



BREAST CANCER EXPERT
TUMOR BOARD:
CURRENT PRACTICE PATTERNS AND
FUTURE DIRECTIONS



Conflict of Interest Disclosure

Edith A. Perez, MD

Has no real or apparent
conflicts of interest to report.



Case 1

Edith A. Perez, MD
Mayo Clinic, Jacksonville



Case Study

- ❖ 48-year-old otherwise healthy woman diagnosed with a 3 cm infiltrating ductal breast cancer managed with mastectomy
- ❖ Tumor characteristics
 - HER2 normal (IHC 1+ by experienced laboratory)
 - ER negative
 - PR negative
 - Grade 2
 - No lymphovascular invasion
 - 3 involved lymph nodes

HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ER = estrogen receptor;
PR = progesterone receptor.



Adjuvant Management, Follow Up

- ❖ FEC x 3 followed by docetaxel x 3
 - As per best arm of PACS 01 trial
 - Excellent tolerability
- ❖ 12 months later
 - RUQ abdominal pain
 - Normal liver enzymes
 - PET scan
 - Multiple hypermetabolic lesions throughout liver
 - 2 in the lungs
 - Liver biopsy
 - Consistent with original triple-negative breast cancer

FEC = fluorouracil, epirubicin, cyclophosphamide; RUQ = right upper quadrant; PET = positron emission tomography. National Comprehensive Cancer Network (NCCN), 2008.

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Initial Management Considerations

- ❖ Recent proven diagnosis of triple-negative metastatic breast cancer after anthracycline-taxane based adjuvant therapy
- ❖ Visceral involvement (liver, lungs)
- ❖ Excellent performance status and end-organ function

NCCN, 2008.

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Question

- ❖ How would you treat this patient?
- ❖ CMF
- ❖ Gemcitabine
- ❖ Capecitabine
- ❖ Ixabepilone
- ❖ Vinorelbine
- ❖ Ixabepilone + capecitabine
- ❖ Other

CMF = cyclophosphamide, methotrexate, fluorouracil.
NCCN, 2008.

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Triple-Negative Breast Cancer

- ❖ What is it?
 - Molecularly-defined subtype that is biologically distinct from other types of breast cancer
- ❖ How do we treat it now?
 - Conventional adjuvant chemotherapy regimens; new data
- ❖ How will we treat it in the future?

Anders & Carey, 2008.

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Identifying Basal-Like Breast Cancer

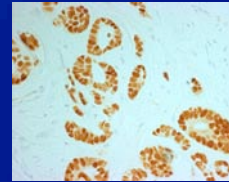
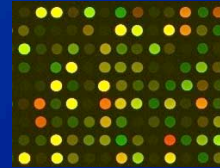
Gene expression array



Immunohistochemical profiling
(eg, ER-, PR-, HER2-, CK5/6+, or EGFR+)



Triple negative
(ER/PR/HER2)



CK = cytokeratin; EGFR = epidermal growth factor receptor.
Anders & Carey, 2008.

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Characteristics of Triple-Negative Breast Cancer

- ❖ Often present as interval cancers
- ❖ Weak relationship between tumor size and node status
- ❖ Rapid rise in risk of recurrence following diagnosis
- ❖ Peak risk of recurrence at 1–3 years
- ❖ Increased mortality rate first 5 years
- ❖ Increased risk of brain metastases
- ❖ Rapid progression from distant recurrence to death
- ❖ Non-validated targets for therapy

Anders & Carey, 2008.

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Therapeutic Strategies for the Management of Triple-Negative Breast Cancer

- ❖ Targeting DNA repair complex
- ❖ Targeting other molecular pathways
 - EGFR
 - VEGF
 - c-KIT, src tyrosine kinase
 - GRB 7
- ❖ Others
 - Androgen receptor
 - TGF β
 - TRAIL

VEGF = vascular endothelial growth factor; TGF β = transforming growth factor beta;
TRAIL = tumor necrosis factor-related apoptosis-inducing ligand.
Rakha et al, 2007; Tan et al, 2008.

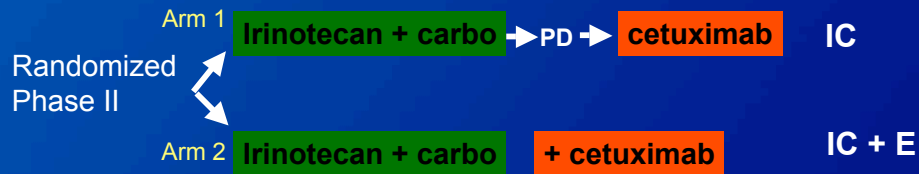
Chemotherapeutic Agents: Double-Strand DNA Breaks

Alkylators	DNA interstrand cross-links → double-strand DNA breaks	Cyclophosphamide
Platinum agents	Form adducts with DNA	Cisplatin Carboplatin Oxaliplatin
Topoisomerase I inhibitors	DNA replication fork arrest	Etoposide Irinotecan Topotecan Mitoxantrone
Topoisomerase II inhibitors	DNA interstrand cross-linking, generation of O ₂ free radicals	Doxorubicin Epirubicin

Kennedy et al, 2004.

Randomized Phase II Irinotecan/Carboplatin + Cetuximab

Stage IV breast cancer, unselected population

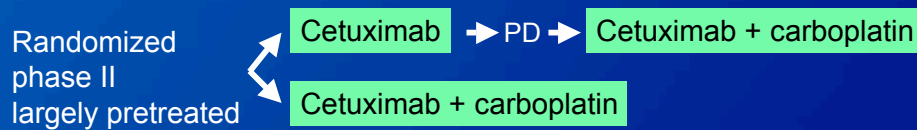


	IC	IC + E
All subjects	21/69 (31%)	26/69 (38%)
Triple negative	10/33 (30%)	19/39 (49%)
ER positive	10/35 (29%)	7/28 (25%)

PD = progressive disease.
O'Shaughnessy et al., 2007.

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Cetuximab/Carboplatin in Stage IV Triple-Negative Breast Cancer



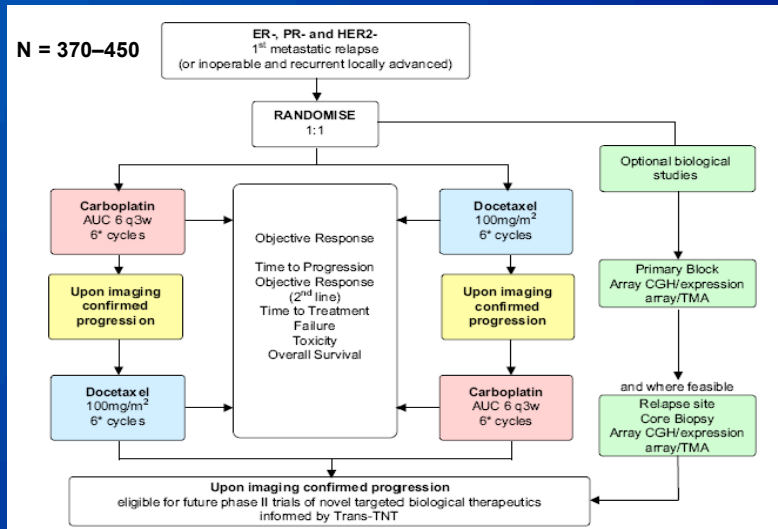
	Cetuximab alone	C and P
N	31	71
CR	-	1%
PR	6%	15%
SD	4%	23%
CB	10%	31%
RR	6%	17%

PFS
triple negative
~ 2 months

PFS = progression-free survival; CR = complete response; PR = partial response; SD = stable disease; CB = clinical benefit;
RR = response rate.
Carey et al., 2008.

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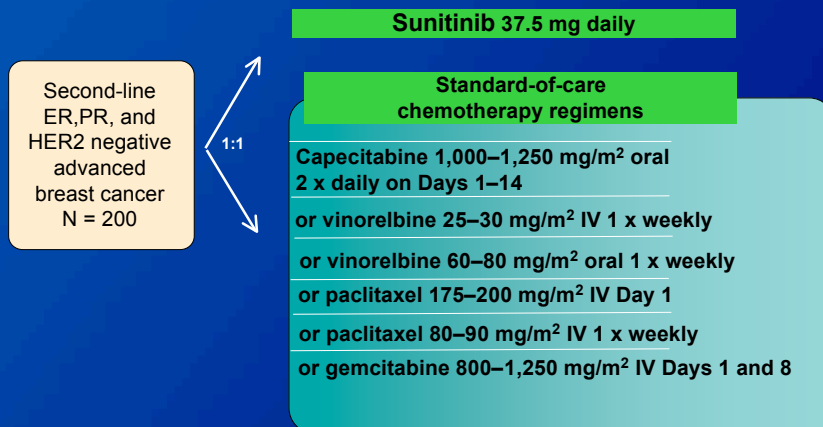
Metastatic Study for Triple-Negative Disease (Carboplatin Vs. Docetaxel)



US National Institutes of Health, 2008a.

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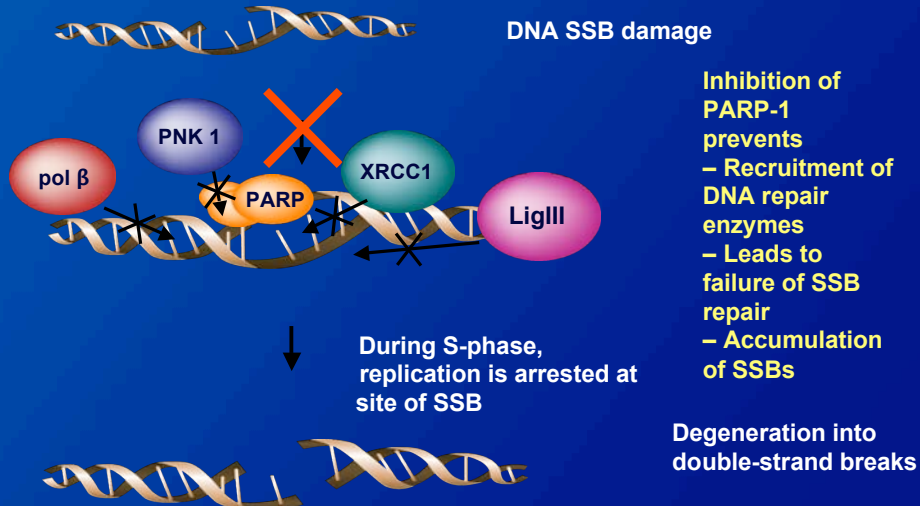
SUN 1077: Sunitinib Vs. Standard of Care in Triple-Negative Advanced Breast Cancer



US National Institutes of Health, 2008b.

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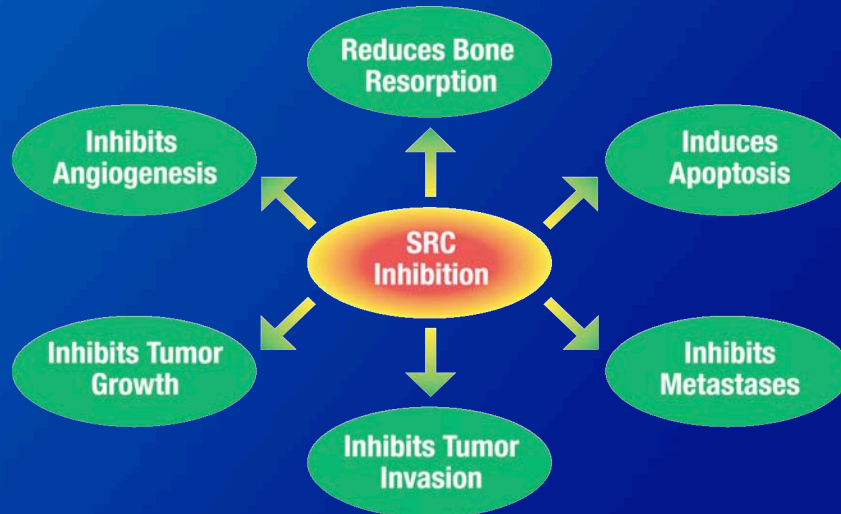
PARP-1: Key Enzyme Involved in Repair of Single-Strand DNA Breaks



SSB = single-strand break; PARP = polymerase; LigIII = ligase III.
Helleday et al, 2005; Helleday et al, 2007.

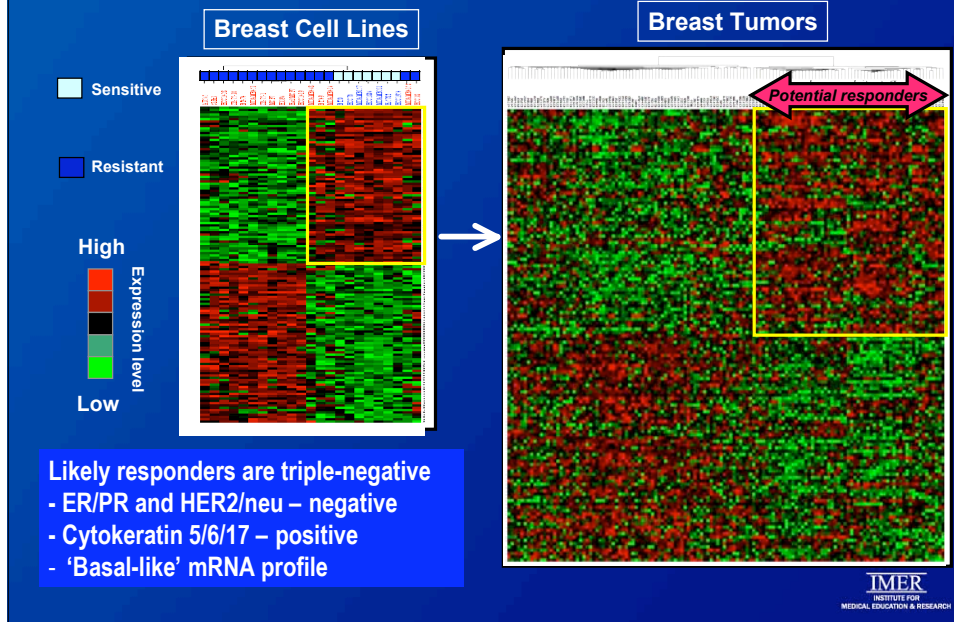
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SRC: Broad Range of Anti-tumor Effects



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“Dasatinib Response Pattern” in Primary Breast Tumors Correlates with T-Neg Subtype



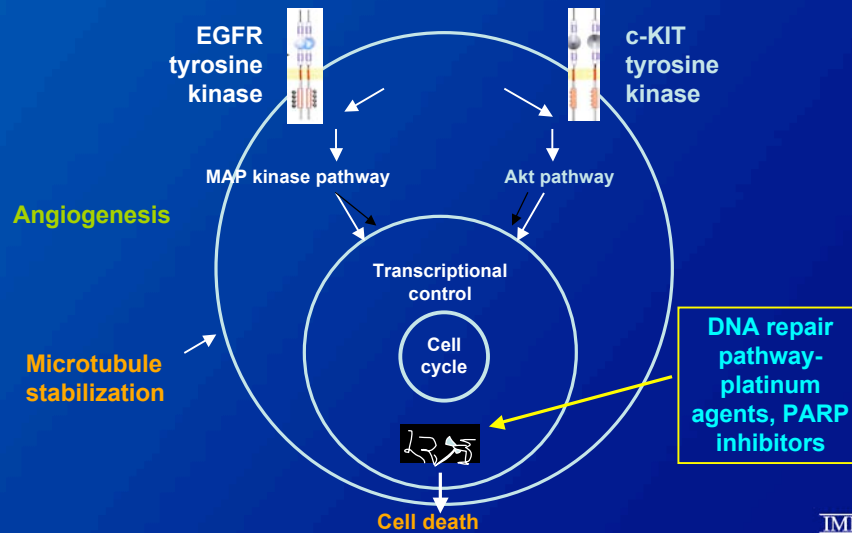
Role of Dasatinib in Triple-Negative Metastatic Breast Cancer

- ❖ Phase II trial of single-agent dasatinib in advanced triple-negative breast cancer
- ❖ Two-stage design with 44
 - Most with 1 prior chemo for metastatic breast cancer
- ❖ Initial dose of 100 mg bid reduced due to tolerability to 70 mg bid (approved dose in advanced CML)
- ❖ Data at SABCS 2008: 5% response rate

bid = twice daily; CML = chronic myeloid leukemia; SABCS = San Antonio Breast Cancer Symposium.
US National Institutes of Health, 2008c; Finn et al, 2008.

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Potential Therapeutic Targets for Triple-Negative Breast Cancer

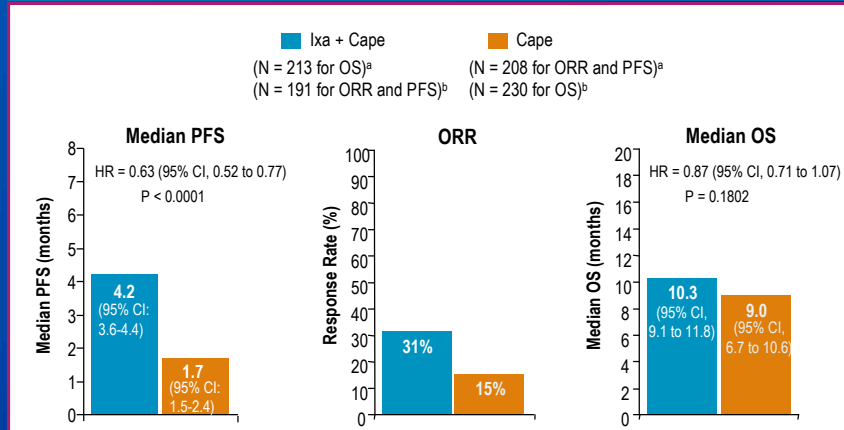


Ixabepilone Plus Capecitabine vs. Capecitabine in Patients with Triple Negative Tumors: A Pooled Analysis of Patients from Two Large Phase III Clinical Studies

Hope S. Rugo, Henri Roche, Eva Thomas, Olivier Rixe, Kimberly Blackwell, H-C Chung, Guillermo L. Lerzo, Lori Volles, Valerie Poulart, Edith Perez

RESULTS: Ixabepilone + Capecitabine vs. Capecitabine Alone

Pooled Analysis of Patients with TN MBC



^a ORR and PFS were computed on all randomized pts in 046 and pts randomized to the measurable disease strata in 048

^b All randomized pts

Rugo et al, 2008.



Conclusions: Ixabepilone + Capecitabine vs. Capecitabine Alone

- ❖ Pooled analysis provides the largest clinical data set recorded for patients with TN MBC
- ❖ In pts with TN MBC, ixabepilone plus capecitabine prolonged the median PFS by 2.5 months, doubled the ORR, but did not significantly increase OS, compared to capecitabine alone
- ❖ Safety of ixabepilone plus capecitabine combination in pts with TN MBC was manageable and similar to the overall population
- ❖ Capecitabine offered little clinical benefit in either ORR or PFS for patients with TN MBC previously treated with an anthracycline and a taxane
- ❖ Promising activity exhibited by ixabepilone plus capecitabine warrants future studies to establish ixabepilone as a preferred treatment option for patients with TN breast cancer

Rugo et al, 2008.



Triple-Negative Breast Cancer: Key Takeaways

- ❖ May have enhanced neoadjuvant response to standard agents, but poor overall prognosis
- ❖ Need studies to validate potential targets
- ❖ Strategies targeting potential BRCA1 pathway dysfunction, such as DNA damaging chemotherapeutic agents, PARP inhibitors, EGFR inhibitors, src inhibitors, newer chemotherapy agents, and anti-angiogenesis agents are ongoing (yet to be validated)
- ❖ Major research focus to identify additional biologically rational targets

What Happened to Our Patient?

- ❖ Treated with combination ixabepilone + capecitabine, on study
 - Based on FDA indication
 - Tumor specimen submitted for predictive testing
 - PET analysis after 2 cycles
 - Significant reduction in liver lesions, disappearance of lung lesions
 - 3 more cycles now administered, solid PR, no more RUQ pain

www.breastcancermarathon.com



- ❖ Marathon
- ❖ Half-marathon
- ❖ Translational breast cancer research
 - Prognosis
 - Prediction
- ❖ Helping underserved women with this disease

**Sunday, February 15, 2009
Jacksonville, Florida**

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Panel Discussion

- ❖ Does adjuvant treatment choice matter?
- ❖ Is there a correct treatment choice for this patient with recurrent MBC?

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Conflict of Interest Disclosure

Clifford A. Hudis, MD

Reported a financial interest/relationship or affiliation in the form of: *Consultant*, Amgen, Inc., Bristol-Myers Squibb Company, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer, Inc. and sanofi-aventis U.S.; *Contracted Research*, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, and Onyx Pharmaceuticals Inc.



Case 2

Clifford Hudis, MD
Memorial Sloan-Kettering Cancer Center



Case Study

- ❖ 54-year-old woman presented in July 2006 with invasive ductal carcinoma
 - 2.2 cm
 - ER positive
 - HER2 positive (FISH 3.0)
 - Involvement of two axillary lymph nodes

ER = estrogen receptor; HER2 = human epidermal growth factor receptor; FISH = fluorescent in situ hybridization.



Adjuvant Treatment Options

- ❖ Hormone therapy
 - AI or tamoxifen
- ❖ Trastuzumab
- ❖ Chemotherapy
 - AC followed by a taxane/trastuzumab
 - Standard or dose-dense
 - TCH
 - Other regimens

AI = aromatase inhibitor; AC = doxorubicin/cyclophosphamide; TCH = docetaxel, carboplatin, and trastuzumab.



Case Study (cont.)

- ❖ Adjuvant treatment
 - AC followed by dose-dense paclitaxel/trastuzumab
 - Anastrozole
 - Radiation therapy
- ❖ She returns in January 2008 with
 - Mild fatigue
 - Elevated alkaline phosphatase
 - Extent of disease reveals two bone lesions (left femur and pelvis) and 1.5 cm suspicious liver metastases
 - A biopsy of the liver confirms ER-positive, HER2-positive adenocarcinoma consistent with known breast primary

Metastatic Treatment Options

- ❖ Hormone therapy
- ❖ Trastuzumab
- ❖ Chemotherapy
- ❖ Combination

TAnDEM: Evaluation of Anastrozole Plus Trastuzumab

Postmenopausal women with HER2-positive (IHC 3+ and/or FISH-positive) and ER- and/or PR-positive MBC

Anastrozole 1 mg/day PO^a
(n = 104)

Anastrozole 1 mg/day PO
Trastuzumab 4 mg/kg IV on Day 1
then 2 mg/kg weekly
(n = 103)

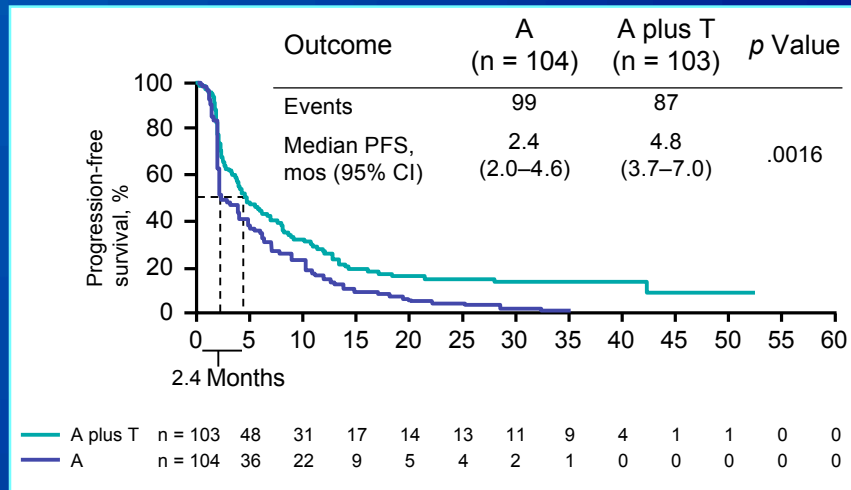
Progressive disease

^aTrastuzumab offered to patients who progressed on anastrozole alone.

IHC = immunohistochemistry; MBC = metastatic breast cancer; IV = intravenously.
Mackey et al. 2006

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TAnDEM: PFS in MBC Patients Treated With A Plus T Combination

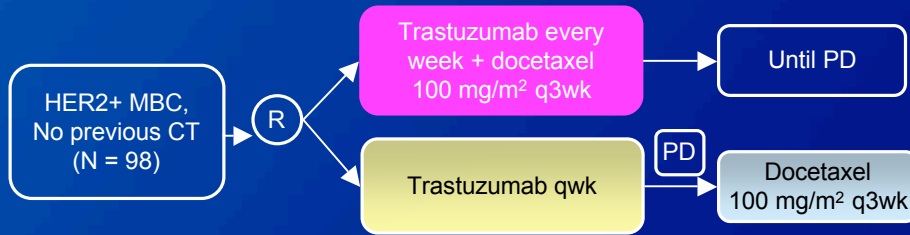


PFS = progression-free survival.
Mackey et al, 2006.

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Should Trastuzumab Be Combined With Chemotherapy?

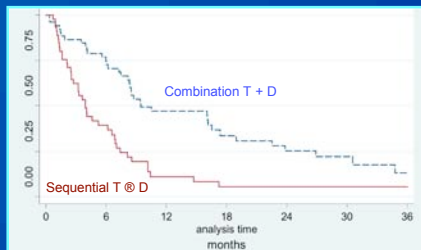
HERTAX Study Design



CT = chemotherapy; PD = progression of disease; R = randomization; q = every; wk = week.
 Botenbal et al., 2008.



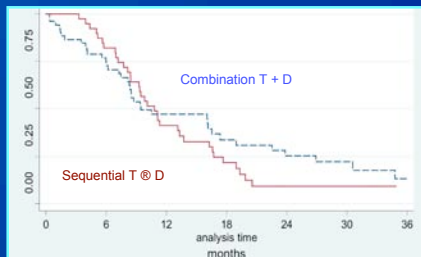
Median Time to First Progression



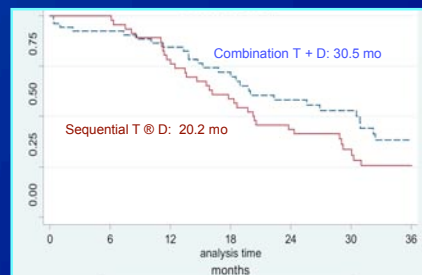
Concurrent Versus Sequential Therapy With Docetaxel and Trastuzumab in HER2+ MBC

--- Combination therapy (DT)
 --- Monotherapy (T)

Progression-Free Survival



Overall Survival



Botenbal et al., 2008.



Case Study (cont.)

- ❖ Treatment
 - Docetaxel + trastuzumab q3wk for 7 months
- ❖ August 2008: Now what?

National Comprehensive Cancer Network, 2008.

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Question

Is there a correct treatment choice for this patient?

1. Vinorelbine/trastuzumab
2. Capecitabine/trastuzumab
3. Capecitabine/lapatinib
4. Trastuzumab/lapatinib
5. Albumin-bound paclitaxel
6. Gemcitabine
7. Other

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Study Design

HER2+ LABC or
MBC with prior
exposure to an
anthracycline, a
taxane, and
trastuzumab^a

N = 528

Stratification

- Disease sites
- Stage of disease

R
A
N
D
O
M
I
Z
E

Lapatinib 1,250 mg PO qd
continuously +
capecitabine 2,000 mg/m²/d
PO Days 1–14 q3wk

Capecitabine 2,500 mg/m²/d
PO Days 1–14 q3wk

Patients receive treatment until
progression or unacceptable toxicity,
then followed for survival

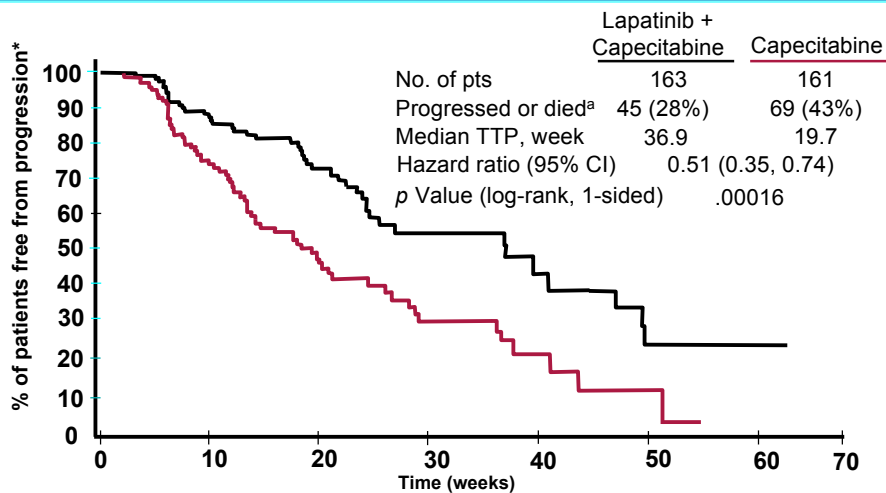
^aTrastuzumab must have been administered for metastatic disease

LABC = locally advanced breast cancer; d = day.

Geyer et al, 2006.

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Time to Progression – ITT Population



^aCensors 4 patients who died due to causes other than breast cancer

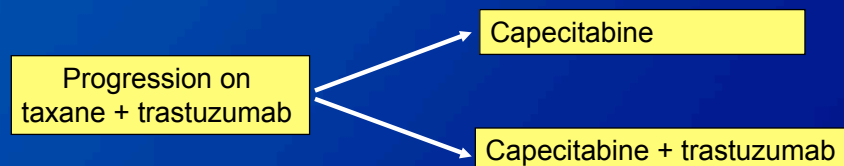
TTP = time to progression.
Geyer et al, 2006.

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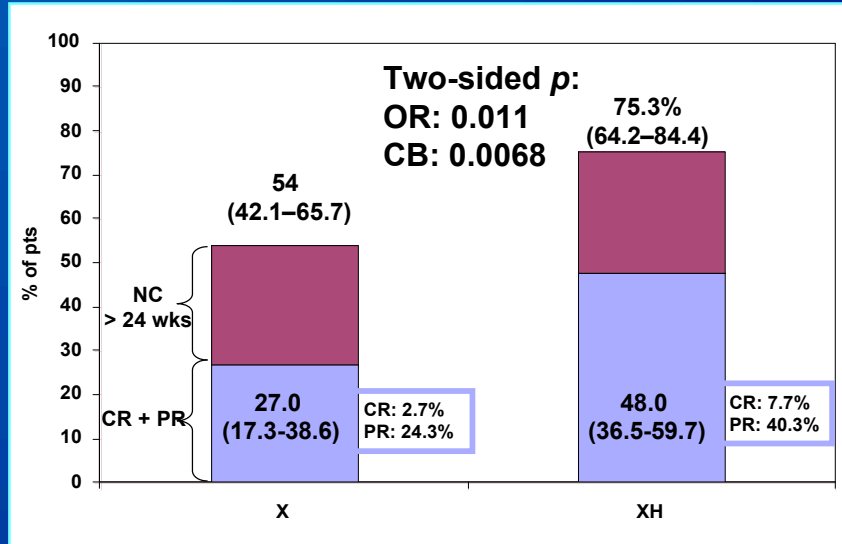


Is it Lapatinib or HER2 Targeting?

German Breast Group Trial GBG 26/BIG 3-05 (Closed Early With Poor Accrual)



Clinical Response (RECIST)

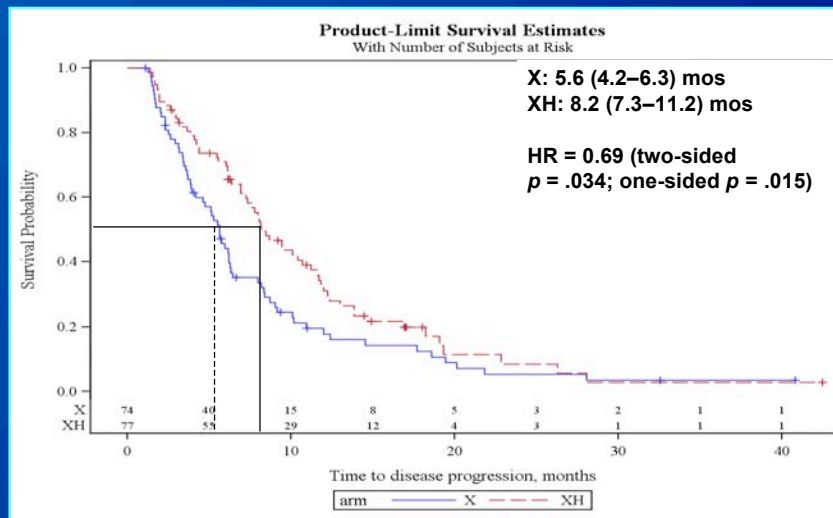


OR = overall response; CB = clinical benefit; CR = complete response; PR = partial response; NC = no change.
 OR defined as CR + PR; CB defined as CR + PR + NC > 24 weeks.

Von Minckwitz et al, 2008.



Time to Progression

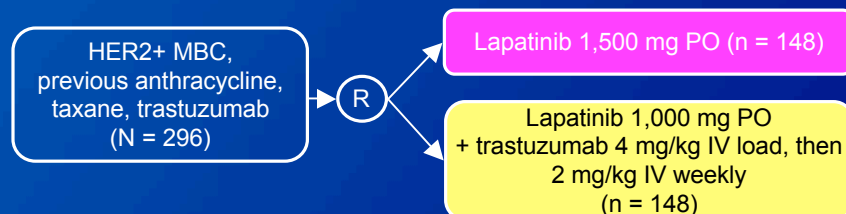


Median follow-up: 15.6 mos

Von Minckwitz et al, 2008.



Should HER2-Targeting Agents Be Combined in Advanced Breast Cancer?



	Lapatinib	Lapatinib + Trastuzumab	Odds Ratio	p Value
Response rate	6.9	10.3	1.5	.46
Clinical benefit rate	12.4	24.7	2.2	.01

O'Shaughnessy et al, 2008.

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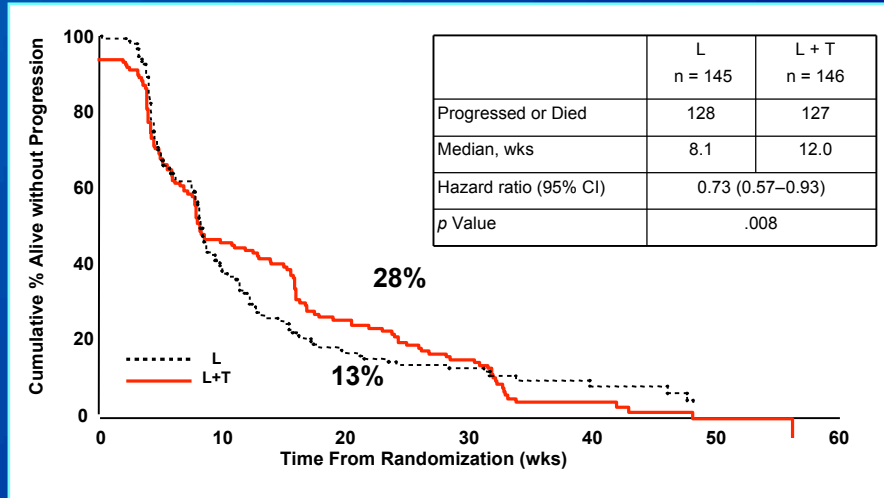
Patient and Tumor Characteristics

Study Arms	L	L + T
ITT Population	n = 148	n = 148
Median age in years (range)	51 (29–78)	52 (26–81)
% ECOG performance status 0/1/2	47/49/4	54/41/5
Median prior CT regimens	4	5
% Patients ≥ 6 prior regimens	28	34
Median prior trastuzumab regimens for MBC	3	3
Median time from last trastuzumab (days)	25	27
No. of patients HER2+	146	147
% ER and PgR negative	51	51
% Visceral disease	74	71

ECOG = Eastern Cooperative Oncology Group; L = lapatinib; T = trastuzumab; PgR = progesterone receptor.
O'Shaughnessy et al, 2008.

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Progression-Free Survival



O'Shaughnessy et al, 2008.

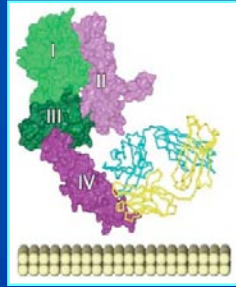
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Newer Drugs Targeting HER2 Used in Combination With Trastuzumab

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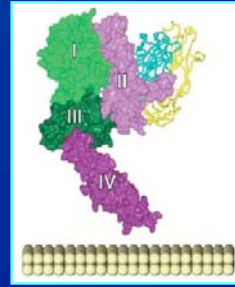
Trastuzumab and Pertuzumab Bind to Distinct Epitopes on HER2 Extracellular Domain

Trastuzumab



- ❖ Activates antibody-dependent cellular cytotoxicity
- ❖ Enhances HER2 internalization
- ❖ Inhibits angiogenesis

Pertuzumab

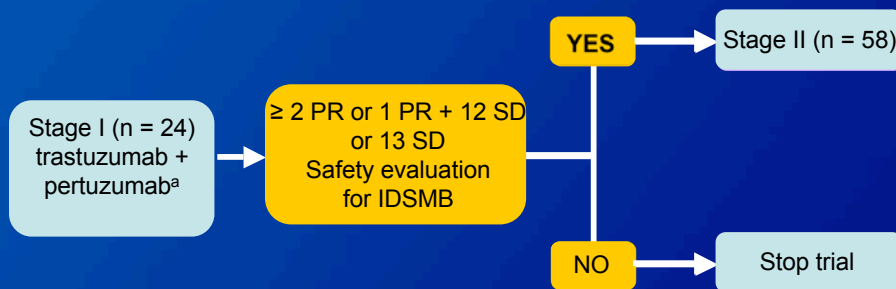


- ❖ Activates antibody-dependent cellular cytotoxicity
- ❖ Prevents receptor dimerization
- ❖ Potent inhibitor of HER-mediated signaling pathways

Hubbard, 2005.

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Phase II Trial of Pertuzumab + Trastuzumab in HER2+ Patients Progressing on Trastuzumab



^aT: 4 mg/kg loading dose → 2 mg/kg qw or 8 mg/kg loading dose → 6 mg/kg q3w;
P: 840 mg loading dose → 420 mg q3w
SD = stable disease; IDSMB = International Data and Safety Monitoring Board.

Baselga et al, 2007.

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Pertuzumab Phase II Study Efficacy Data: Best Overall Response

Response	n (%)
	n = 33
Complete response	1 (3.0)
Partial response	5 (15.2)
Overall response rate	6 (18.2)
Stable disease for 6 mos (\geq cycle 8)	7 (21.2)
Clinical benefit rate	13 (39.4)
Stable disease (< 6 mos)	10 (30.3)
Progressive disease	10 (30.3)

Baselga et al, 2007.

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Anatomy of Trastuzumab-DM1

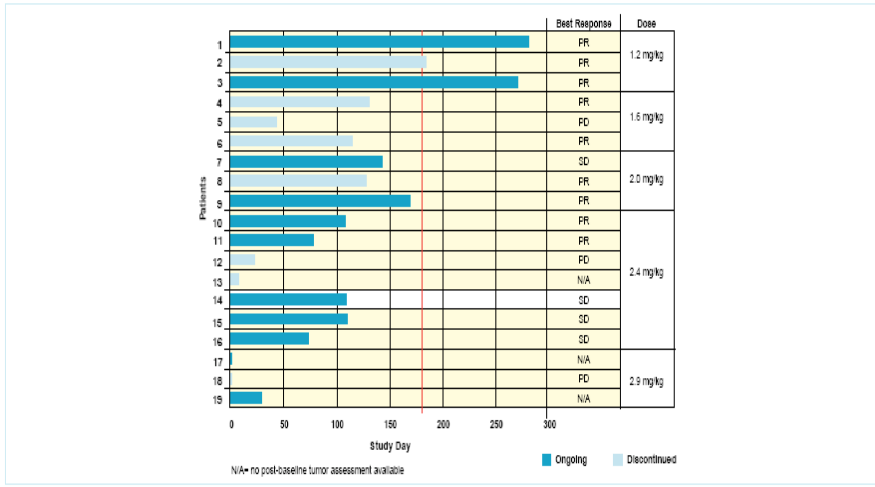


Beeram et al, 2008.

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Weekly Trastuzumab-DM1

Figure 2. Duration of therapy. Yellow shading indicates patients who had measurable disease at baseline.

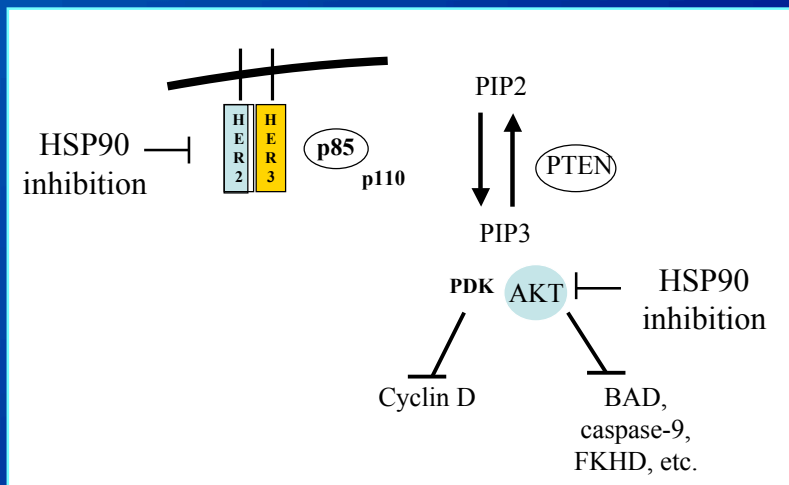


Holden et al., 2008.



HER2 Pathway: HSP90 Inhibition

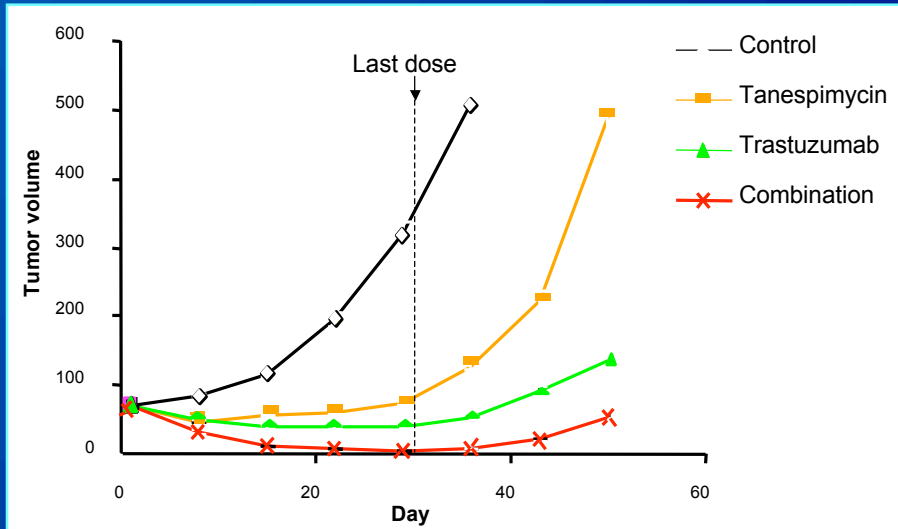
- ❖ Disrupts multiple oncogenic clients simultaneously



HSP = heat shock protein.
N Rosen personal communication, n.d.



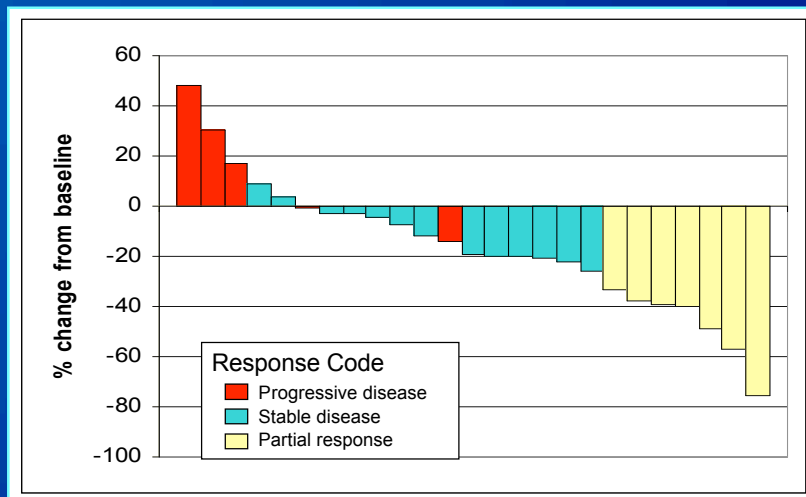
Multiple Targeting of HER2 Signaling Using Tanespimycin Plus Trastuzumab: BT-474 HER2+ Xenograft



Solit et al, in press.

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Phase II: Best Response and Target Lesion Change (n = 25)^a



^aOne additional patient had complete regression of a single target lesion but overall response of progressive disease based on non-target lesions. One patient withdrawn for clinical progression without radiological assessment.

Modi et al, 2008.

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Panel Discussion

- ❖ Does adjuvant treatment choice matter?
- ❖ Is there a correct treatment choice for this patient?

Conflict of Interest Disclosure

Jose Baselga, MD

Reported a financial interest/relationship or affiliation in the form of: *Consultant*, Exelixis, Inc., Novartis Pharmaceuticals Corporation, and Merck & Co., Inc.; *Contracted Research*, GlaxoSmithKline.



Case 3

José Baselga, MD
Vall d'Hebron University Hospital
Barcelona, Spain



Case Study

- ❖ 61-year-old woman presented in March 2005
- ❖ 3-cm ER-positive, HER2-negative infiltrating ductal carcinoma
- ❖ 5/18 axillary lymph nodes

ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2.



Adjuvant Therapy

❖ Options

- Chemotherapy (Europe)
 - FEC/FAC or similar
 - AC→taxane (paclitaxel or docetaxel)
 - AT→CMF
- Hormone therapy
 - AI or tamoxifen

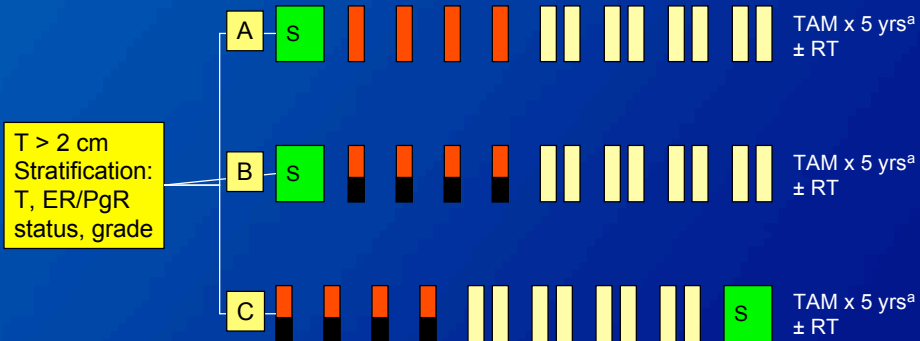
❖ Adjuvant treatment was

- AT→CMF
- Followed by radiation therapy and anastrozole

FEC = 5-fluorouracil (5-FU), epirubicin, cyclophosphamide; FAC = 5-FU, doxorubicin, cyclophosphamide; AC = anthracycline/cyclophosphamide; AT = doxorubicin/paclitaxel; CMF = cyclophosphamide, methotrexate, 5-FU; AI = aromatase inhibitor.



ECTO Study Design



A vs. B; B vs. C. Endpoints: Disease-free and overall survival

^aSince December 2000 in only women whose tumors were ER-positive and/or PgR-positive.

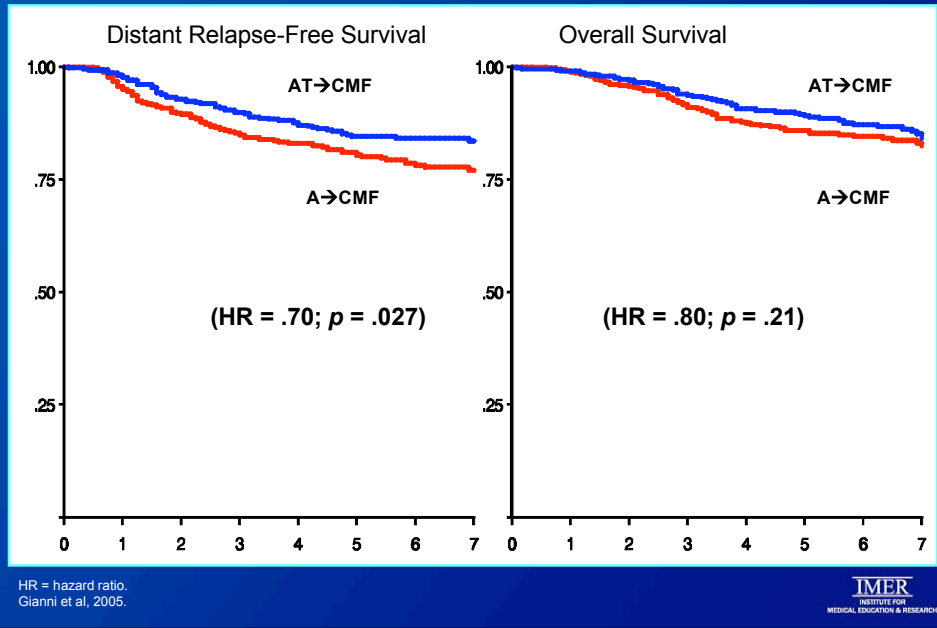
N = 1,350



ECTO = European Cooperative Trial in Operable breast cancer; T = Tumor; PgR = progesterone receptor; TAM = tamoxifen; RT = radiation therapy; AT = doxorubicin/paclitaxel. Gianni et al, 2005.



ECTO Study Results



Case Study (cont.)

- ❖ June 2007 presents with retrosternal pain
- ❖ KPS 90%
- ❖ Pain controlled with mild analgesics
- ❖ Disease work-up shows recurrence in lymph nodes and sternum

KPS = Karnofsky performance status.

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Metastatic Therapy Options in the First-Line Setting

❖ Hormone therapy

- AI
- Fulvestrant

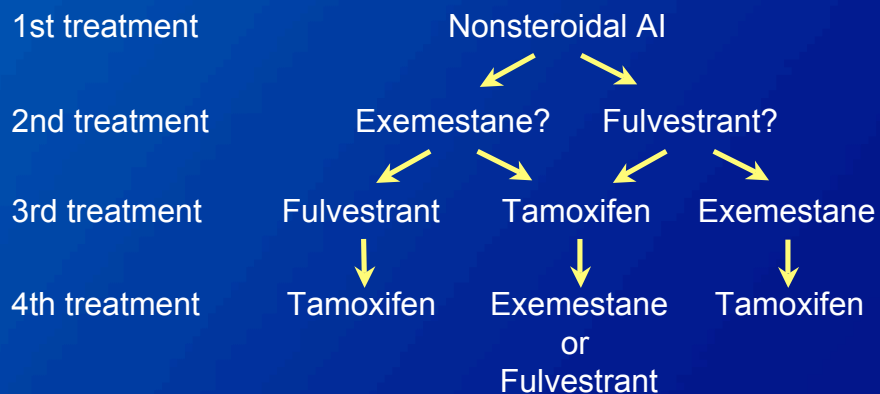
❖ Chemotherapy*

- Taxanes
 - Paclitaxel
 - Docetaxel
 - Albumin-bound paclitaxel
- Antimetabolites
 - Capecitabine
 - Gemcitabine
- Other microtubule inhibitors
 - Vinorelbine
- Others

* Preferred single agents; NCCN, 2008.



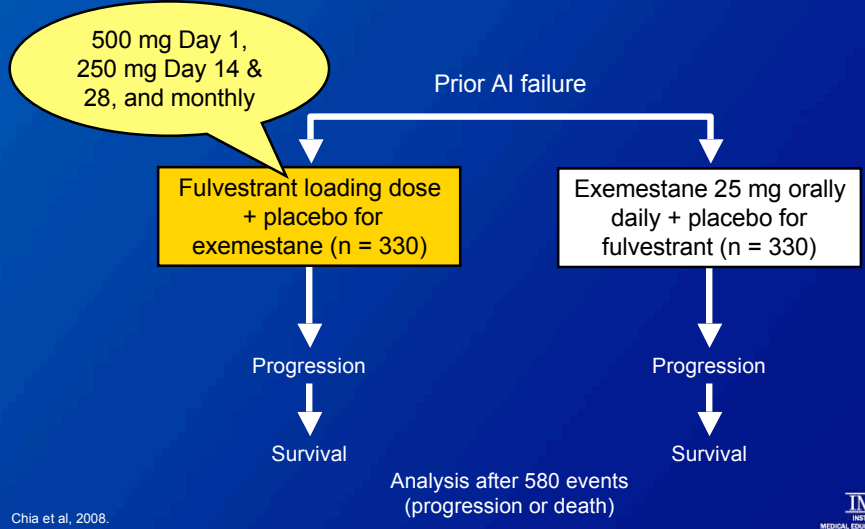
Options Following Adjuvant/First-Line Nonsteroidal AI



NCCN, 2008.



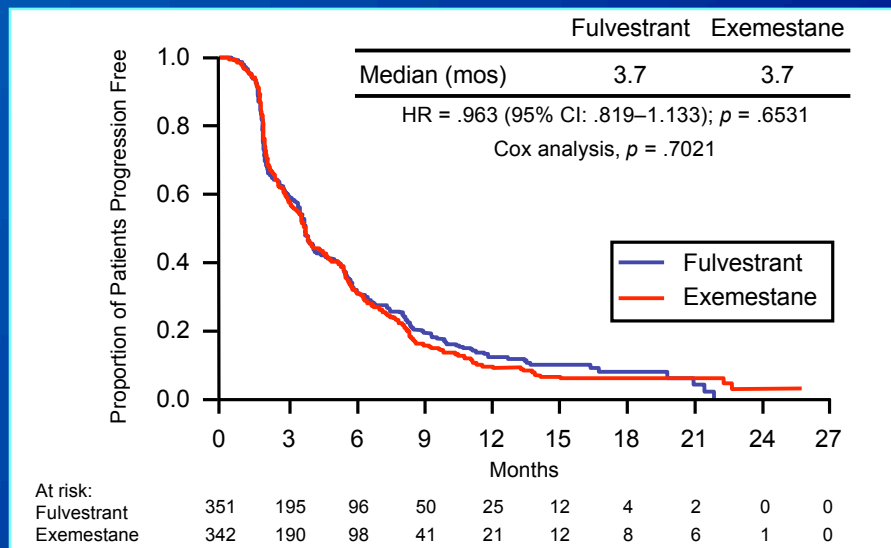
EFACT: Evaluation of Faslodex and Exemestane Clinical Trial



Chia et al., 2008.



Time to Progression (ITT)



CI = confidence interval; ITT = intent to treat.
Chia et al., 2008.



Objective Response and Clinical Benefit Rate

	Fulvestrant	Exemestane	Odds Ratio ^a (95% CI)	p Value
ORR (CR + PR)	7.4% (20/270)	6.7% (18/270)	1.120 (0.578–2.186)	.7364
CBR (OR + SD ≥ 24 wks)	32.2% (87/270)	31.5% (85/270)	1.035 (0.720–1.487)	.8534

^aAnalyses are not adjusted for baseline covariates.

ORR = overall response rate; CR = complete response; PR = partial response; CBR = clinical benefit rate; SD = stable disease.
Chia et al, 2008.



Case Study (cont.)

- ❖ November 2007 presents with increased fatigue
- ❖ KPS 80%
- ❖ Mild elevation of LFTs
- ❖ CT scan of the liver shows several metastatic lesions consistent with progression of disease

LFTs = liver function test; CT = computed tomography.



Now What?

- ❖ Gemcitabine-based therapy
- ❖ Vinorelbine-based therapy
- ❖ Capecitabine-based therapy
- ❖ Taxane-based therapy
- ❖ Other

NCCN, 2008.

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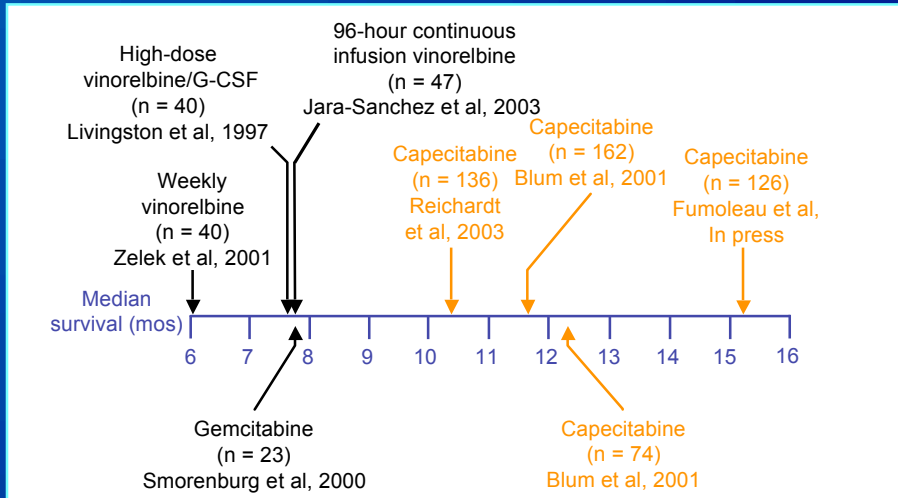
Capecitabine: Activity in Pretreated MBC

	CR + PR (%)	ORR + SD (%)	Median TTP (mos)	Median OS (mos)
Blum (n = 162)	20	73	3.0	12.6
Blum (n = 74)	26	57	3.2	12.2
Reichardt (n = 136)	15	62	3.5	10.1
Fumoleau (n = 126)	28	63	4.9	15.2
Maung (n = 230)	19	N/A	4.1	N/A

MBC = metastatic breast cancer; TTP = time to progression; OS = overall survival.
Blum et al, 2001; Reichardt et al, 2003; Fumoleau et al, 2003; Maung, 2003.

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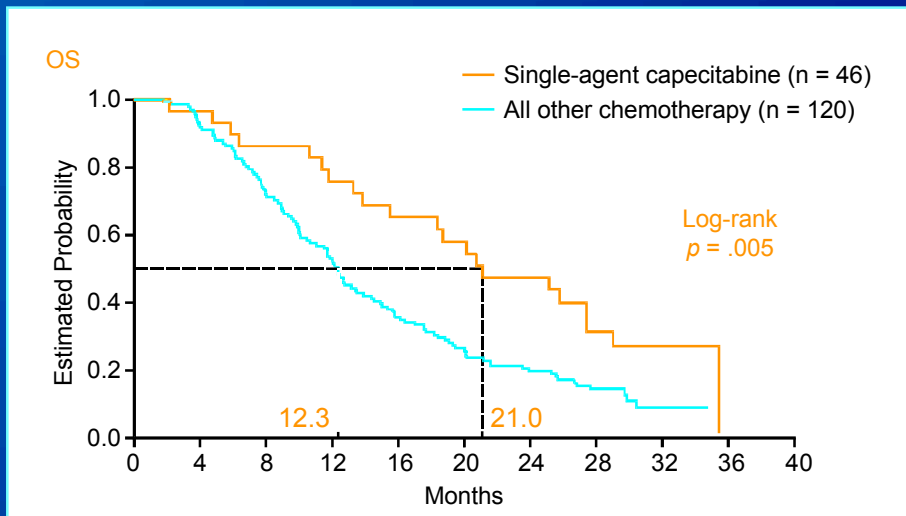
Capecitabine: Superior OS to Gemcitabine and Vinorelbine



G-CSF = granulocyte-colony stimulating factor.



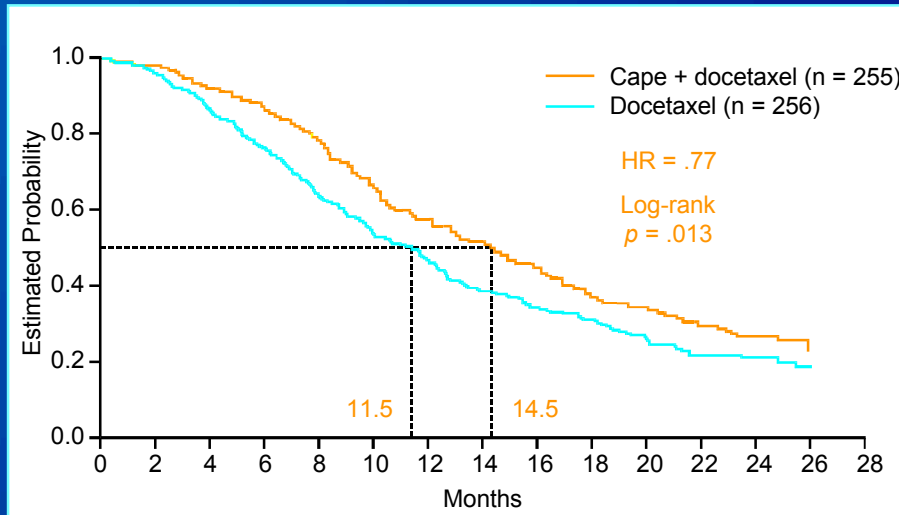
Capecitabine After Docetaxel



Miles et al, 2001.



Capecitabine and Docetaxel in Combination



O'Shaughnessy et al, 2002.

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Case Study (cont.)

- ❖ Patient received capecitabine (2,000 mg/m²) and docetaxel (60 mg/m²) achieving a response at the end of the second cycle
- ❖ Five months later (May 2008), she presents with progression of disease in the liver
- ❖ KPS 80%

Xeloda® (prescribing information), 2006; Taxotere® (prescribing information), 2006.

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Question

How would you now treat this patient?

1. Cyclophosphamide
2. Mitoxantrone
3. Ixabepilone
4. Oral etoposide
5. Cisplatin
6. Other

NCCN, 2008


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Treatment of MBC After Anthracyclines, Taxanes, and Capecitabine

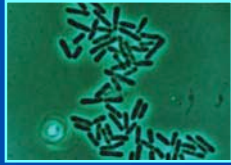
- ❖ Several chemotherapeutic options are available
- ❖ There are a lack of prospective data in this patient population

Donato et al, 2007.

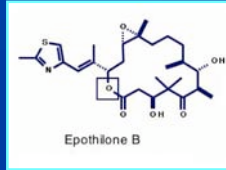

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Epothilones: Ixabepilone (BMS-247550)

- ❖ New antineoplastic class - the natural epothilones and their analogs



S. cellulosum



Epothilone B



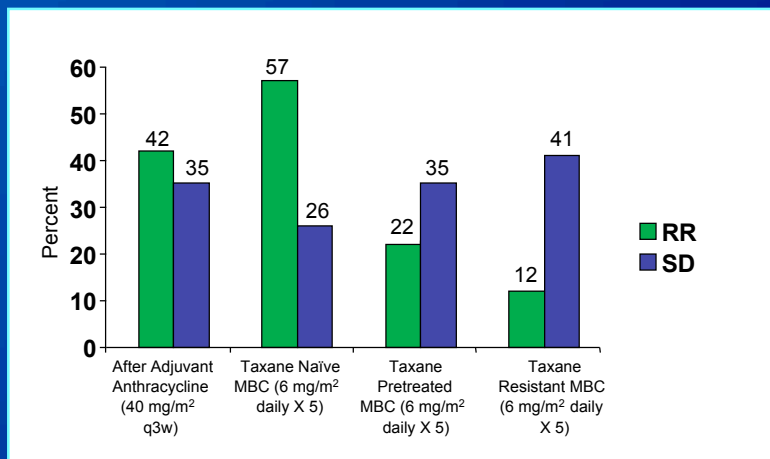
Ixabepilone
(BMS-247550)

- ❖ 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 preclinical synergy with capecitabine

MRP = multidrug resistance-associated protein; P-gp = P-glycoprotein.
Vadhat, 2008.

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Ixabepilone in MBC: Summary of Single-Agent Phase II Trials



RR = response rate; q = every; w = week
Roche et al, 2007; Denduluri et al, 2007; Low et al, 2005; Thomas et al, 2007.

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Registrational Studies

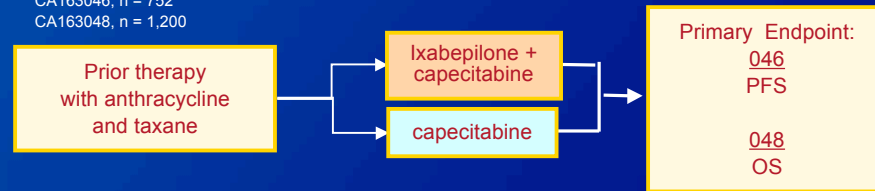
Phase II: Single-agent ixabepilone in triple-refractory patients

CA163081, n = 126



Phase III: Ixabepilone plus capecitabine

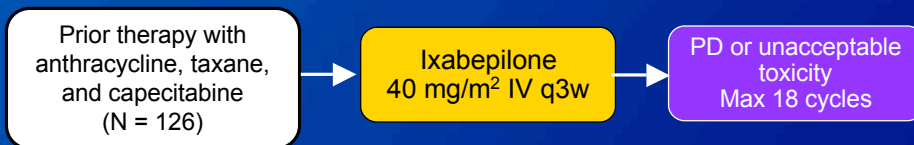
CA163046, n = 752
CA163048, n = 1,200



PFS = progression-free survival.
Perez et al, 2007; Vadhat et al, 2007; Hortobagyi et al, 2008.



Phase II Study 081: Ixabepilone in Triple-Refractory MBC



Primary endpoint: ORR

❖ Resistance Criteria

- Neoadjuvant or adjuvant: ≤ 6 months of last dose
- Metastatic: ≤ 8 weeks of last dose
- Progression during or after discontinuation of trastuzumab in HER2+ patients

IV = intravenously; PD = progression of disease.
Perez et al, 2007.



Phase II Study 081: Ixabepilone in Triple-Refractory MBC

Characteristic	Patients, no. (%) (N = 126)
Median age (min–max) in years	51 (30–78)
Visceral disease (liver and/or lung)	97 (77)
No. of disease sites: 3–4	62 (49)
≥ 5	19 (15)
ER-, PR-, HER2-	42 (33)
Prior neoadjuvant/adjuvant chemotherapy	95 (75)
No. of prior chemotherapy regimens for metastatic disease	
1	15 (12)
2	51 (40)
3	60 (48)
No. of prior taxane-containing regimens	
Any	126 (100)
≥ 2	38 (30)
≥ 3	7 (6)

Perez et al, 2007.



Phase II Study 081: Efficacy

	Response-Evaluable (n = 113)
Tumor response rate, % (95% CI)	
IRR assessment	12.4 (6.9–19.9)
Investigator assessment	18.6 (18.3–26.2)
Median response duration, mos (95% CI)	6.0 (5.0–7.6)
Stable disease rate, %	49.6
Median duration of stable disease, mos (95% CI)	4.5 (3.7–6.0)
	Treated Patients (n = 126)
Median PFS, mos (95% CI)	3.2 (2.8–4.3)
Median survival, mos (95% CI)	9.0 (7.3–11.2)

IRR - independent radiology review.
Perez et al, 2007.



Phase II Study 081: Safety

Grade 3/4 Toxicity	% of Patients (n = 126)
<i>Hematologic</i>	
Neutropenia	54
Febrile neutropenia	2
Leukopenia	49
Anemia	8
Thrombocytopenia	7
<i>Nonhematologic</i>	
Peripheral sensory neuropathy	14
Fatigue	13
Myalgia/arthralgia	8
Stomatitis	6

Perez et al., 2007.

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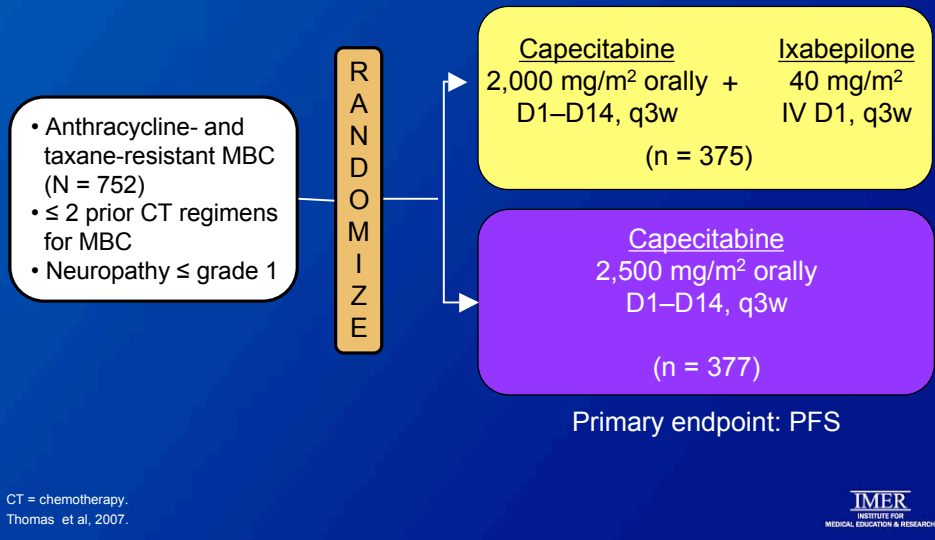
Conclusions

- ❖ This is the first large prospective trial in triple-therapy refractory MBC
- ❖ Ixabepilone demonstrates efficacy in patients with anthracycline-, taxane-, and capecitabine-refractory MBC
 - Overall population
 - Median PFS: 3.2 months
 - Median OS: 9 months
 - RR: 18%
- ❖ Safety profile is acceptable
- ❖ In summary, ixabepilone represents a new choice for patients with triple-therapy refractory MBC

Perez et al., 2007

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Phase III Trial 046: Capecitabine ± Ixabepilone in Anthracycline-Pretreated, Taxane-Resistant MBC



Patient Eligibility Criteria

❖ Inclusion Criteria

- Women ≥ 18 years
- Locally advanced or MBC
- Anthracycline-resistant or minimum cumulative dose
- Taxane-resistant
- KPS 70–100
- Life expectancy ≥ 12 wk

❖ Exclusion Criteria

- > 3 prior chemo regimens (adjuvant and metastatic)
- ≥ G2 motor/sensory neuropathy
- Reduced hematologic/renal function
- ≥ G2 LFTs^a
- CNS metastases

^aProtocol amendment excluded patients with ≥ G2 liver function tests regardless of liver metastases; 377 patients (33 with ≥ G2 LFTs) had been enrolled before amendment.
 CNS = central nervous system; G = grade.
 Thomas et al, 2007.

Capecitabine ± Ixabepilone Study 046: Clinical Eligibility Criteria for Resistance

- ❖ Strict definition: Patients whose tumors rapidly progressed in the adjuvant or metastatic setting after receiving both anthracyclines and taxanes

Setting	Anthracycline	Taxane
Metastatic	≤ 3 months of last dose	≤ 4 months of last dose
Neo/adjuvant	≤ 6 months of last dose	≤ 12 months of last dose
Any	Minimum cumulative dose Doxorubicin: 240 mg/m ² Epirubicin: 360 mg/m ²	

Thomas et al, 2007.



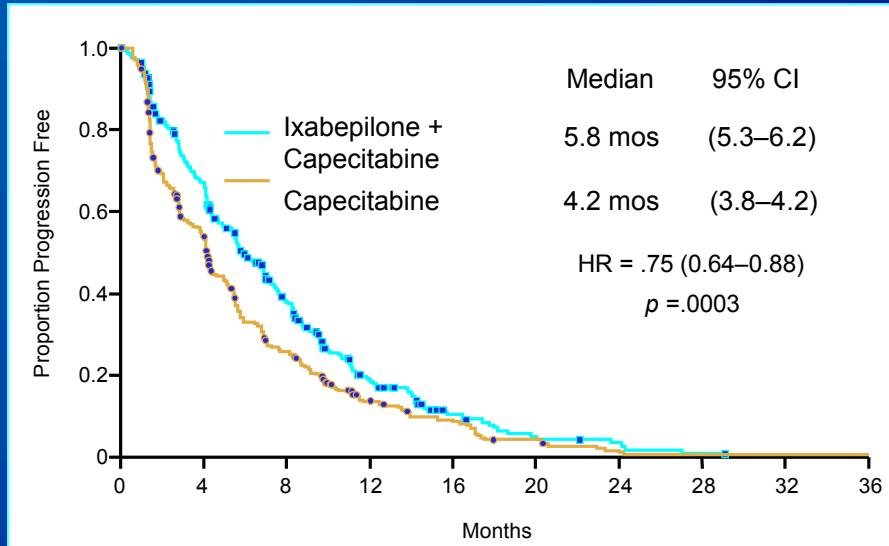
Capecitabine ± Ixabepilone Study 046: Key Baseline Patient Demographics

Characteristic	Patients, no. (%)	
	Ixabepilone + Capecitabine (n = 375)	Capecitabine (n = 377)
Median age (min–max) in years	53 (25–76)	52 (25–79)
Visceral disease (liver and/or lung)	316 (84)	315 (84)
≥ 2 disease sites	332 (89)	341 (90)
ER-, PR-, HER2-	91 (24)	96 (26)
Prior neoadjuvant/adjuvant chemotherapy	282 (75)	285 (76)
No. of prior chemotherapy regimens for metastatic disease		
0	27 (7)	33 (9)
1	179 (48)	184 (49)
2	152 (41)	138 (37)
≥ 3	17 (5)	22 (6)
Anthracycline resistance	164 (44)	165 (44)
Taxane resistance		
Neoadjuvant/adjuvant setting	40 (11)	44 (12)
Metastatic setting	327 (87)	319 (85)
Progressive disease as best response to prior taxane	144 (38)	130 (35)

Thomas et al, 2007.



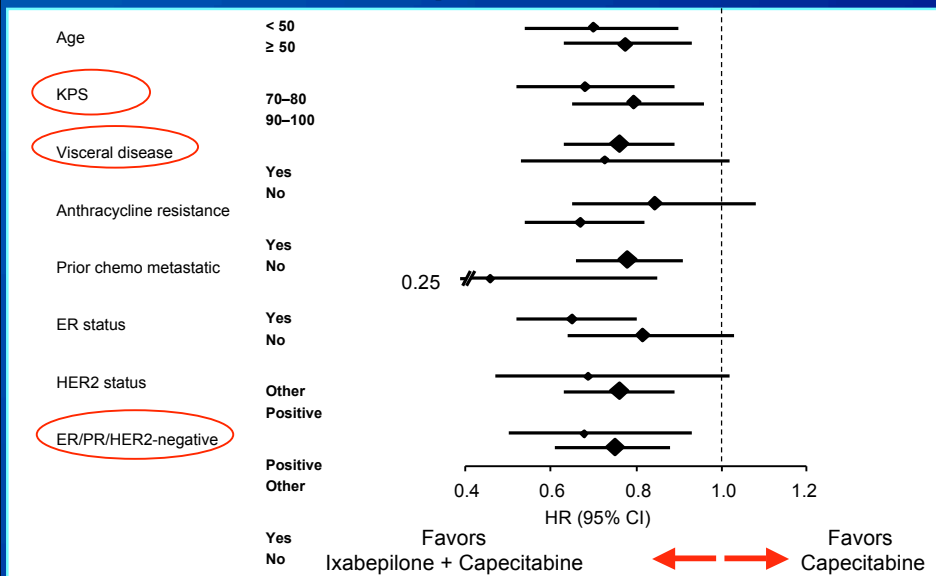
PFS: Total Population



Thomas et al, 2007.

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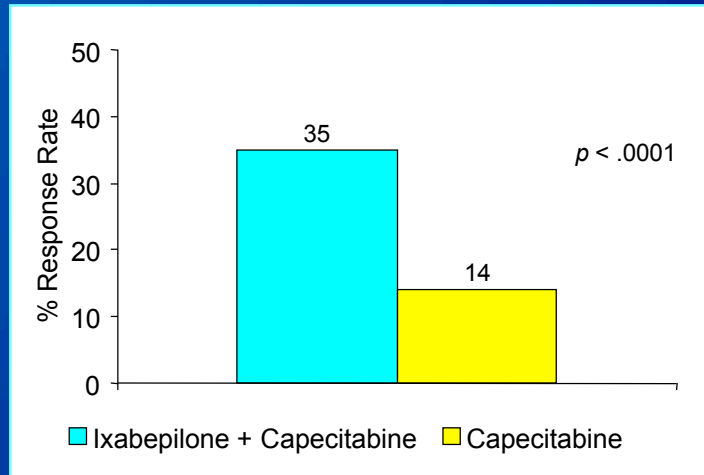
PFS in Prespecified Subsets



Thomas et al, 2007.

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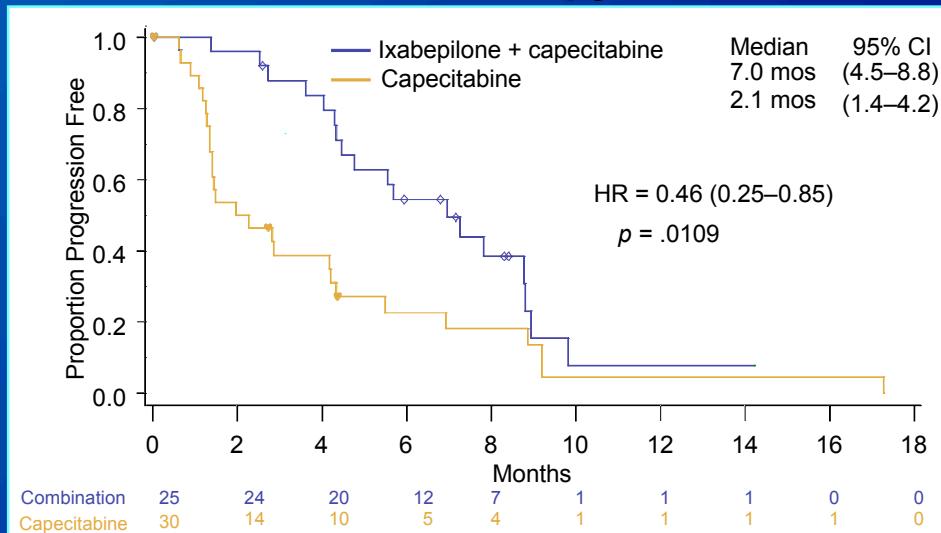
Response Rate: Total population



Thomas et al, 2007.

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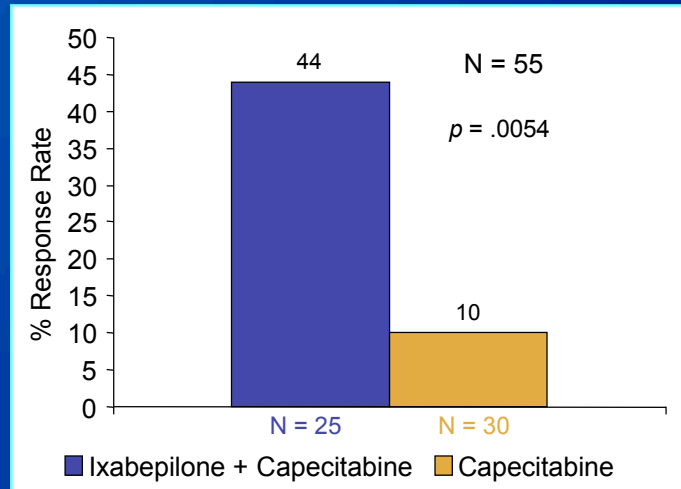
Ixabepilone Plus Capecitabine as First-Line Therapy: PFS



Thomas et al, 2007.

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Ixabepilone Plus Capecitabine as First-Line Therapy: Response Rate



Thomas et al, 2007.

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Capecitabine ± Ixabepilone Phase III Study 046: Safety

Grade 3/4 Toxicity	% of Patients	
	Cape + Ixa (n = 369)	Cape (n = 368)
<i>Hematologic</i>		
Neutropenia	68	11
Febrile Neutropenia	4	1
Leukopenia	57	6
Anemia	10	5
Thrombocytopenia	8	4
<i>Nonhematologic</i>		
Peripheral sensory neuropathy ^a	21	0
Hand-foot syndrome	18	17
Fatigue	9	4
Diarrhea	6	9

^aGrade 3/4 peripheral neuropathy 23% (21% sensory and 5% motor).
Thomas et al, 2007.

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Conclusions

- ❖ A combination of ixabepilone plus capecitabine demonstrates superior efficacy compared to capecitabine alone in patients with MBC
 - Overall population
 - Improvement in median PFS from 4.2 months to 5.8 months (HR = 0.75)
 - 2.5-fold increase in ORR (35% vs. 14%)
 - Ixabepilone plus capecitabine as first-line treatment
 - Improvement in median PFS from 2.1 months to 7.0 months (HR = 0.46)
 - 4.4-fold increase in ORR (44% vs. 10%)
- ❖ Manageable safety profile
- ❖ Ixabepilone plus capecitabine represents a new choice in the treatment of patients with HER2/neu-negative anthracycline-taxane resistant breast cancer

Thomas et al , 2007.


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046/048 Phase III MBC Trials: Ixabepilone and Capecitabine Combination

- ❖ Pivotal trial CA163-046:
 - Patients prospectively defined using a strict definition of resistance to previous anthracycline and taxane therapy
- ❖ Confirmatory trial CA163-048:
 - Patients with metastatic disease who were pretreated with or resistant to an anthracycline and a taxane
 - 50% met strict resistance criteria in pivotal trial

Hortobagyi et al, 2008.


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046/048 Phase III MBC Trials: Study Design

Metastatic/locally advanced breast cancer pretreated with or resistant to taxanes and anthracyclines

Ixabepilone
(40 mg/m² IV over 3 hr D1 q3wk)
+

Capecitabine
(2,000 mg/m²/day BID 14 days q3wk)

Capecitabine
(2,500 mg/m²/day BID 14 days q3wk)

BID = twice daily.
Hortobagyi et al., 2008.

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046/048 Phase III Trials:PFS

	Study 046		Study 048	
	Ixa + Cape n = 375	Cape n = 377	Ixa + Cape n = 480	Cape n = 480
Median PFS, mos	5.26	3.81	6.24	4.40
HR (95% CI)	0.78 (0.67–0.91)		0.79 (0.69–0.90)	
Stratified log-rank p value	.0011		.0005	

Hortobagyi et al., 2008.

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046/048 Phase III Trials: Objective Response Rate

	Study 046 ^a		Study 048	
	Ixa + Cape n = 375	Cape n = 377	Ixa + Cape n = 462	Cape n = 462
Objective response rate, %	42.1	22.5	43.3	28.8
95% CI	37.1–47.3	18.4–27.1	38.7–47.9	24.7–33.2
Best response, N (%)				
Complete response	12 (3)	3 (1)	16 (3)	11 (2)
Partial response	146 (39)	82 (22)	184 (40)	122 (26)
Stable disease	136 (36)	144 (38)	170 (37)	182 (39)
Progressive disease	51 (14)	109 (29)	57 (12)	111 (24)
Unable to determine	30 (8)	39 (10)	35 (8)	36 (8)

^aObjective response rate in 046 presented by investigator assessment.
Hortobagyi et al, 2008.

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046/048 Phase III Trials: OS

	Study 046		Study 048	
	Ixa + Cape n = 375	Cape n = 377	Ixa + Cape n = 609	Cape n = 612
Median OS, mos	12.9	11.1	16.4	15.6
No. of events	318	321	430	450
HR (95% CI)	0.90 (0.77–1.05)		0.90 (0.78–1.03)	
Stratified log-rank p value	.1936		.1162	

Hortobagyi et al, 2008.

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Panel Discussion

- ❖ Does adjuvant treatment choice matter?
- ❖ Is there a correct treatment choice for this patient with recurrent MBC?



Conflict of Interest Disclosure

Linda T. Vahdat, MD

Reported a financial interest/relationship or affiliation in the form of: *Consultant*, Eisai Inc. and Bristol-Myers Squibb Company; *Speakers' Bureau*, Bristol-Myers Squibb Company; *Contracted Research*, Eisai Inc., Bristol-Myers Squibb Company, Pfizer, Inc., CuraGen Corporation, and Merck & Co. Inc.





Case 4

Linda Vahdat, MD
Weill Medical College of Cornell University



Case Study

- ❖ 68-year-old woman with a prior history of inflammatory breast cancer in 2000
- ❖ Her left breast biopsy indicated poorly differentiated invasive ductal cancer with dermal lymphatic invasion
- ❖ ER/PR negative
- ❖ HER2/neu
 - 3+ by DAKO
- ❖ Treatment
 - Neoadjuvant doxorubicin/cyclophosphamide followed by weekly paclitaxel x 4 cycles (all given every 3 weeks)
 - LMRM: Residual tumor 1.5 cm
 - 3/38 nodes with tumor emboli in breast tissue
 - CWRT

ER = estrogen receptor; PR = progesterone receptor; LMRM = left modified radical mastectomy; CWRT = chest wall radiation therapy.
Mehta et al., 2005.



Case Study (cont.)

- ❖ August 2007
- ❖ Large mass superior to mastectomy scar and nodules on chest wall
- ❖ Interferes with work
- ❖ Biopsy positive for breast cancer
- ❖ ER/PR negative and HER2/neu 3+ by DAKO
- ❖ CT CAP and bone scan (+ lung metastasis)

CT = computed tomography; CAP = chest, abdomen, pelvis.

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Question

What would be your treatment choice for this patient?

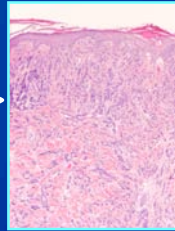
1. Best supportive care
2. Clinical trial
3. Trastuzumab alone
4. Trastuzumab plus chemotherapy
5. Combination of chemotherapeutic agents

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Patient Case: Clinical Studies



Chest wall disease



Skin biopsy



Chest radiograph

Images courtesy of Linda Vahdat, MD.

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Treatment Options for Stage IV Breast Cancer

Standard treatments

1. Chemotherapy
2. Hormonal therapy
3. Radiation therapy
4. Biologic therapy

Clinical trials

1. Phase I trials
2. Phase II trials
3. Phase III trials

NCI, 2008.

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Treatment for Advanced Breast Cancer

- ❖ No standard approach
- ❖ Many options
- ❖ QOL important endpoint
- ❖ Site-specific palliation frequently used
 - VAT
 - Bisphosphonates
- ❖ Many good clinical trials are available

QOL = quality of life; VAT = video-assisted thoracoscopy.

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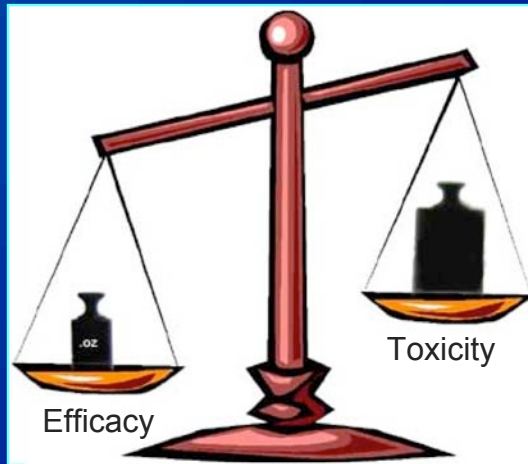
Management of Advanced Breast Cancer: Efficacy Versus Toxicity



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Case Study (cont.)

- ❖ Symptomatic from disease
- ❖ “Long” disease-free interval



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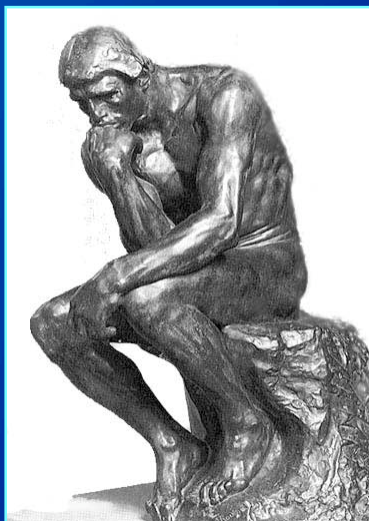
Consideration Points

- ❖ Prior anthracycline/taxane use
- ❖ No prior history of trastuzumab use
- ❖ Disease-free interval 7 years
- ❖ Becoming symptomatic from her breast cancer
- ❖ Has a good KPS

KPS = Karnofsky performance status.

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Options?



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Potential Options

- ❖ Chemotherapy alone
 - Single agent
 - Combination chemotherapy
- ❖ Chemotherapy + biologic
 - HER2/neu directed therapy
 - Lapatinib versus trastuzumab
 - Bevacizumab
- ❖ Biologics alone

NCCN, 2008.

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Chemotherapy Issues

- ❖ Single agent versus combination chemotherapy
 - With combination
 - Higher RR
 - Greater TTP
 - Increased toxicity
 - Minimal impact (if any) on OS

RR = response rate; TTP = time to progression; OS = overall survival.
NCCN, 2008.



First-Line Monotherapy Regimens in Advanced Breast Cancer

Regimen	No. Patients	RR (%)	TTP (months)	OS (months)
Capecitabine ¹	61	30	4.1	19.6
Gemcitabine ²	47	29	8.1	18.6
Vinorelbine ³	145	41	6	18
Paclitaxel ⁴	224	25	3.6	12.7
Docetaxel ⁴	225	32	5.7	15.4
<i>nab</i> -Paclitaxel ⁵	76	33	10	–
Ixabepilone ⁶	65	42	8.2	22

¹O'Shaughnessy et al, 2001; ²Spielman et al, 2001; ³Fumoleau et al, 1993; ⁴Jones et al, 2005; ⁵Gradishar et al, 2006; ⁶Roche et al, 2007.



Phase III Trials of Single Versus Combination Chemotherapy

Regimen	No. Patients	RR (%)	TTP (months)	OS (months)
E 1193¹				
Doxorubicin	224	36	5.6	19
Paclitaxel	229	34	5.8	22
Combination	230	47	8	22
Docetaxel ²	256	30	4.2	11.5
Docetaxel + capecitabine ²	255	42	6.1	14.5
Paclitaxel ³	262	26	2.9	15.8
Gemcitabine + paclitaxel ³	267	32	5.2	18.5

¹Sledge et al, 2003; ²O'Shaughnessy et al, 2002; ³Albain et al, 2004.

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Chemotherapy Alone Is Not the Best Option

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Chemotherapy + Biologic

- ❖ Chemotherapy + HER2/neu directed therapy
- ❖ Randomized data
 - With taxanes (trastuzumab and lapatinib): First line
 - With doxorubicin (trastuzumab): First line
 - Capecitabine (lapatinib): > first line
- ❖ Phase II data with other chemotherapeutic agents
 - Capecitabine (trastuzumab and lapatinib)
 - Vinorelbine (trastuzumab)
 - Gemcitabine (trastuzumab)
 - Ixabepilone (trastuzumab)

Chia et al, 2006; Chan et al, 2007; Lee et al, 2005; Beltran et al, 2007; Geyer et al, 2006; Burstein et al, 2008.



First-Line Therapy in MBC: Trastuzumab Trials

Chemotherapy	No. Patients	RR (%)		TTP (months)	
		Chemotherapy	Chemotherapy + trastuzumab	Chemotherapy	Chemotherapy + trastuzumab
Docetaxel	186	34	61	6.1	11.7
Paclitaxel	188	17	41	3.0	6.9
Paclitaxel	124	56	75	9.1	12.3
Doxorubicin	241	42	56	6.1	7.8

MBC = metastatic breast cancer.
Marty et al, 2005; Slamon et al, 2001.



Phase III Trials of Lapatinib in MBC

First line

Chemotherapy	No. Patients	RR (%)		TTP (months)	
		Chemotherapy	Chemotherapy + lapatinib	Chemotherapy	Chemotherapy + lapatinib
Capecitabine	324	14	22	4.3	5.9
Paclitaxel	86	17	41	6.1	9.0

Geyer et al, 2006; Cameron et al, 2008; Di Leo et al, 2008.

Biologics Alone

- ❖ Trastuzumab alone
- ❖ Lapatinib alone
- ❖ Trastuzumab + lapatinib
- ❖ Trastuzumab + bevacizumab

Burstein et al, 2008; O'Shaughnessy et al, 2008; Pegram et al, 2007.

Biologic Therapy in HER2/neu MBC

Drug	Setting	No. Patients	RR (%)	SD (%)	TTP (months)
Trastuzumab ¹	First line	114	26	12	3.8
Lapatinib ²	First line	138	24	31	5
Lapatinib ³	No limit ^a	140	4.3	6	2.1
Lapatinib + trastuzumab ⁴	No limit ^b	296	10.3	15	3
Lapatinib + bevacizumab ⁵	No limit ^c	31	14	50	–

^aPrior number of chemotherapy regimens 4.

^bPrior number of chemotherapy regimens 6.

^cOngoing trial.

SD = stable disease.

¹Vogel et al, 2002; ²Gomez et al, 2008; ³Burstein et al, 2008; ⁴O'Shaughnessy et al, 2008; ⁵Rugo et al, 2008.

Case Study (cont.)

- ❖ Treated with docetaxel and trastuzumab
- ❖ Initial partial regression of chest wall nodules (lung nodules lasting 6 months)
- ❖ Options after failure of first-line trastuzumab + chemotherapy

Question

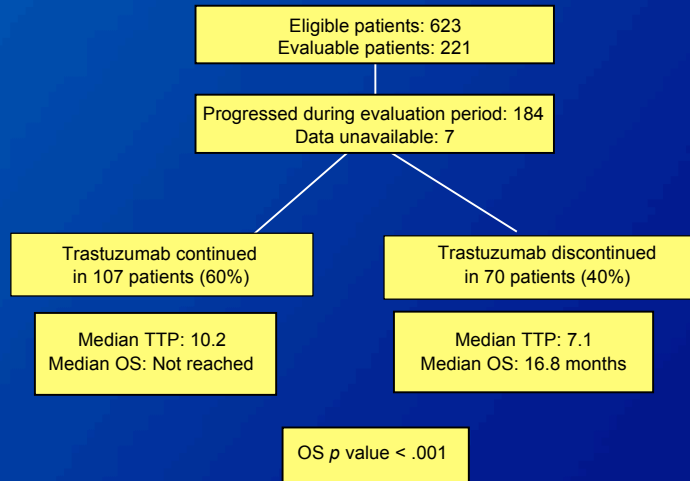
What would be your treatment choice for this patient be now?

1. Continue trastuzumab, discontinue chemotherapy
2. Change trastuzumab to lapatinib/capecitabine
3. Continue trastuzumab, change chemotherapy

French Hermine Cohort Study

- ❖ Research question
 - In the first-line setting of MBC, evaluate outcome (TTP, OS) of those who discontinued trastuzumab at progression versus those who continued
- ❖ Additional information
 - Retrospective and prospective observational study
 - 102 oncologists in practice
 - Patients started with trastuzumab from January through December, 2002
 - Data collection from November, 2003 to March, 2005

French Hermine Cohort Study (cont.)



Extra et al, 2006.

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Options

- ❖ Favor continuing HER2/neu directed therapy
 - Continue trastuzumab
 - Stop trastuzumab and begin lapatinib

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Phase III Study of Capecitabine ± Lapatinib

HER2+ LABC or
MBC with prior
exposure to an
anthracycline, a
taxane, and
trastuzumab^a
N = 528

R
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Lapatinib 1,250 mg po every day
continuously +
Capecitabine 2,000 mg/m²/d
po Days 1–14 every 3 weeks

Capecitabine 2,500 mg/m²/d po
Days 1–14 every 3 weeks

Patients on treatment until
progression or unacceptable toxicity,
then followed for survival

^aTrastuzumab must have been administered for metastatic disease.
LABC = locally advanced breast cancer; PO = by mouth.
Geyer et al, 2006.

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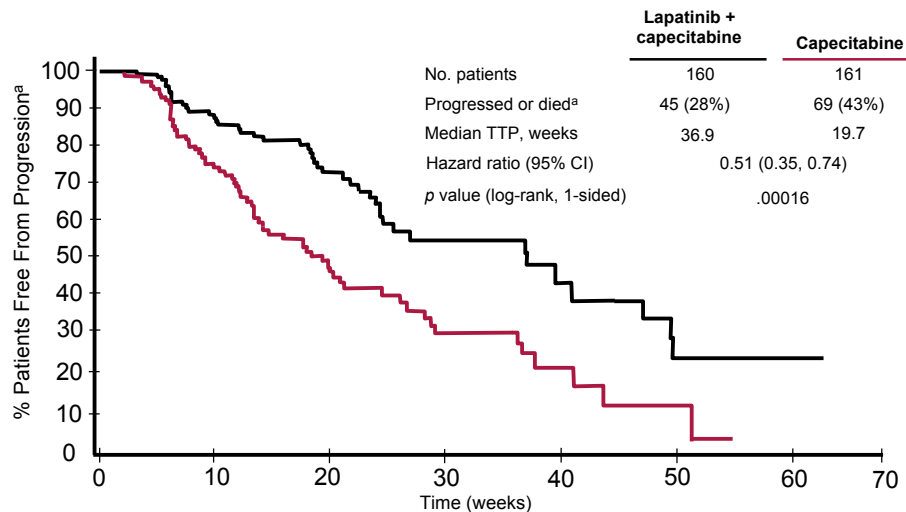
Phase III Study Capecitabine ± Lapatinib: Prior Therapy

	Lapatinib + Capecitabine (n = 163)	Capecitabine (n = 161)
Anthracyclines	158 (97%)	156 (97%)
Taxanes	159 (98%)	156 (97%)
Trastuzumab	157 (96%)	156 (97%)
– 98% “Resistant”		
– Prior adjuvant/ neoadjuvant use	7 (4%)	9 (6%)
– Median duration (range)	42 weeks (3–296)	44 weeks (5–329)

Geyer et al, 2006.

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Phase III Study Capecitabine ± Lapatinib: TTP (ITT Population)



^aCensors 4 patients who died due to causes other than breast cancer. Geyer et al, 2006.



Phase III Study Capecitabine ± Lapatinib: Adverse Events

Table 3. Adverse Events.

Event	Lapatinib plus Capecitabine (N=164)					Capecitabine Alone (N=152)					P Value ^a
	Grade 1	Grade 2	Grade 3	Grade 4 [†]	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4 [†]	Any Grade	
	Number of events (percent)										
Diarrhea	44 (27)	33 (20)	19 (12)	2 (1)	98 (60)	21 (14)	22 (14)	17 (11)	0	60 (39)	<.0001
Nausea	48 (29)	22 (13)	3 (2)	0	73 (44)	42 (28)	18 (12)	3 (2)	0	63 (42)	0.83
Vomiting	30 (18)	10 (6)	3 (2)	0	43 (26)	22 (14)	11 (7)	3 (2)	0	37 (24)	0.80
Stomatitis	17 (10)	7 (4)	0	0	24 (15)	12 (8)	5 (3)	1 (<1)	0	18 (12)	0.57
Abdominal pain	13 (8)	10 (6)	2 (1)	0	25 (15)	17 (11)	13 (9)	2 (1)	0	32 (21)	0.23
Constipation	14 (9)	2 (1)	0	0	16 (10)	15 (9)	3 (2)	1 (<1)	0	17 (11)	0.82
Dyspepsia	13 (8)	5 (3)	0	0	18 (11)	4 (3)	1 (<1)	0	0	5 (3)	0.014
Hand-foot syndrome	16 (10)	22 (13)	12 (7)	0	50 (30)	18 (12)	22 (14)	10 (7)	0	50 (33)	1.00
Rash	32 (20)	11 (7)	2 (1)	0	45 (27)	14 (9)	7 (5)	2 (1)	0	23 (15)	0.01
Dry skin	18 (11)	0	0	0	18 (11)	6 (4)	2 (1)	0	0	8 (5)	0.10
Fatigue	16 (10)	10 (6)	3 (2)	0	29 (18)	17 (11)	18 (12)	5 (3)	1 (<1)	41 (27)	0.06
Mucosal inflammation	11 (7)	7 (4)	0	0	18 (11)	7 (5)	9 (6)	3 (2)	0	19 (12)	0.80
Asthenia	6 (4)	4 (2)	0	0	10 (6)	7 (5)	8 (5)	3 (2)	0	18 (12)	0.11
Headache	9 (5)	6 (4)	0	0	15 (9)	13 (9)	4 (3)	1 (<1)	1 (<1)	20 (13)	0.34
Pain in extremity	13 (8)	6 (4)	1 (<1)	0	21 (13)	9 (6)	2 (1)	1 (<1)	0	13 (9)	0.30
Back pain	9 (5)	6 (4)	2 (1)	0	17 (10)	5 (3)	3 (2)	1 (<1)	0	9 (6)	0.22
Anorexia	18 (11)	6 (4)	1 (<1)	0	25 (15)	21 (14)	8 (5)	1 (<1)	0	30 (20)	0.37
Dyspnea	8 (5)	5 (3)	5 (3)	0	18 (11)	4 (3)	3 (2)	3 (2)	0	10 (7)	0.24

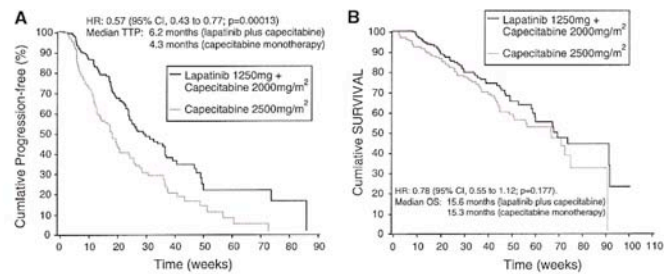
^a P values were calculated with Fisher's exact test for differences in toxicities of any grade.
[†] A total of 13 grade 4 adverse events occurred among 10 (6%) of the patients receiving lapatinib plus capecitabine, and 16 grade 4 adverse events occurred among 11 (7%) of the patients receiving capecitabine alone. These differences are not significant.
[‡] The number includes one event with an unknown grade.

Geyer et al, 2006.



Updated Results

Fig. 2 Kaplan-Meier estimates of time to progression (a) (five patients with competing risk were censored for purposes of generating the Kaplan-Meier curve) and overall survival (b) in ITT population by Independent Review Committee



Cameron et al, 2008.

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Case Study (cont.)

- ❖ Second-line regimen
 - She began lapatinib and capecitabine as second-line therapy for HER2/neu-positive breast cancer
 - Doing well with good tumor response for 7 months followed by slow progression in mass superior to mastectomy scar

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Many New Agents Targeting HER2/neu

- ❖ HKI-272
- ❖ Pertuzumab
- ❖ T-DM1

US National Institutes of Health, 2008d; Hudis, 2007.

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Panel Discussion

- ❖ Does adjuvant treatment choice matter?
- ❖ Is there a correct treatment choice for this patient?

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Thank You!



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