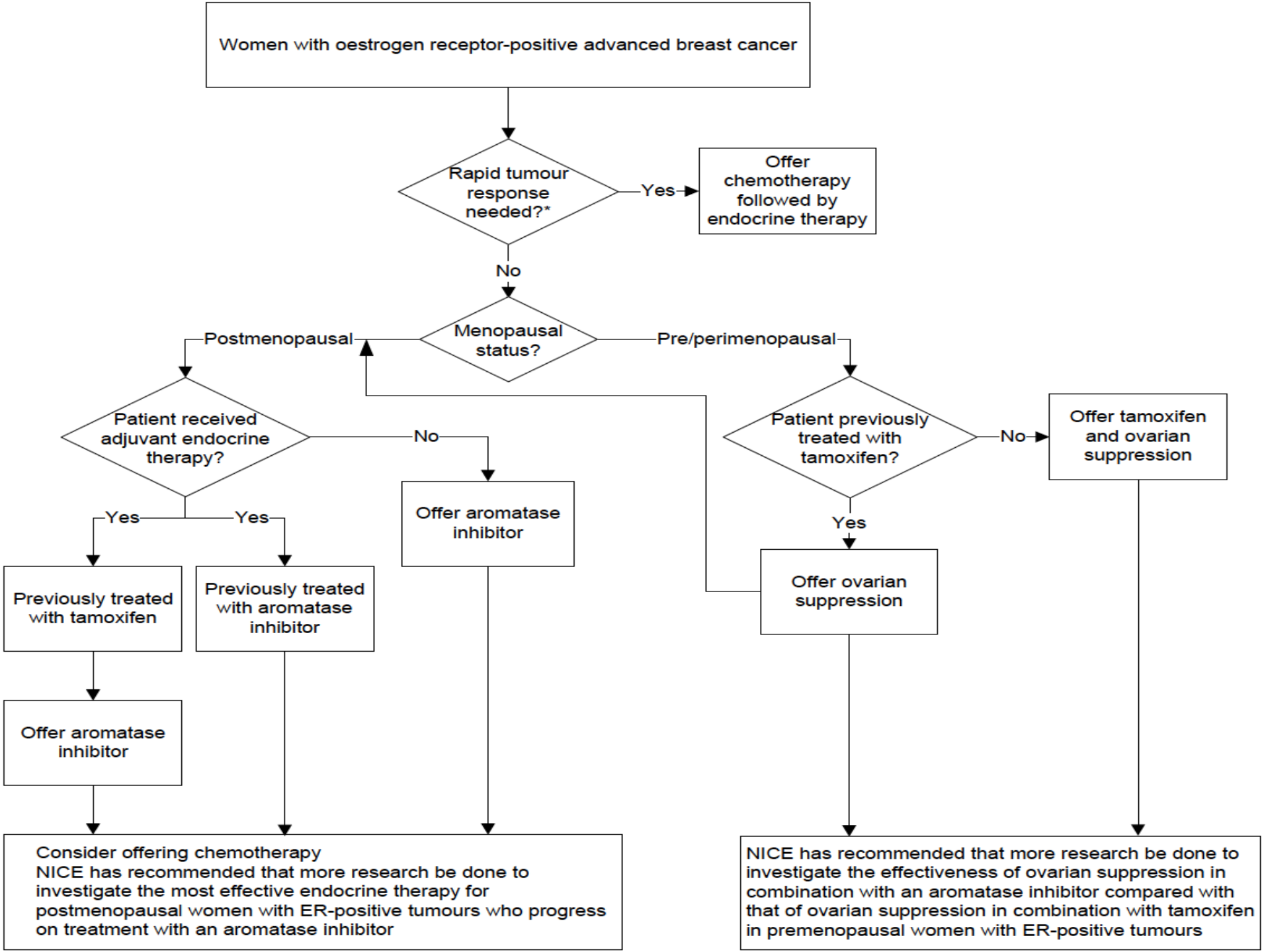
Trastuzumab with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

PREFERRED AGENTS FOR TRASTUZUMAB-EXPOSED HER2-POSITIVE DISEASE
- Lapatinib + capecitabine
- Trastuzumab + other first-line agents
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)

[1]There is no compelling evidence that combination regimens are superior to sequential single agents.
[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first or second line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time to progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 2.2011, 01/05/11 © National Comprehensive Cancer Network, Inc. 2011, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.


Women with oestrogen receptor-positive advanced breast cancer
Rapid tumour response needed?*
Yes
Offer chemotherapy followed by endocrine therapy
No
Menopausal status?
Postmenopausal
Pre/perimenopausal
Patient received adjuvant endocrine therapy?
No
Offer aromatase inhibitor
Yes
Yes
Previously treated with tamoxifen
Previously treated with aromatase inhibitor
Offer aromatase inhibitor
Consider offering chemotherapy
NICE has recommended that more research be done to investigate the most effective endocrine therapy for postmenopausal women with ER-positive tumours who progress on treatment with an aromatase inhibitor
Patient previously treated with tamoxifen?
No
Offer tamoxifen and ovarian suppression
Yes
Offer ovarian suppression
NICE has recommended that more research be done to investigate the effectiveness of ovarian suppression in combination with an aromatase inhibitor compared with that of ovarian suppression in combination with tamoxifen in premenopausal women with ER-positive tumours

THANK YOU