

**Advances in the Management of
METASTATIC BREAST CANCER**

Hormonal Therapy and Targeted Agents

Faculty

- **Debu Tripathy, MD (chair)**
Professor of Medicine
Director, Breast Cancer Research Program
University of Texas Southwestern Medical Center, Dallas, TX
- **Lyndsay N. Harris, MD**
Associate Professor of Medicine, Medical Oncology
Director, Yale Cancer Center Breast Cancer Program
Yale School of Medicine, New Haven, CT
- **Hope S. Rugo, MD**
Clinical Professor of Medicine
Director, Breast Oncology Clinical Trials Program
Div. of Hematology and Oncology, Cancer Research Institute
University of California, San Francisco

At the conclusion of this activity, participants should be able to:

- Explain and discuss hormonal therapy options for postmenopausal patients with advanced hormone receptor-positive breast cancer
- Apply data from clinical trials and consensus guidelines in the management of patients with advanced HER2+ breast cancer
- Assess the efficacy and side effects of antiangiogenic agents in combination with chemotherapy in formulating treatment for advanced breast cancer

The Issue

- More than 40,000 women will die annually due to metastatic breast cancer (MBC)
- 6% of breast cancer patients are found to be metastatic at the time of diagnosis
- The median survival for these patients is approximately two to three years
- SEER data demonstrate a 5-year MBC survival rate of 26%

The Issue

- Framework of BC management has evolved
- Rapidly changing environment
 - New agents
 - New combinations
- Controversies about the appropriate use of the new agents and combinations

The framework of breast cancer management has evolved over the years. There is a rapidly changing environment that involves the development of new agents and new combinations. There are ongoing controversies about the appropriate use of the new agents and combinations in defined clinical situations.

Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

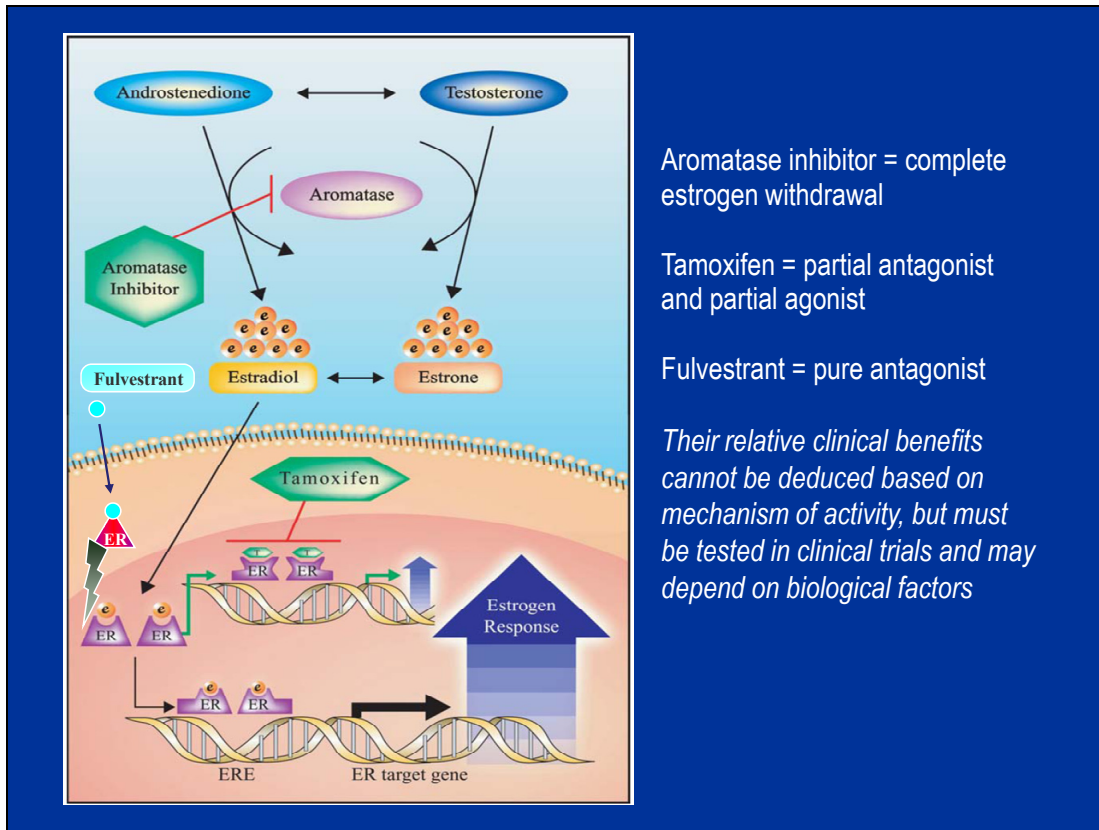
CASE STUDY 1:

Hormonal Therapy in Metastatic Breast Cancer

- 66-year-old woman with 6 months of fatigue, and hip and back pain
- *Exam:* left central breast mass and left axillary adenopathy
- *Spine x-rays:* osteoblastic lesions, thoracic and lumbar spine
- *Bone scan:* uptake in the spine and left hip
- *CT:* bony metastases in the spine and pelvis; no lesions in the lung and liver
- *Needle biopsy left breast:* adenocarcinoma, Grade II, ER++/PR++/HER2-negative
- *Blood work:* Hgb 10.2 g/dL, Hct 29%, and mildly elevated alkaline phosphatase

The first case study is a 66-year-old woman who presents with 6 months of fatigue as well as hip and back pain. Examination reveals a left central breast mass and a left axillary adenopathy. Spine X-rays show osteoblastic lesions in the thoracic and lumbar spin. A bone scan shows uptake in the spine in the left hip and CT scan confirms bony metastases in the spine and pelvis with no lesions seen in the lung and liver. A needle biopsy is done of the left breast and this shows adenocarcinoma, Grade II, which is ER+, PR+, and HER2-. Blood works shows a hemoglobin of 10.2 g/dL, hematocrit of 29%, and a mildly elevated alkaline phosphatase.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.



Aromatase inhibitor = complete estrogen withdrawal

Tamoxifen = partial antagonist and partial agonist

Fulvestrant = pure antagonist

Their relative clinical benefits cannot be deduced based on mechanism of activity, but must be tested in clinical trials and may depend on biological factors

Aromatase inhibitors (AIs) suppress activity of the cytochrome P450 enzyme aromatase in peripheral tissues, reducing circulating estradiol levels and eluding estradiol-induced transcription via nuclear and non-nuclear pathways. Third-generation AIs can be divided into two main classes, nonsteroidal (anastrozole, letrozole) and steroidal (exemestane), and subclassified according to the reversibility of their inhibitor activity. Nonsteroidal inhibitors bind reversibly to the aromatase enzyme, resulting in competitive inhibition, and steroidal inhibitors irreversibly inhibit the aromatase enzyme by covalent binding to it.

Tamoxifen is a nonsteroidal triphenylethylene derivative, classified as a selective estrogen receptor modulator. Tamoxifen binds to ER, with low affinity compared with estrogens, and the complex homodimerizes and translocates to the nucleus, where it inhibits coactivator binding and promotes corepressor binding, blocking the transcription of AF2, while AF1 remains active. The inhibition of AF2 explains the antagonist effect of tamoxifen in the breast, whereas partial agonist effect in bone, liver and the uterus results from the activation of AF1.

Fulvestrant, a new hormonal agent, is a selective ER downregulator that impairs dimerization and translocation of the ER and blocks cofactors' recruitment at both activating sites. Moreover, the ER–fulvestrant complex is unstable and is rapidly degraded, leading to a reduction of cellular levels of the ER. Because fulvestrant blocks both AF1 and AF2, it results in complete abrogation of estrogen signaling through the ER.

Reference: Adamo V, Iorfida M, Montalto E, et al. Overview and new strategies in metastatic breast cancer (MBC) for treatment of tamoxifen-resistant patients. *Ann Oncol* 2007;18 Suppl 6:vi53-7.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. *Medscape CME Spotlight*. Oct 2008.

Hormonal Therapy for Metastatic Breast Cancer

- Generally used initially for ER+ and/or PR+ tumors
- Chemotherapy may be used as induction for aggressive visceral disease with the possible conversion to maintenance hormonal therapy
- Goal is to palliate and delay start of chemotherapy
 - Treatments have not changed survival, but have improved duration of response, hence improving quality of life
- Sequential therapies used until exhausted, then change to chemotherapy
- Responses to salvage therapy not likely if there was no response to initial therapy
- Recurrence or progression may lose ER or PR positivity

The patient in Case Study 1 is a postmenopausal woman with newly diagnosed metastatic breast cancer that is not only hormone receptor-positive, but clinically presents like a hormone-sensitive cancer. Bone is the predominant site of metastatic disease. Hormone therapy for metastatic breast cancer is generally the initial approach to treatment in patients who have hormone receptor-positive disease, although occasionally chemotherapy will be started first. The goal in using hormone therapy in the metastatic setting is to palliate symptoms, help patients to live as long as possible with the best quality of life, and to delay the start of chemotherapy since chemotherapy will always require more visits to the clinic and result in more side effects.

To date, survival with metastatic breast cancer has not changed markedly, but quality of life and duration of response have improved. This is due to increased treatment options with hormonal therapy being the cornerstone. Multiple sequential therapies can be used until therapeutic options are exhausted, at which point treatment is switched to chemotherapy. Hormone therapy can also be used as maintenance after a response to chemotherapy in situations where chemotherapy is indicated.

One very important thing to keep in mind when patients recur or progress is to biopsy. As the disease progresses, hormone receptors are often lost. Typically, first is loss of progesterone receptor and less sensitivity to hormone-directed therapy is observed. Subsequently, loss of estrogen receptor is observed and therefore real hormone-resistant disease.

Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Randomized Phase III Trials of AIs vs Tamoxifen as First-line Treatment of MBC

	Anastrozole	Anastrozole	Letrozole	Exemestane
No. patients	170 vs 182	340 vs 328	453 vs 454	182 vs 189
ORR, %	21 vs 17	33 vs 33	30 vs 20*	46 vs 31*
CBR, %	59 vs 46*	56 vs 56	49 vs 38*	66 vs 49*
TTP or PFS, months	11 vs 6*	8 vs 8	9 vs 6*	10 vs 6*
ER status unknown, %	11 vs 11	56 vs 54	34 vs 33	15 vs 11

ORR = overall response rate; CBR = clinical benefit rate; TTP = time to progression; PFS = progression-free survival; ER = estrogen receptor

* Statistically significantly different

Nabholtz JM et al. *J Clin Oncol*, 2000;18:3758-3767.

Bonneterre J et al. *J Clin Oncol*. 2000;18:3748-3757.

Mouridsen H et al. *J Clin Oncol*, 2003;21:2101-2109.

Paridaens R et al. Presented at: American Society of Clinical Oncology, 2004; Abstract 515.

In studies comparing anastrozole 1 mg once daily relative to tamoxifen 20 mg once daily in patients with hormone receptor–positive tumors or tumors of unknown receptor status, anastrozole was as effective as tamoxifen in terms of ORR (21% v 17% of patients, respectively), with clinical benefit observed in 59% of patients on anastrozole and 46% on tamoxifen (two-sided $P = .0098$, retrospective analysis).¹ In the second anastrozole study, anastrozole was also as effective as tamoxifen in terms of ORR (32.9% of anastrozole and 32.6% of tamoxifen patients achieved a complete response or partial response). Clinical benefit rates were 56.2% and 55.5% for patients receiving anastrozole and tamoxifen, respectively.²

Letrozole versus tamoxifen was analyzed as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. The superiority of letrozole to tamoxifen was confirmed for time to progression (median, 9.4 v 6.0 months, respectively; $P < .0001$) overall objective response rate (32% v 21%, respectively; $P = .0002$), and overall clinical benefit.³

In a study of exemestane versus tamoxifen in postmenopausal metastatic breast cancer patients with hormone responsive disease, the median PFS is significantly longer under exemestane than tamoxifen (10.9 vs 6.7 months, $p = 0.04$) with an HR of 0.79 (95% CI 0.62 - 0.99) in favor of exemestane.⁴

1. Nabholz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol*. 2000;18:3758-67.

2. Bonneterre J, Thürlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol*. 2000;18:3748-57.

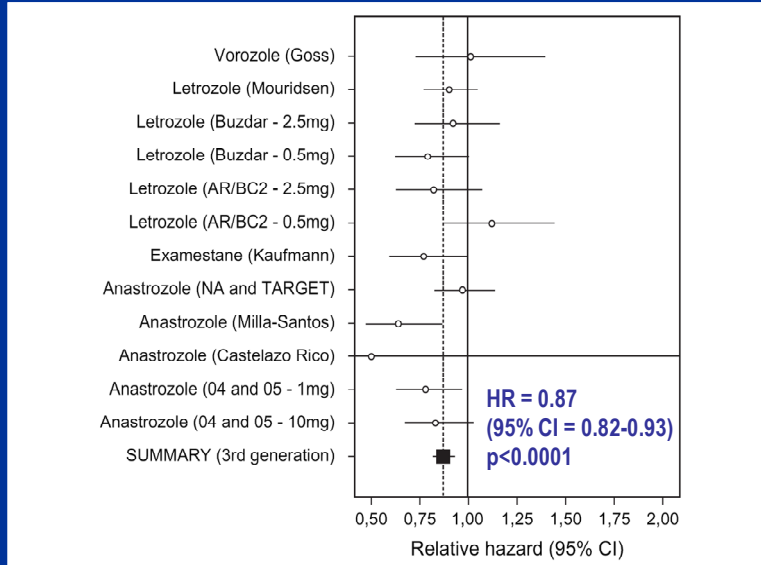
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4. Paridaens R, Therasse P, Dirix L, et al. First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts) – A randomized phase III trial of the EORTC Breast Group. Presented at: American Society of Clinical Oncology, 2004; Abstract 515.

5. Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Meta-analysis of Survival

3rd Generation Aromatase Inhibitors vs. Standard Hormonal Therapy for Metastatic Breast Cancer



Mauri D et al JNCI 2006

To address whether aromatase inhibitors and inactivators of different generations offer survival benefits, a meta-analysis was performed of randomized trials among patients with advanced breast cancer, in which aromatase inhibitors or inactivators were compared with the standard hormonal treatments (either tamoxifen or progestins) in a first-line or second-line (or subsequent-line) setting. In this study, third-generation aromatase inhibitors were associated with statistically significant (RH = 0.87, 95% CI = 0.82 to 0.93; $P < .001$) increased survival compared with standard hormone therapy.

Reference: Mauri D, Pavlidis N, Polyzos NP, et al. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst.* 2006;98:1285-91.

First-Line Fulvestrant vs Tamoxifen

Summary of Results

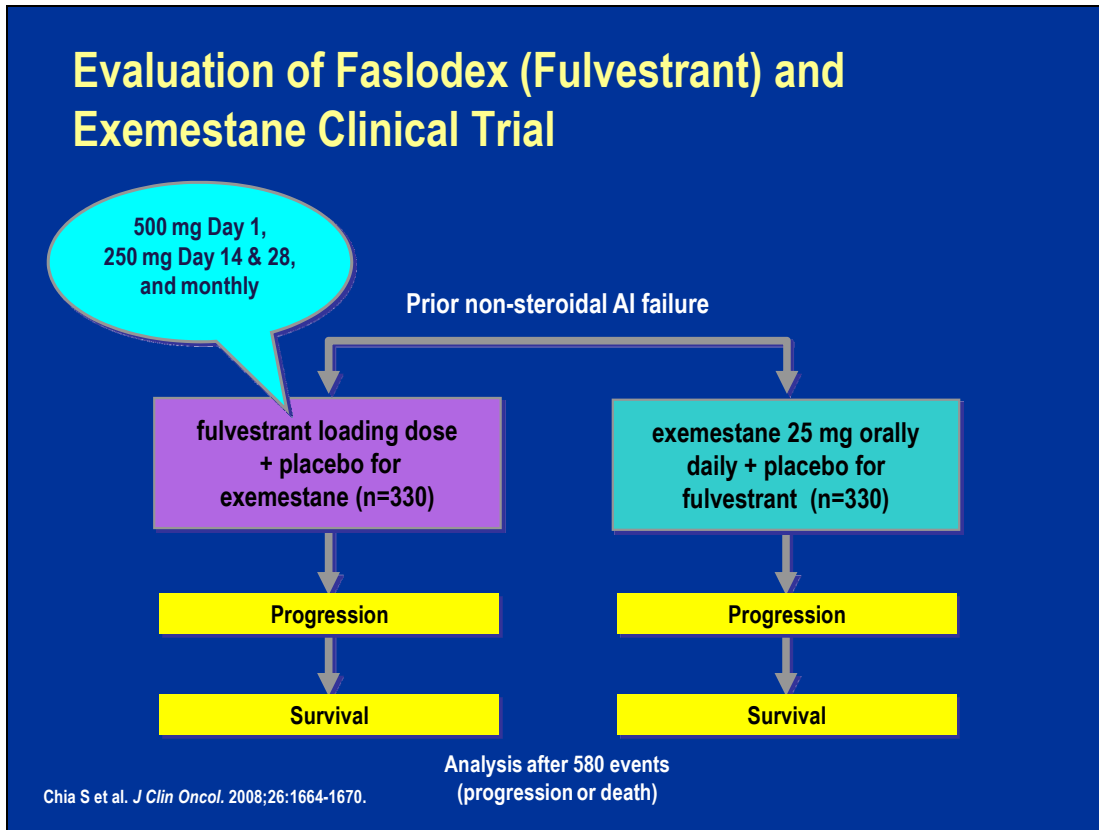
Outcome	Fulvestrant (n = 313)	Tamoxifen (n = 274)	Statistical Significance
TTP (months)	6.8	8.3	$P = .088$
ORR (%)	32	34	$P = .451$
Clinical benefit (%)	54.3	62.0	$P = .026$
Median DOR (months)	17.3	19.8	NS
TTF (months)	5.9	7.8	$P = .039$
Median survival (months)	36.9	38.7	$P = .04$
ER+ and PR+ (79%)			
Median survival (months)	39.3	40.7	$P = .30$

DOR = duration of response; NS = not significant; TTF = time to treatment failure.

Howell A et al. JCO 2004

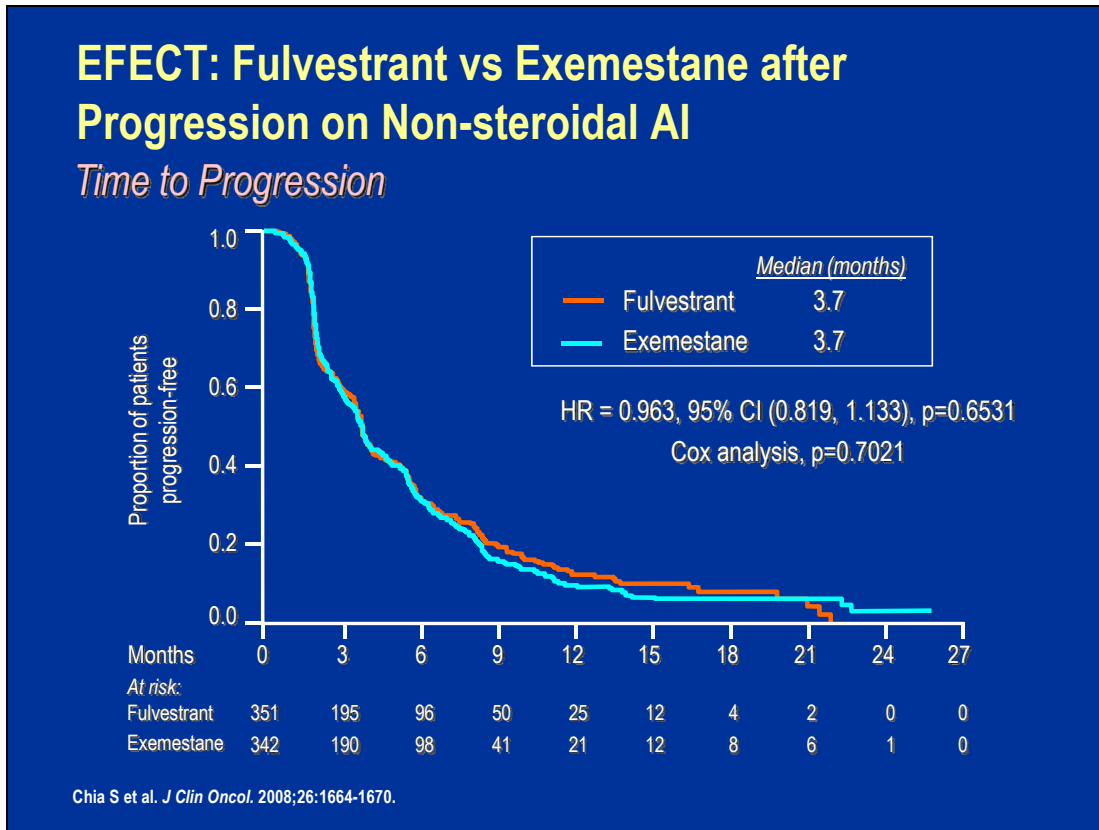
In this multicenter, double-blind, randomized trial, patients with metastatic/locally advanced breast cancer previously untreated for advanced disease were randomly assigned to receive either fulvestrant (250 mg, via intramuscular injection, once monthly; n = 313) or tamoxifen (20 mg, orally, once daily; n = 274). Patients' tumors were ER+ and/or PR+, or had an unknown receptor status. In patients with hormone receptor–positive tumors, fulvestrant had similar efficacy to tamoxifen and was well tolerated.

Reference: Howell A, Robertson JF, Abram P, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol*. 2004;22:1605-13.



The study design of Evaluation of Faslodex (Fulvestrant) versus Exemestane Clinical Trial (EFACT). EFACT is a randomized, double blind, double-dummy, phase III international trial designed to compare the efficacy and tolerability of a loading dose (LD) schedule of fulvestrant to exemestane in postmenopausal women with hormone positive breast cancer with disease progression after prior nonsteroidal aromatase inhibitor therapy. Fulvestrant 250 mg/5mL(x2) as an intramuscular injection or a matching 5mL(x2) oily excipient placebo was injected into each buttock (500mg or matching placebo) on day 1, followed by a single injection of 250 mg fulvestrant/placebo at day 14 and again on day 28. Treatment after day 28 was every 28 days (+/-3 days) thereafter. Exemestane 25mg and a matching placebo were to be taken orally once daily. Patients continued treatment until objective disease progression or other events that required withdrawal. Thereafter, patients were followed up until death.

Reference: Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFACT. *J Clin Oncol.* 2008;26:1664-70.



The purpose of the EFECT trial was to answer the question of what is the proper course of treatment for patients with metastatic disease who have been exposed to a non-steroidal aromatase inhibitor. At the time of analysis, 82.1% (n=288) of the fulvestrant group and 87.4% (n=299) of the exemestane group had experienced a defined progression event. The median time to progression in both groups was 3.7 months (P=.65) with a hazard ratio of 0.93 (95% CI, 0.819 to 1.133). Both treatments were well tolerated, with no significant differences in the incidence of adverse events or quality of life.

Reference: Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol.* 2008;26:1664-70.

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EFFECT: Objective Response and Clinical Benefit Rate Evaluable for Response Population

	Fulvestrant	Exemestane	Odds ratio* (95% CI)	p-value
OR rate (CR + PR)	7.4% (20/270)	6.7% (18/270)	1.120 (0.578, 2.186)	0.7364
CB rate (OR + SD ≥24 wks)	32.2% (87/270)	31.5% (85/270)	1.035 (0.720, 1.487)	0.8534

* Analyses are not adjusted for baseline covariates

Chia S et al. *J Clin Oncol*. 2008;26:1664-1670.

A total of 540 patients (270 in each arm) had measurable disease by RECIST criteria at trial entry. Overall, 20 patients in the fulvestrant arm (7.4%) and 18 patients in the exemestane arm (6.7%) had a documented response (odds ratio 1.12; 95% CI, 0.578 to 2.186; P=.736). The clinical benefit rate was 32.2% and 31.5% in the fulvestrant and exemestane arms, respectively (odds ratio 1.03; 95% CI, 0.72 to 1.487; P .853). This data indicated that sequential non-cross resistant hormone therapy is a good option for patients with progressive metastatic disease, including patients who have progressed after adjuvant non-steroidal aromatase inhibitors.

Reference: Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFFECT. *J Clin Oncol*. 2008;26:1664-70.

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Differences in Side-effect Profiles

Between Hormonal Therapy Options

- Tamoxifen (oral)
 - Less vaginal dryness, joint pains, bone fractures and bone mineral density loss
 - Improves cholesterol
 - More thromboembolic disease, vaginal bleeding, gyn disorders, hot flashes
- AI (oral)
 - Less hot flashes, thromboembolic disease, vaginal bleeding,
 - More bone fractures and BMD loss, increase cholesterol, joint pains
- Fulvestrant* (injectable)
 - Same as tamoxifen, but less TE disease, vaginal bleeding
- Other side effects similar among options
 - Depression, GI disturbances, lethargy, weight gain
- Individualize therapy based on safety profile and patient compliance

*Typically used in second line

Vergote I, Abram P. *Ann Oncol.* 2006;17:200-204.

When treating patients, it is important to keep in mind the differential side effect profiles between different hormone agents.

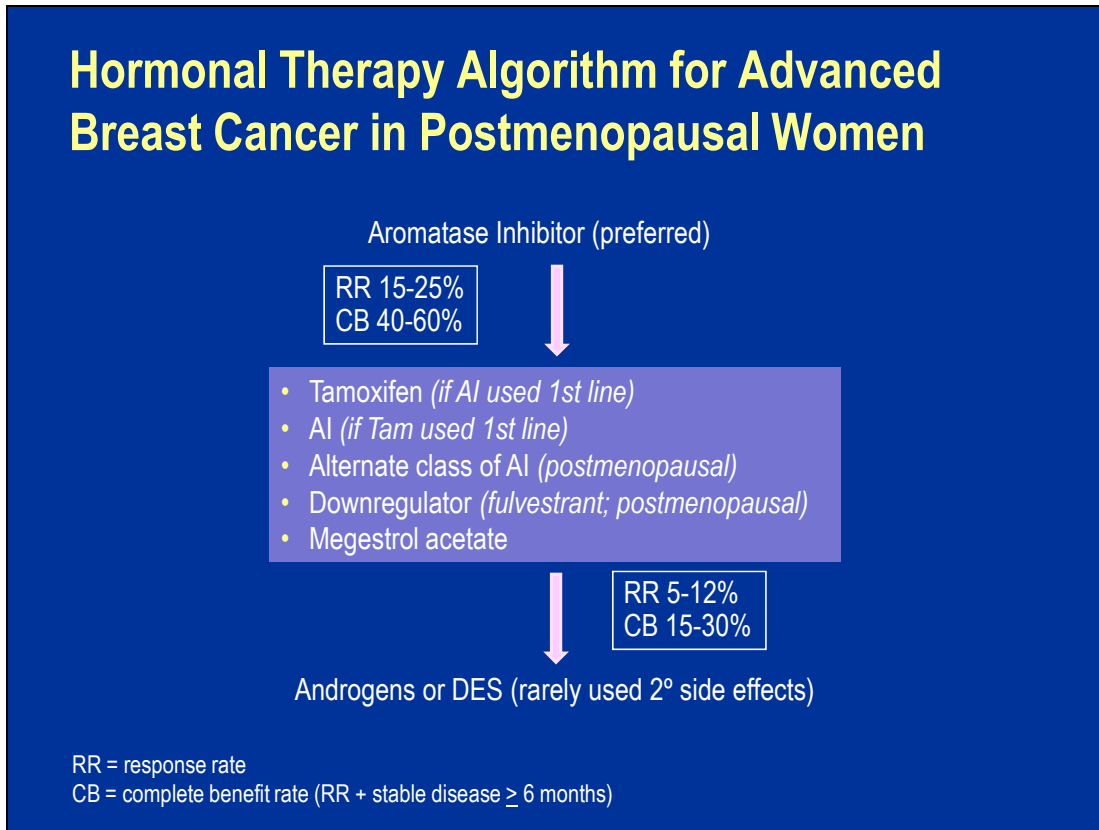
Tamoxifen treatment is associated with gynecological disorders, hot flushes, and an increased risk of thromboembolic disease. The agonist activity of tamoxifen may, however, have beneficial effects on bone mineral density, particularly with long-term treatment, e.g. in the adjuvant setting.

Bone loss and significant joint pain have been reported for all of the third-generation aromatase inhibitors. Compared with tamoxifen, aromatase inhibitors are associated with less hot flushes and vaginal discharge. Exemestane has weak androgenic properties and has been associated with androgenic side-effects such as weight gain, alopecia and acne, particularly when used at higher doses.

Fulvestrant has a similar side effect profile as tamoxifen, but is less significant. Fulvestrant is associated with a lower incidence of joint disorders (including arthralgia, arthrosis and arthritis). In a study comparing fulvestrant with tamoxifen, there was a trend for fewer gastrointestinal disturbances (nausea, vomiting, diarrhea and constipation) and a lower incidence of hot flashes in the fulvestrant group than in the tamoxifen group.

Reference: Vergote I, Abram P. Fulvestrant, a new treatment option for advanced breast cancer: tolerability versus existing agents. *Ann Oncol.* 2006;17:200-4.

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For postmenopausal women with advanced breast cancer, aromatase inhibitors (AI) are preferred as first-line treatment. Second-line therapy that can be considered is tamoxifen, AI if tamoxifen was used as first-line, an alternate class of AI, fulvestrant, or megestrol acetate. However, megestrol acetate is being used more as third- and fourth-line now because of its side effects. Finally, older therapies, such as androgen type therapies and high dose estrogen, can be effective as third-line therapy for postmenopausal women with advanced breast cancer.

Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

CASE STUDY 1:
Clinical Management

- 66-year-old woman presenting with ER++/PR++/HER2-negative metastatic breast cancer
- Options for management
 - AI or Tamoxifen
 - AI preferred
 - Higher response rate and longer TTP
 - Anemic and Symptomatic

The treatment goals for this patient is to palliate symptoms and manage bone metastases. The patient is not experiencing severe pain, so radiation treatment can be delayed. Options for treatment are an aromatase inhibitor or tamoxifen. Treatment with an aromatase inhibitor is preferred due to the higher response rate and longer time to progression. The goal of a higher response rate rather than stable disease is favored, since the patient is symptomatic and anemic, indicating significant bone marrow involvement.

Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

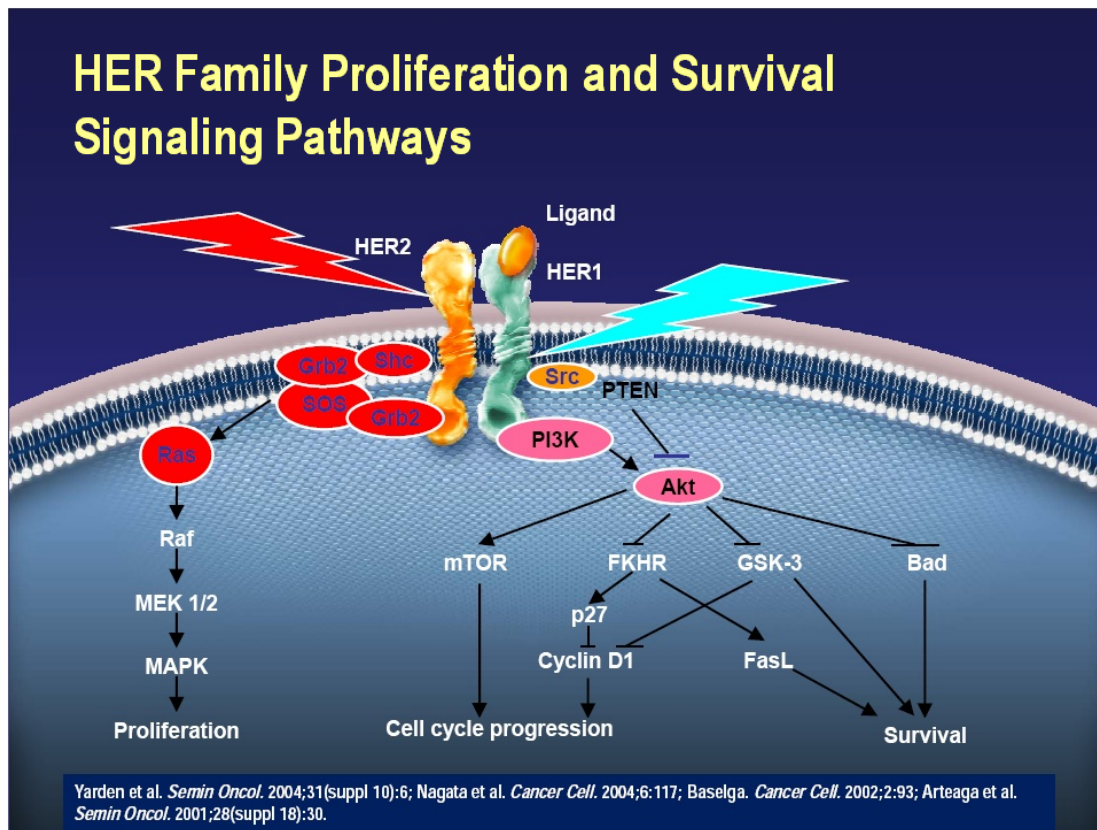
CASE STUDY 2:

HER2 + Metastatic Breast Cancer

- 64-year-old African American woman with left breast mass found on routine mammography
- Lumpectomy and node dissection
- IHC: ER 3+, PR 2+, HER2-/neu 3+. Pathologic stage: T2N1M0
- Initiated on AC X 4, followed by weekly paclitaxel/trastuzumab X 12 → locoregional radiation therapy with completion of one year of trastuzumab therapy
- Disease free for 16 months following completion of trastuzumab, returns complaining of chest pain
- Left 6th rib metastatic lesion, and multiple sub-centimeter hepatic metastases are found
- FNA of the liver: adenocarcinoma, ER+/PR+ and HER2 + by FISH
- Cardiac ejection fraction: 58%

Case Study 2 centers around the therapy for HER2-positive metastatic breast cancer. This is a case of a 64-year-old African-American woman who notices a lump on, a mass is actually found on routine mammography. She undergoes a lumpectomy and lymph node dissection and is determined to have an infiltrating ductal carcinoma that is ER3+, PR2+, and HER2 3+ pathologic stages T2, N1, M0. She is treated with adjuvant therapy. She received doxorubicin and cyclophosphamide for 4 cycles followed by paclitaxel and trastuzumab and locoregional radiation therapy. She then completes 1 year of trastuzumab and she remains disease-free for 16 months following completion of trastuzumab. She then returns at this point complaining of chest pain and is noted to have left sixth rib metastatic lesion and multiple sub-centimeter hepatic metastases. She has a fine-needle aspirate of the liver, which does show adenocarcinoma, again ER/PR-positive and HER2-positive this time by FISH. Her cardiac ejection fraction is 58%. How does one manage this patient?

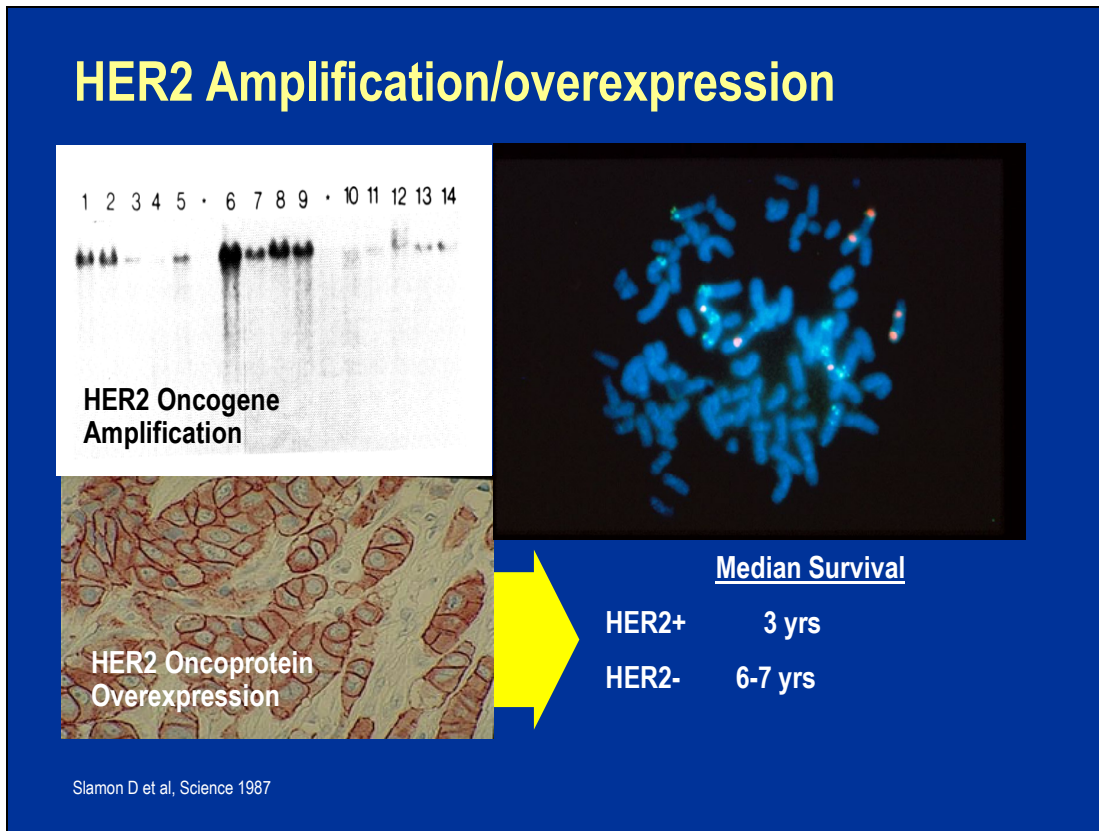
Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.



In unperturbed conditions, HER2 is activated by ligand-induced heterodimerization with other HER receptors.^{1,2} In cell overexpressing HER2, HER2 can spontaneously form active ligand-less homodimers thus activating downstream pathways.¹ Phosphorylation of the tyrosine kinase domain by means of homodimerization or heterodimerization induces both cell proliferation and survival signaling. HER2 is the preferred dimerization partner for the other HER family members.³ The phosphorylated (activated) tyrosine residues on the intracellular domain of HER2 activate the lipid kinase phosphoinositide 3-kinase (PI3-K), which phosphorylates a phosphatidylinositol that in turn binds and phosphorylates the enzyme Akt transforming factor (Akt), driving cell survival. In parallel, a guanine nucleotide exchange factor, the mammalian homologue of the son of sevenless (SOS), activates the rat sarcoma (RAS) enzyme that, in turn, activates receptor activation factor (RAF) and then the mitogen-activated protein kinase (MAPK) and mitogen extracellular signal kinase (MEK). MEK phosphorylates, among others, the MAPK, driving cellular proliferation. The critical role of the HER family of receptors in the development of solid tumors has made these receptors attractive targets for pharmacological intervention.^{4,5}

References:

1. Baselga J. A new anti-ErbB2 strategy in the treatment of cancer: prevention of ligand-dependent ErbB2 receptor heterodimerization. *Cancer Cell.* 2002;2:93-5.
2. Nagata Y, Lan KH, Zhou X, et al. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. *Cancer Cell.* 2004 Aug;6:117-27.
3. Hudis CA. Trastuzumab--mechanism of action and use in clinical practice. *N Engl J Med.* 2007;357:39-51.
4. Arteaga CL, Chinratanalab W, Carter MB. Inhibitors of HER2/neu (erbB-2) signal transduction. *Semin Oncol.* 2001;28(6 Suppl 18):30-5.
5. Yarden Y, Baselga J, Miles D. Molecular approach to breast cancer treatment. *Semin Oncol.* 2004;31(5 Suppl 10):6-13.
6. Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.



HER2/neu is overexpressed in a wide variety of tumors including breast colorectal, ovarian, and non-small lung cancers.¹ Approximately 25-30% of human breast tumors contain multiple copies of HER2/neu proto-oncogene.^{2,3} Overexpression and activation of HER2 tyrosine kinase provides signals that drive dysregulated proliferation, invasion, metastasis, angiogenesis, and cell survival.⁴ Amplification of Her2/neu is therefore a significant predictor of both overall survival and time to relapse in patients with breast cancer.³

Multiple genetic copies of HER2 are often found in breast tumors leading to overexpression of the oncoprotein. This overexpression can be detected by Southern blot, FISH, or immunostaining of tumor tissue. In a seminal initial report, patients with early stage HER2+ tumors had a median survival of approximately 3 years, whereas patients with HER2- status had a median survival of 6-7 years.³

References:

1. Roskoski R Jr. The ErbB/HER receptor protein-tyrosine kinases and cancer. *Biochem Biophys Res Commun.* 2004;319:1-11.
2. Berger MS, Locher GW, Saurer S, et al. Correlation of c-erbB-2 gene amplification and protein expression in human breast carcinoma with nodal status and nuclear grading. *Cancer Res.* 1988;48:1238-43.
3. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235:177-82.
4. Rowinsky EK. The erbB family: targets for therapeutic development against cancer and therapeutic strategies using monoclonal antibodies and tyrosine kinase inhibitors. *Annu Rev Med.* 2004;55:433-57.

HER-2/neu Positivity is an Independent Predictor of Poor Prognosis

Predicts reduced response and survival

Correlates with aggressive tumor behavior

- Short disease-free interval
- Large tumor size
- Positive nodal status
- Ductal rather than lobular histology
- Aneuploidy
- High S-phase fraction
- High nuclear grade
- Decreased ER/PR expression
- Mutated p53
- Expression of VEGF

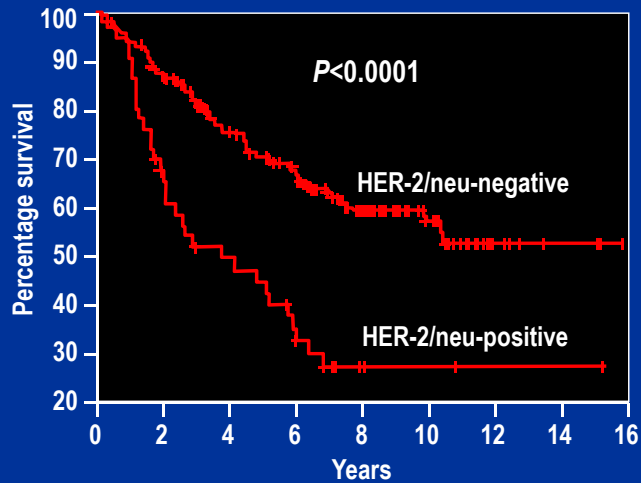
ER = estrogen receptor; PgR = progesterone receptor; VEGF = vascular endothelial growth factor.

Tumors expressing HER2/neu is indicative of poor prognosis, with patients having reduced response to therapies and decrease in survival. Aggressive tumor behavior, such as short disease-free interval, high S-phase fraction, large tumor size, high nuclear grade, positive nodal status, decreased ER/PR expression, ductal histology, p53 mutations, aneuploidy, and expression of VEGF are correlated with HER2/neu positivity.

Reference: Baselga J. A new anti-ErbB2 strategy in the treatment of cancer: prevention of ligand-dependent ErbB2 receptor heterodimerization. *Cancer Cell*. 2002;2:93-5.

HER-2/neu Positivity Correlates with Decreased Survival in Breast Cancer

In this study, strongly positive IHC scores (3+) were associated with significantly decreased survival




IHC = immunohistochemistry.
Witton CJ et al. *J Pathol.* 2003;200:290-297.

Survival is decreased for patients with intensely staining 'HER2-positive' tumors. In this study, the relative risk of death with a HER2-positive tumor was 1.18 (0.88–1.60, Cox's multiple regression) versus HER2-negative. HER2 staining using the ICR12 antibody correlated strongly with quantitative HER2 expression determined in the same patients ($p < 0.00001$, χ^2 test).

Reference: Witton CJ, Reeves JR, Going JJ, et al. Expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. *J Pathol.* 2003;200:290-7.

Trastuzumab

Humanized Anti-HER-2/neu Monoclonal Antibody



- Targets HER-2/neu protein
- Selectively binds with high affinity ($K_d \leq 0.5$ nM)
- 95% human, 5% murine

Carter P et al. *Proc Natl Acad Sci U S A.* 1992;89:4285-4289.

Trastuzumab, a humanized HER2/neu specific monoclonal antibody, was created by engineering the murine variable antigen binding loops to the human constant and other consensus immunoglobulin regions. This design allows for the potency of the murine antibody in blocking cell proliferation to be combined with the immune activating potential of the human antibody resulting in tighter antigen binding than either the human or mouse antibody and the ability to engage antibody-dependent cellular cytotoxicity.

Reference: Carter P, Presta L, Gorman CM, et al. Humanization of an anti-p185HER2 antibody for human cancer therapy. *Proc Natl Acad Sci U S A.* 1992;89:4285-9.

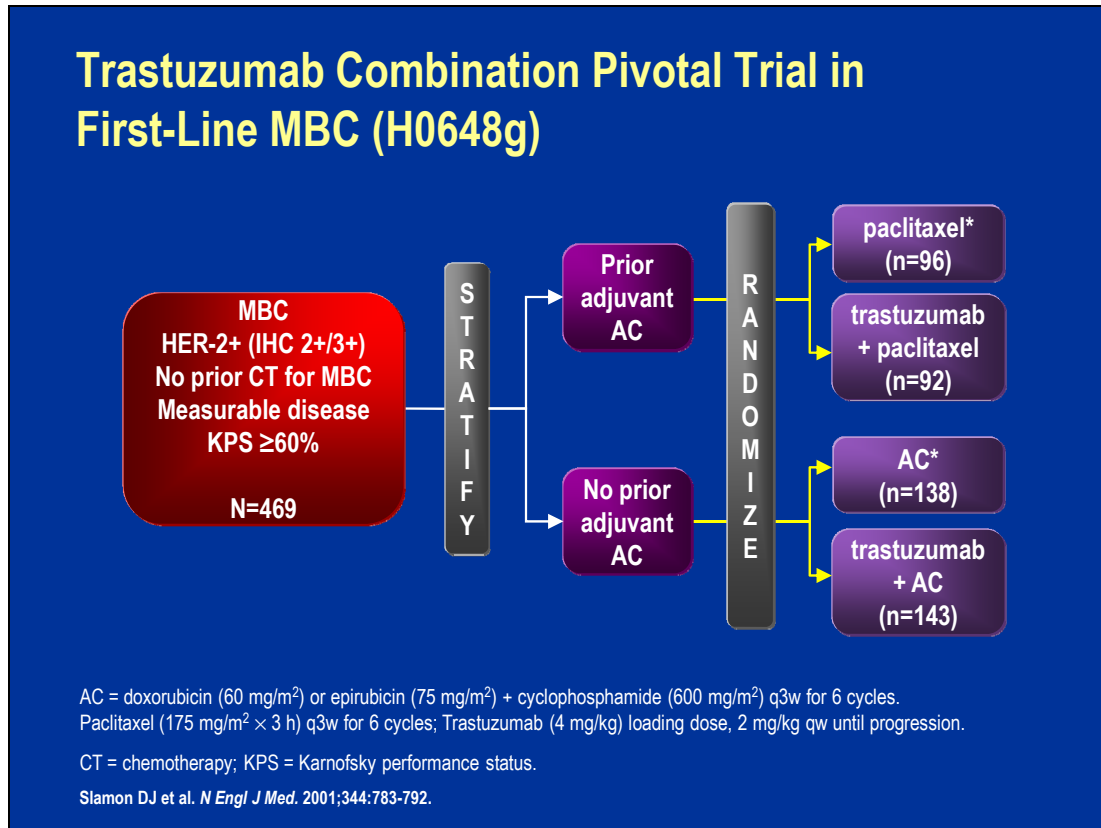
Trastuzumab

Proposed Mechanisms of Action

- Cytostatic
 - In vitro studies support the cytostatic mechanism of trastuzumab
 - This may help stabilize HER-2/neu-positive disease and maintain a durable response
- Cytotoxic
 - In early clinical trials, trastuzumab in combination with chemotherapy achieved significant response rates by reducing tumor burden, supportive of its cytotoxic action
 - Preclinical studies suggest trastuzumab is a mediator of antibody-dependent cellular cytotoxicity

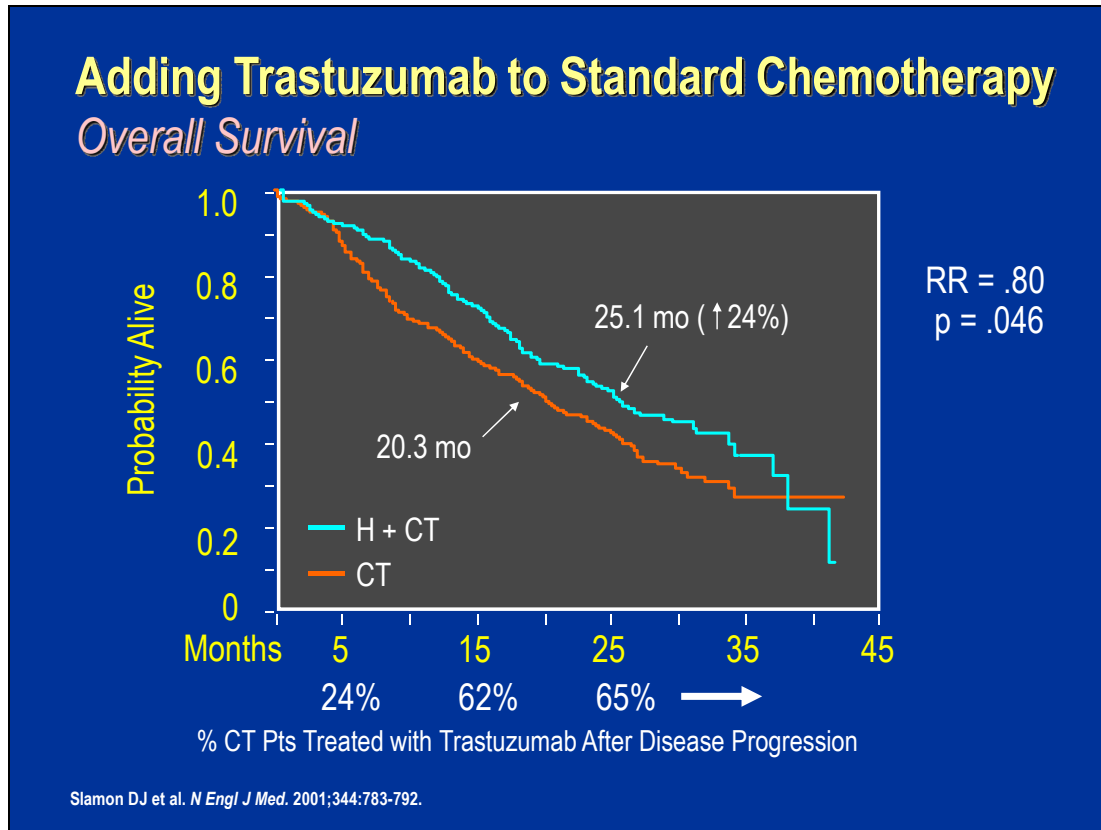
In vivo breast cancer models and clinical trials have demonstrated that trastuzumab has not only cytostatic but also cytotoxic properties. At least in part, these properties may be due to the activation of antibody-dependent cellular cytotoxicity (ADCC). ADCC is mainly due to the activation of natural killer cells, expressing the Fc gamma receptor, which can be bound by the Fc domain of trastuzumab. This event activates the lysis of cancer cells bound to trastuzumab. Several clinical studies also show that a decline in serum HER2 extracellular domain during trastuzumab treatment predicts tumor response and improves progression-free survival, which indirectly supports the hypothesis that trastuzumab may act by inhibiting HER2 cleavage.

Reference: Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. *Ann Oncol.* 2007;18: 977–984.



The efficacy and safety of trastuzumab was evaluated in women with metastatic breast cancer that overexpressed HER2. Patients were randomly assigned to receive standard chemotherapy (n=234) or standard chemotherapy plus trastuzumab (n=235). Chemotherapy consisted of an anthracycline (doxorubicin at a dose of 60 mg per square meter of body-surface area or epirubicin at a dose of 75 mg per square meter) plus cyclophosphamide (at a dose of 600 mg per square meter) for patients who had never before received an anthracycline, or paclitaxel (at a dose of 175 mg per square meter) for patients who had received adjuvant (postoperative) anthracycline. Chemotherapy was administered once every three weeks for six cycles, and additional cycles were administered at the investigator's discretion. Trastuzumab was administered intravenously in a loading dose of 4 mg per kilogram of body weight, followed by a dose of 2 mg per kilogram once a week, until there was evidence of disease progression. On the detection of disease progression, patients were given the option of entering a nonrandomized, open-label study in which trastuzumab was administered at double the dose alone or in combination with other therapies. Sixty-six percent of such patients elected to do so.

Reference: Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344:783-92.

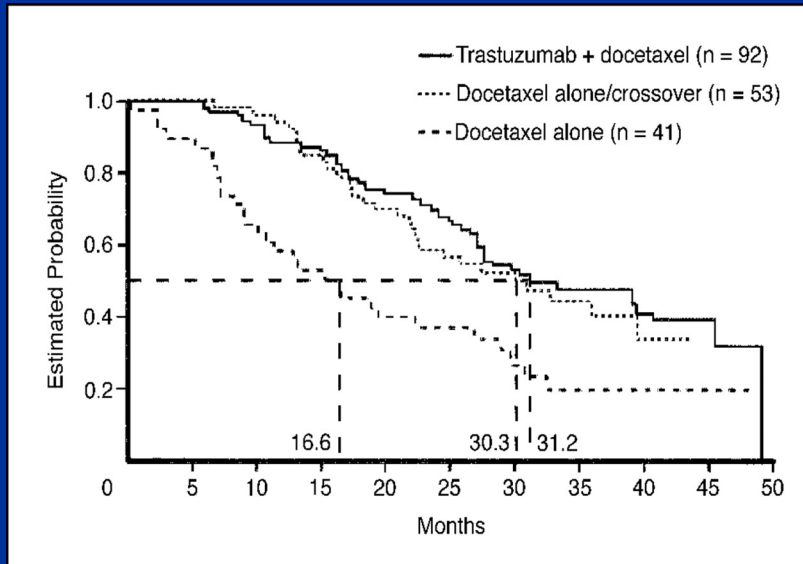


In this study, the median survival was 25.1 months in the group given chemotherapy plus trastuzumab and 20.3 months in the group that received chemotherapy alone ($P=0.046$). The median time to disease progression was 7.4 months in the group assigned to chemotherapy plus trastuzumab, whereas in the group given chemotherapy alone it was 4.6 months ($P<0.001$). As compared with chemotherapy alone, treatment with chemotherapy plus trastuzumab, was associated with a significantly higher rate of overall response (50% vs. 32%, $P<0.001$), a longer duration of response (median, 9.1 vs. 6.1 months; $P<0.001$), and a longer time to treatment failure (median, 6.9 vs. 4.5 months; $P<0.001$).

References: Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344:783-92.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

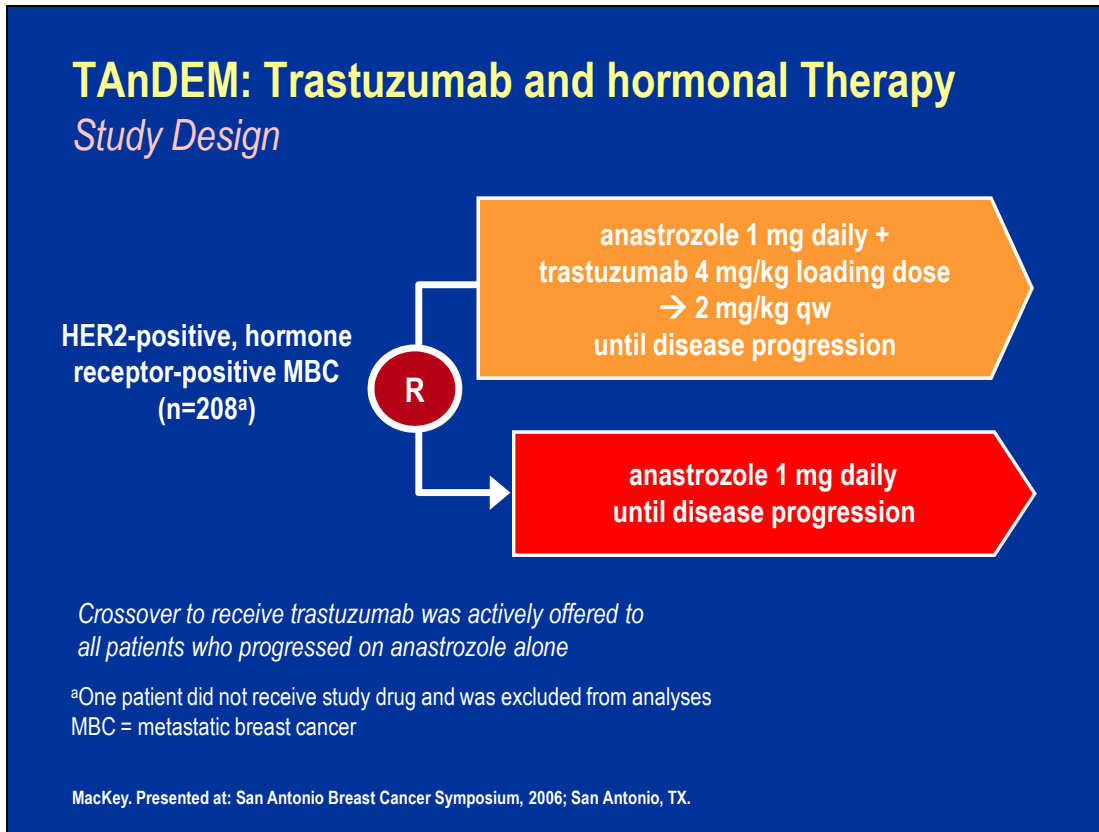
M 77001 Phase II Trial of Docetaxel +/- Trastuzumab with Cross-Over: Survival



Marty M et al JCO 2005

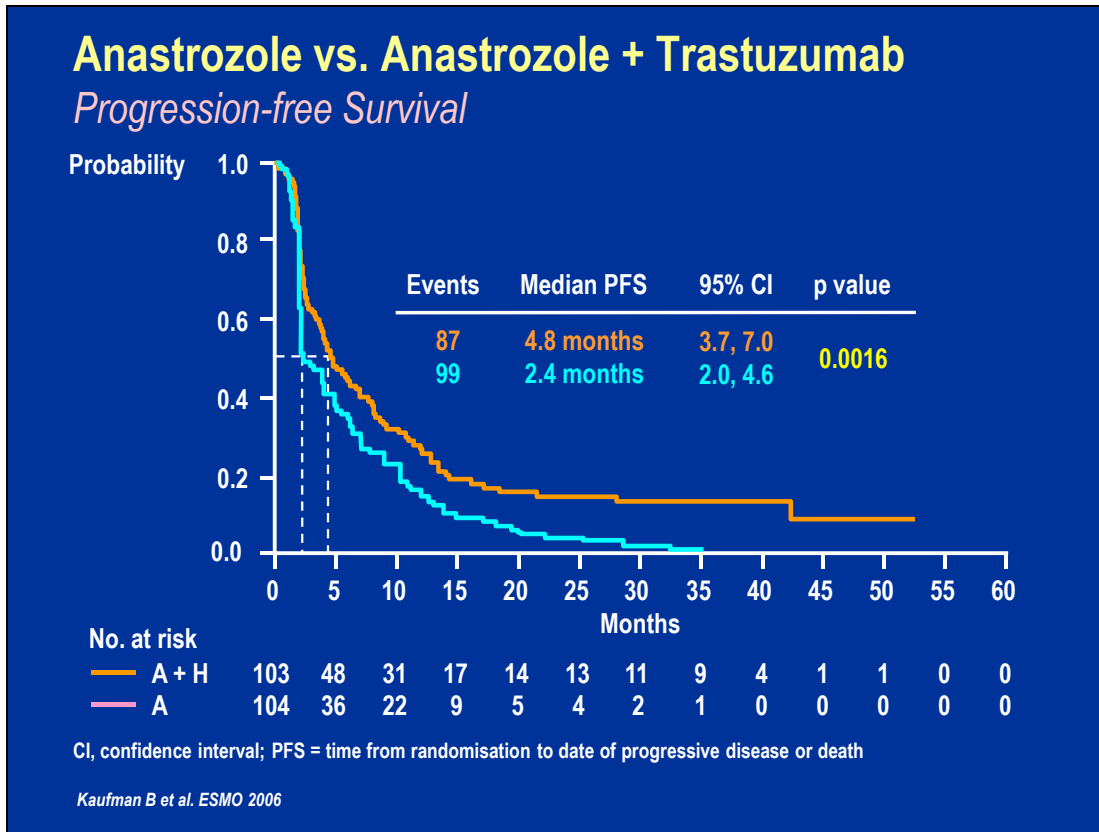
This Kaplan-Meier plot compares the estimated overall survival in patients who received trastuzumab and docetaxel first-line treatment versus those who crossed over to receive trastuzumab after progressing on docetaxel alone versus patients who received docetaxel only. Fifty-three patients (57%) in the docetaxel-alone arm were reported to have crossed over to receive trastuzumab. The median estimated overall survival in patients who received docetaxel only was 16.6 months, and it was 30.3 months for patients who crossed over to receive trastuzumab at any time point after progression on docetaxel alone.

Reference: Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol.* 2005;23:4265-74.



The study design for TAnDEM, a randomised, controlled, open-label, multicenter, Phase III trial. The objective of this study was to evaluate the efficacy and safety of trastuzumab plus anastrozole compared to anastrozole alone in postmenopausal women with HER2-positive (IHC 3+ and/or FISH+) and ER- and/or PR-positive metastatic breast cancer. Eligible patients were randomized to anastrozole only (1 mg/day po) or anastrozole +trastuzumab (4 mg/kg iv infusion on Day 1 then 2 mg/kg qw) until progressive disease. The primary end point was progression-free survival (PFS). Women whose disease progressed on the single drug were given the option to switch to trastuzumab therapy.

Reference: Mackey JR, Kaufman B, Clemens M, et al. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. San Antonio Breast Cancer Symposium. 2006; San Antonio, TX.



The combination of anastrozole +trastuzumab in first-line treatment of women with ER- and/or PR-positive, HER2-positive metastatic breast cancer leads to doubling of progression free survival compared to treatment with anastrozole alone. Progression free survival was 4.8 months on average, compared with 2.4 months in the single-drug group (P=0.0016). Investigators reported that women who took both drugs experienced significant improvements in the length of time it took for their disease to worsen. Overall survival was also prolonged (28.5 months compared with 23.9) but this difference was not statistically significant.

Reference: Kaufman B, et al. ESMO 31st Congress: Abstract LBA2. Presented October 2, 2006.

Trastuzumab after Progression

Trastuzumab Extension Study – Efficacy and Safety Results

	CT Alone*	CT + Trastuzumab†
	↓	↓
	CT+ Trastuzumab	Alternate CT+ Trastuzumab
Overall	21/154 (14%)	10/93 (11%)
Prior response on randomized trial	8/42 (19%)	7/45 (16%)
No prior response on randomized trial	13/112 (12%)	3/48 (6%)
Cardiomyopathy	13/153 (8%)	2/93 (2%)

CT=chemotherapy
 * AC or paclitaxel
 † AC or paclitaxel + trastuzumab

Tripathy D et al. *J Clin Oncol.* 2004;22:1063-1070.

This study was not designed to specifically assess the benefit of sustained trastuzumab therapy after tumor progression. Nevertheless, a response rate of 11% and a clinical benefit rate of 22% for group 2 (CT + Trastuzumab → Alternate CT + Trastuzumab) was observed. This indicates that some women who did not respond to prior trastuzumab plus chemotherapy may have an opportunity to respond to trastuzumab in the second-line setting. Also, cardiac dysfunction was uncommon, occurring in approximately 2% of group 2 patients and 9% of group 1 patients.

References: Tripathy D, Slamon DJ, Cobleigh M, et al. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. *J Clin Oncol.* 2004;22:1063-70.
 Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Activity of Second-Line Trastuzumab Regimens

*Trastuzumab regimens after progression on first-line
trastuzumab or trastuzumab-based regimens (retrospective study)*

Agents	No. of Patients (%)	
	Responses	Benefits*
Trastuzumab	4/11 (36)	7/11 (64)
Trastuzumab + taxane	8/21 (38)	14/21 (67)
Trastuzumab + vinorelbine	9/33 (27)	17/33 (52)
Total	21/65 (32)	38/65 (54)

Median TTP = 6 months

*** CR + PR + SD > 6 Mo**

Gelmon K et al. Clin Breast Cancer 2004

In this retrospective case review of women with HER2-positive metastatic breast cancer who continued to receive trastuzumab beyond disease progression, the overall response rates were 36% and 38% after a second regimen of trastuzumab alone or with vinorelbine. Women had received ≤ 6 chemotherapy regimens before trastuzumab therapy. The overall response rate to trastuzumab alone or with a taxane as the first regimen was 39%; a further 30% of patients had stable disease as the best response. Overall, some patients responded to both the first and second regimens; others responded to the second regimen after the first had failed. Trastuzumab treatment beyond progression produced responses and clinical benefit, and was well tolerated without significant cardiac toxicity.

Reference: Gelmon KA, Mackey J, Verma S, et al. Use of trastuzumab beyond disease progression: observations from a retrospective review of case histories. *Clin Breast Cancer*. 2004;5:52-8.

Trastuzumab Treatment in Multiple Lines

Line	n	CR	PR	SD	PD	Non-Eval.	Median TTP, mo. (range)
Second	80	3 (4%)	16 (20%)	22 (28%)	29 (36%)	10 (13%)	5.2 (0.5-1.7)
Third	49	1 (2%)	6 (12%)	12 (24%)	21 (43%)	9 (18%)	3.5 (0-18.3)
Fourth	26	-	5 (19%)	8 (31%)	9 (35%)	4 (15%)	4.9 (0.3-21.8)

CR: Clinical Response PR: Partial Response SD: Stable Disease
PD: Progressive Disease TTP: Time To Progression

Fountzilias et al., Clin Breast Cancer 2003

In a retrospective review of medical records of 80 patients with HER2-overexpressing metastatic breast cancer who received trastuzumab monotherapy or combination chemotherapy beyond disease progression a total of 32 responses were observed. Most responses were during the second or third line of treatment. Median survival from diagnosis of advanced disease was 43.4 months (range, 6.4-91.7+), whereas median survival from disease progression after trastuzumab administration was 22.2 months (range, 0.01-32.9+).

Reference: Fountzilias G, Razis E, Tsavdaridis D, et al. Continuation of trastuzumab beyond disease progression is feasible and safe in patients with metastatic breast cancer: a retrospective analysis of 80 cases by the hellenic cooperative oncology group. *Clin Breast Cancer*. 2003;4:120-5.

Capecitabine ± Trastuzumab

Trastuzumab Beyond Progression (TBP) Trial

Eligibility criteria:

- HER2+ locally advanced or MBC
- Progression on trastuzumab
- ≤ 1 palliative chemo
- LVEF ≥ 50%

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capecitabine
2500 mg/m² d1-14 q 22

capecitabine
2500 mg/m² d1-14 q 22
+ cont. trastuzumab 6 mg/kg q22

- Primary endpoint: time to progression (TTP)
- Secondary endpoints include: OS, ORR, safety
- Study closed at 156 patients due to slow accrual following FDA registration of lapatinib for this indication

Von Minckwitz G et al. Presented at: American Society of Clinical Oncology, 2008; Abstract 1025.

The goal of this study presented at ASCO this year was to determine if trastuzumab should be continued beyond progression. Patients with HER-2 positive, locally advanced or metastatic breast cancer that progressed during treatment with trastuzumab with or without adjuvant and/or first-line metastatic chemotherapy were prospectively randomized to capecitabine (2,500 mg/m² on days 1-14, q21) or capecitabine plus continuation of trastuzumab (6 mg/kg, q3w). The primary end point was time to progression. With registration of lapatinib, the slowly accruing trial was closed prematurely.

Reference: Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1025).

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Capecitabine ± Trastuzumab

Trastuzumab Beyond Progression (TBP) Trial Results

Administered pre-treatments (N=156)

- 1st-line taxane + trastuzumab (N=111)
- Trastuzumab alone or with other 1st-line chemotherapy (N=42)
- Taxane + trastuzumab as adjuvant therapy (N=3)

	CAPECITABINE	CAPECITABINE + TRASTUZUMAB	HR	P-value
Median TTP	5.6 months	8.2 months	0.69	.034
Median OS	20.4 months	25.5 months	0.76	.26
ORR	27%	48%	-	.011
CBR	54%	75%	-	.0068

ORR: Overall Response Rate (CR+PR)

CBR: Clinical Benefit Rate (CR+PR+SD >24 weeks)

Von Minckwitz G et al. Presented at: American Society of Clinical Oncology, 2008; Abstract 1025.

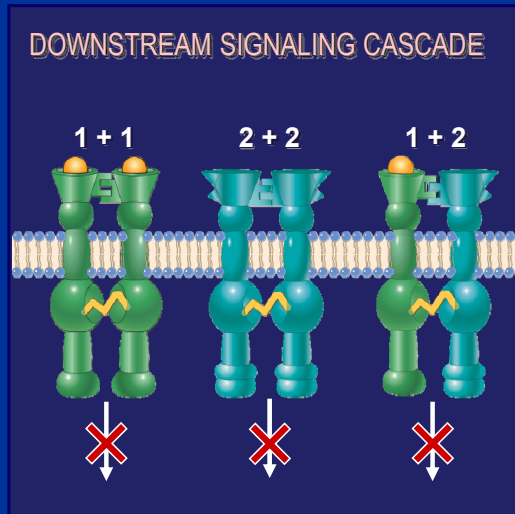
Results of the TBP study suggest a higher efficacy for continuing trastuzumab beyond trastuzumab progression when second-line chemotherapy with capecitabine is initiated. Analysis revealed a median time to progression of 5.6 months for capecitabine and 8.2 months for capecitabine + trastuzumab. Overall response rates (ORR) and clinical benefit rates (CBR) for capecitabine were 27% and 54%, respectively, compared to 48% and 75% for capecitabine + trasuzumab.

Reference: Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1025).

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Lapatinib Blocks Signaling Through Multiple Receptor Combinations

- Blocks signaling through ErbB1 and ErbB2 homodimers and heterodimers
- Might also prevent signaling through heterodimers between these receptors and other ErbB family members
- Potentially blocks multiple ErbB signaling pathways



Another recently developed treatment option is lapatinib, which is a small molecule dual (ErbB1 and ErbB2) tyrosine kinase inhibitor (TKI). Preclinical studies have shown its efficacy in both HER2-overexpressing and in normally expressing breast cancers by efficiently blocking the signal transduction downstream EGFR and HER2. Lapatinib may also block signaling with other ErbB family member, thus potentially blocking multiple ErbB signaling pathways.

References: Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. *Ann Oncol.* 2007;18: 977–984.
Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Single Agent Lapatinib Summary

SETTING	N	DOSE (MG/DAY)	CR	PR	SD	MEDIAN PFS
First line, HER2+ LABC or MBC <i>Gomez HL et al JCO 2008</i>	69	1500	0	20%	29%	16.1 wk (TTF)
	69	500 bid	0	26%	33%	15.7 wk (TTF)
	138	Both doses	0	24%	51%	-
Refractory, HER2+ <i>Burstein H et al Ann Oncol 2008</i>	140	1500	0	1%	33%	9.1 wk
Refractory, HER2- <i>Burstein H et al Ann Oncol 2008</i>	89	1500	0	0	11%	7.6 wk
Refractory, HER2+ <i>O'Shaughnessy J et al ASCO 2008</i>	145	1500	6.9%		12.4%	8.1 wk

N=number; CR=complete response, PR=partial response; SD=stable disease \geq 6 months; PFS=progression-free survival; wk=weeks; TTF=time to treatment failure

The results from these studies show that lapatinib is a reasonable option as a single agent treatment for HER2 positive breast cancer. Gomez et al. assessed the efficacy and tolerability of two lapatinib administration schedules. The overall response rate was 24% in the intent-to-treat population, and 31% of patients derived clinical benefit (CR, PR, or stable disease for \geq 24 weeks). The median time to response was 7.9 weeks, and the progression-free survival rates at 4 and 6 months were 63% and 43%, respectively.¹ Burstein and colleagues assessed the efficacy and tolerability of lapatinib in a phase II, open-label study, with patients previously treated HER2-positive (n = 140) or HER2-negative (n = 89) metastatic breast. Assessments established that approximately 6% of HER2-positive patients derived clinical benefit from lapatinib, being progression free for \geq 6 months. No objective tumor responses occurred in the HER2-negative cohort. Independent review assessments of median time to progression and median progression-free survival were similar in the HER2-positive and HER2-negative cohorts (9.1 and 7.6 weeks, respectively).² O'Shaughnessy et al. studied patients with refractory HER2+ metastatic breast cancer. Eligible women had received prior anthracycline and taxane therapy, had metastatic breast cancer with measurable lesions or bone-only disease, and had progressed on prior trastuzumab-containing therapy. Overall response rate was 6.9% with median free progression of 8.1 wk.³

References:

1. Gomez HL, Doval DC, Chavez MA, et al. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. *J Clin Oncol.* 2008;26:2999-3005.
2. Burstein HJ, Storniolo AM, Franco S, et al. A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer. *Ann Oncol.* 2008;19:1068-74.
3. O'Shaughnessy J, Blackwell KL, Burstein H, et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. *J Clin Oncol.* 2008;26:(May 20 suppl) abstr 1015).
4. Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

EGF100151: Phase III Study Comparing Lapatinib/Capecitabine vs. Capecitabine

In Women with Refractory Advanced or Metastatic Breast Cancer

Eligibility Criteria

- Progressive MBC or stage IIIB/IIIC LABC with T4 lesion
- HER2 overexpression (IHC3+ or 2+ and FISH+)
- Unlimited prior therapies, but no prior capecitabine
- Prior therapies must include:
 - Trastuzumab in metastatic setting
 - Anthracycline and taxane in either metastatic or adjuvant setting

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Lapatinib
1250 mg/day p.o. daily
Capecitabine
2000 mg/m²/day,
days 1-14, q 21 days

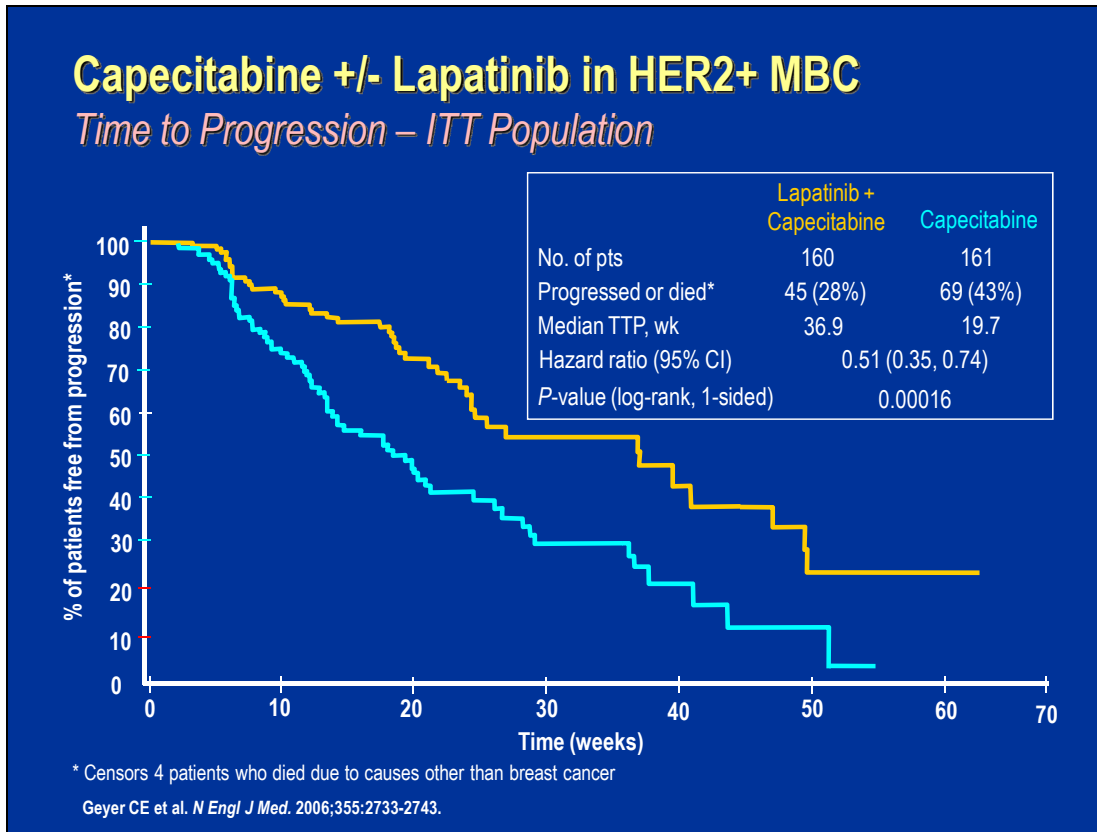
Capecitabine
2500 mg/m²/day
days 1-14, q 21 days

Primary endpoint: TTP
Secondary endpoints: OS, PFS, ORR

Geyer CE et al. *N Engl J Med.* 2006;355:2733-2743.

In this phase 3, randomized, open label study comparing lapatinib plus capecitabine with capecitabine, eligible patients had HER2-positive, locally advanced breast cancer (a T4 primary tumor and stage IIIB or IIIC disease) or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab. The combination regimen consisted of lapatinib at a dose of 1250 mg daily on a continuous basis, and capecitabine at a dose of 2000 mg per square meter of body-surface area in two divided doses on days 1 through 14 of a 21-day cycle. Capecitabine monotherapy was administered at a dose of 2500 mg per square meter of body-surface area in two divided doses on days 1 through 14 of a 21-day cycle.

References: Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355:2733-43.
Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.



During the interim analysis of this trial, 45 disease progression events occurred in the combination therapy group and 69 occurred in the monotherapy group (hazard ratio for disease progression, 0.51; 95% confidence interval [CI], 0.35 to 0.74; $P < 0.001$). By the end of the trial, a total of 49 disease-progression events occurred in the combination therapy group and 72 occurred in the monotherapy group (hazard ratio, 0.49; 95% CI, 0.34 to 0.71; $P < 0.001$). The median time to progression was 8.4 months with lapatinib + capecitabine and 4.4 months with capecitabine alone. The average hazard ratio for combination therapy as compared with capecitabine was 0.47 (95% CI, 0.32 to 0.68; $P < 0.001$). These data indicate that lapatinib + capecitabine is superior to capecitabine alone in women with HER2 positive breast cancer that has progressed after treatment regimens that included trastuzumab.

References: Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355:2733-43.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Phase III Trial of Capecitabine +/- Lapatinib in MBC

- 4/163 women in combination arm with asymptomatic drop in EF. All were at or above normal EF at subsequent assessment.
- No symptomatic CHF.
- No discontinuation of lapatinib due to cardiac toxicity.
- CNS as 1st site of progression: 11 patients in capecitabine arm, 4 in combination arm. Not statistically significant.

Geyer CE et al. *N Engl J Med.* 2006;355:2733-2743.

Asymptomatic cardiac events were identified in four women in the combination-therapy group. All of these events in the combination-therapy group were considered to be related to treatment, and all women had an left ventricular ejection fraction (LVEF) value that was at or above the lower limit of the normal range on subsequent assessment. There were no symptomatic cardiac events, and lapatinib was not discontinued because of a decrease in the LVEF. In the monotherapy group, 11 women had progressive CNS metastases, as compared with 4 women in the combination-therapy group. This difference was not statistically significant ($P = 0.10$ by Fisher's exact test).

Reference: Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355:2733-43.

CASE STUDY 2:
Clinical Management

- 64-year-old African American woman with recurring HER2+ breast cancer
- She was disease free for 16 months following completion of trastuzumab
- Options for management:
 - Capecitabine /Trastuzumab
 - Lapatinib/Capecitabine

In the context of this specific patient, an African-American woman with recurrent breast cancer who is not progressing on trastuzumab, rather she is progressing after trastuzumab in the adjuvant setting. There are not a lot of patients who meet this situation to date. However, more and more women are progressing after receiving adjuvant therapy and therefore this type of situation needs to be considered. In this case, based on extrapolation from the presented trials, two options would be either combination of capecitabine plus trastuzumab or lapatinib plus capecitabine.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Trastuzumab and Pertuzumab

Distinct Epitopes on HER2 Extracellular Domain

Trastuzumab

- Potent inhibitor of HER2-mediated signaling pathways
- Activates antibody-dependent cellular cytotoxicity
- Inhibits shedding and, thus, formation of p95

Pertuzumab

- Prevents receptor dimerization
- Potent inhibitor of HER-mediated signaling pathways

Gelmon KA, et al. ASCO 2008. Abstract 1026.

Pertuzumab is a humanized monoclonal antibody that is at the forefront of several clinical trials. Pertuzumab binds to the dimerization epitope (subdomain II) of HER2. HER2 homodimerization and heterodimerization with HER3 is blocked thereby preventing signal transduction. In comparison, trastuzumab binds to subdomain IV of HER2 and abrogates signaling without affecting ligand-driven HER2-HER3 dimerization. Xenograft studies suggest that trastuzumab and pertuzumab have a synergistic effect due to their complementary mechanisms of action.

Reference: Gelmon KA, Fumoleau P, Verma S, et al. Results of a phase II trial of trastuzumab (H) and pertuzumab (P) in patients (pts) with HER2-positive metastatic breast cancer (MBC) who had progressed during trastuzumab therapy. *J Clin Oncol.* 2008;26(May 20 suppl):abstr 1026

Phase II Trial of Pertuzumab plus Trastuzumab in Patients with HER2+ MBC

Objective: Evaluate the efficacy and safety of combination therapy using anti-HER2 antibodies with distinct binding modes in patients who progressed on trastuzumab.

Trastuzumab: 4 mg/kg load → 2 mg/kg qw or 8 mg/kg load → 6 mg/kg q3w
 Pertuzumab: 840 mg load → 420 mg q3w

Response	% patients (N=66)
Complete Response	8%
Partial Response	17%
Stable Disease ≥ 6months	26%
Objective Response Rate	24%
Clinical Benefit Rate	50%

Median PFS:
24 weeks

32% of patients had not progressed at data cut-off

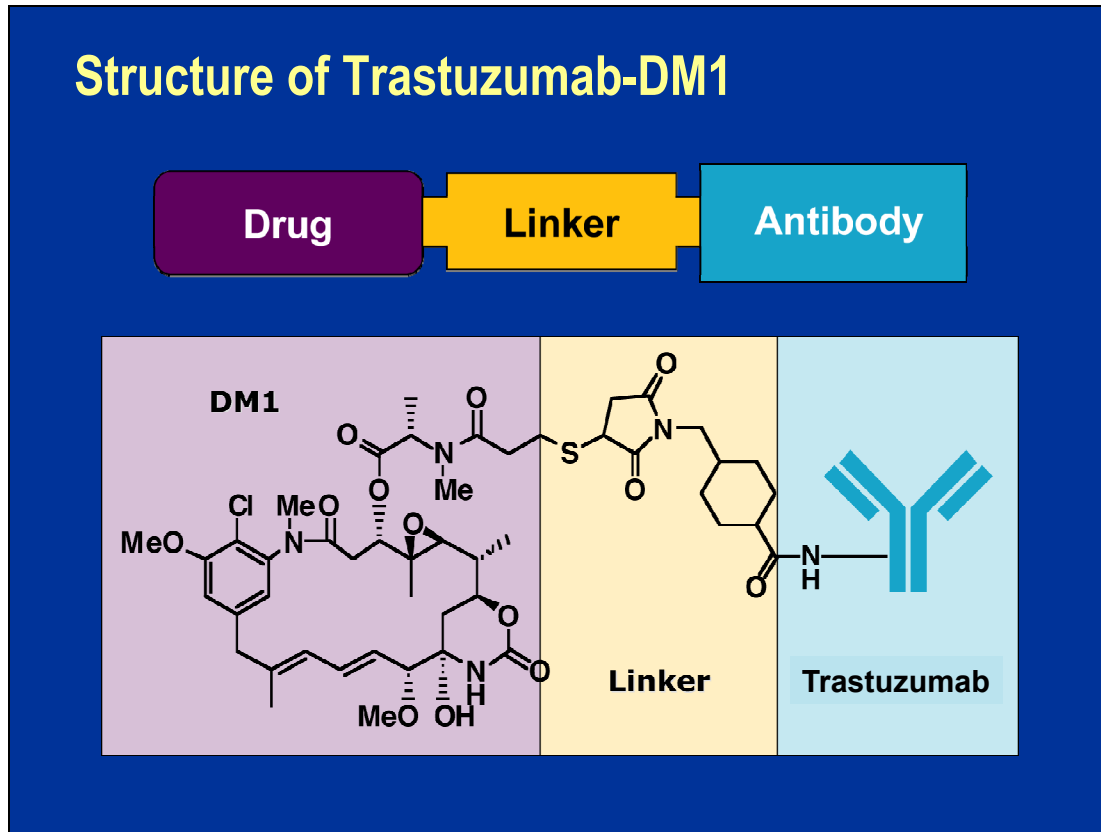
- 4 out of 66 patients with grade 3 AE: diarrhea (2); central line infection (1); rash (1)
- No significant cardiac events observed: 3 pts with LVEF declines <50% absolute and ≥10% points.

Phase III study (CLEOPATRA): Trastuzumab + Docetaxel pertuzumab

Gelmon, ASCO 2008, Abstract 1026

This single-arm, Simon-type, two-stage phase II trial included patients with measurable, centrally tested HER2-positive metastatic breast cancer, ≥3 lines of prior therapy (including adjuvant therapy), and disease progression during prior trastuzumab therapy. Consenting patients received trastuzumab at 2 mg/kg qw (4 mg/kg loading dose [LD]) or 6 mg/kg q3w (8 mg/kg LD) plus pertuzumab at 420 mg q3w (840 mg LD) starting within 9 weeks of the last dose of trastuzumab. Sixty-six patients have been enrolled and all have received ≥2 doses of study medication. Only 3 treatment-related adverse events of severity G3, and none of G4, have been observed (diarrhea, rash, and a central line infection), all of which resolved and treatment continued. No patients withdrew due to treatment-related or cardiac adverse events. Preliminary data shows objective responses observed in 6 of the 33 evaluable pts (1 CR, 5 PRs). Additionally, 7 pts achieved SD ≥6 mths and 10 patients SD <6 mths. The combination of trastuzumab and pertuzumab in this study was well tolerated and active in patients with metastatic breast cancer whose disease had progressed during therapy with trastuzumab. There is now a Phase III trial called CLEOPATRA studying the effect of trastuzumab plus docetaxel with or without pertuzumab.

Reference: Gelmon KA, Fumoleau P, Verma S, et al. Results of a phase II trial of trastuzumab (H) and pertuzumab (P) in patients (pts) with HER2-positive metastatic breast cancer (MBC) who had progressed during trastuzumab therapy. *J Clin Oncol.* 2008;26(May 20 suppl):abstr 1026



Trastuzumab-DM1 (T-DM1) is another molecule being studied in clinical trials. T-DM1 is a first-in-class HER2 antibody-drug conjugate designed to combine the biological activity of trastuzumab with the targeted delivery of the highly potent antimicrotubule agent, DM1, to HER2 expressing cells. The MCC linker molecule of T-DM1 provides a stable bond between trastuzumab and DM1 that is designed to prolong exposure and reduce toxicity of T-DM1 while maintaining activity.

References:

1. Beeram M, Burris III HA, Modi S, et al. A phase I study of trastuzumab-DM1 (T-DM1), a first-in-class HER2 antibody-drug conjugate (ADC), in patients (pts) with advanced HER2+ breast cancer (BC). *J Clin Oncol.* 2008;26 (May 20 suppl): abstr 1028.
2. Holden SN, Beeram M, Krop IE, et al. A phase I study of weekly dosing of trastuzumab-DM1 (T-DM1) in patients (pts) with advanced HER2+ breast cancer (BC). *J Clin Oncol.* 2008;26(May 20 suppl): abstr 1029.

Phase I Studies of Trastuzumab-MCC-DM1 (T-DM1) In Patients With HER2-Overexpressing MBC

Objectives: To assess the dose, safety, tolerability and pharmacokinetics of weekly* or every 3 weekly† antibody-trastuzumab conjugate (T-DM1) continuously in patients with HER2+ breast cancer who have progressed on trastuzumab.

Dose schedules (mg/kg, N):

Weekly: **A** (1.2,N=3), **B** (1.6,N=3), **C** (2.0,N=3), **D** (2.4,N=7), **E** (2.9,N=3)

3 weekly: **A** (0.3,N=3), **B** (0.6,N=1), **C** (1.2,N=1), **D** (2.4,N=1), **E** (4.8,N=3), **F** (3.6,N=15)

	Safety	Antitumor Activity
Weekly T-DM1* (N=19)	- Grade 3 AEs (>1 pt): Thrombocytopenia (2 pts; B and E) Hypokalemia (2 pts; A and D) - No grade 4 AEs or cardiac toxicity	15 evaluable patients Confirmed ORR: 53%
3 weekly T-DM1† (N=24)	- Grade 3/4 AEs (>1 pt): Thrombocytopenia (3 pts; E and F). One serious drug-related AE: pulmonary hypertension (F) - No cardiac toxicity observed	9 evaluable patients Confirmed RR: 44%

* DLT in 2/3 patients in cohort **E** † DLT in 2/3 patients in cohort **E**

*Holden, ASCO 2008, Abstract 1029

†Beeram, ASCO 2008, Abstract 1028

Clinical phase I trials are underway to study the dose, safety, tolerability, and pharmacokinetics of weekly¹ or every 3 weekly² T-DM1 in patients with HER2 positive breast cancer who have progressed while on trastuzumab containing regimens. Adverse events observed with weekly T-DM1 is grade 3 thrombocytopenia and hypokalemia.¹ No grade 4 adverse events or cardiac toxicity have been noted. The overall response rate thus far is 53%. With every 3 weekly T-DM1 adverse events include thrombocytopenia and pulmonary hypertension, however no cardiac toxicity has been observed.² Currently, the confirmed response rate is 44%.

References:

1. Holden SN, Beeram M, Krop IE, et al. A phase I study of weekly dosing of trastuzumab-DM1 (T-DM1) in patients (pts) with advanced HER2+ breast cancer (BC). *J Clin Oncol.* 2008;26(May 20 suppl): abstr 1029.
2. Beeram M, Burris III HA, Modi S, et al. A phase I study of trastuzumab-DM1 (T-DM1), a first-in-class HER2 antibody-drug conjugate (ADC), in patients (pts) with advanced HER2+ breast cancer (BC). *J Clin Oncol.* 2008;26 (May 20 suppl): abstr 1028.

Conclusions

Management of HER2 + Metastatic Breast Cancer

- First line
 - Survival benefit with trastuzumab single agent or in combination with taxanes
 - Cardiotoxicity
- Progression while on trastuzumab
 - Improved with TTP trastuzumab-capecitabine or lapatinib-capecitabine
- Additional combinations and potential for targeted delivery of chemotoxic agents

The management of HER2-positive metastatic breast cancer in the first-line setting is typically trastuzumab with chemotherapy. However, there is activity of trastuzumab as a single agent and it can be considered in that setting. In women who have progressed on trastuzumab, there are several options including trastuzumab with capecitabine, lapatinib with capecitabine. Some newer agents undergoing study in clinical trials currently may provide additional options in the future.

Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

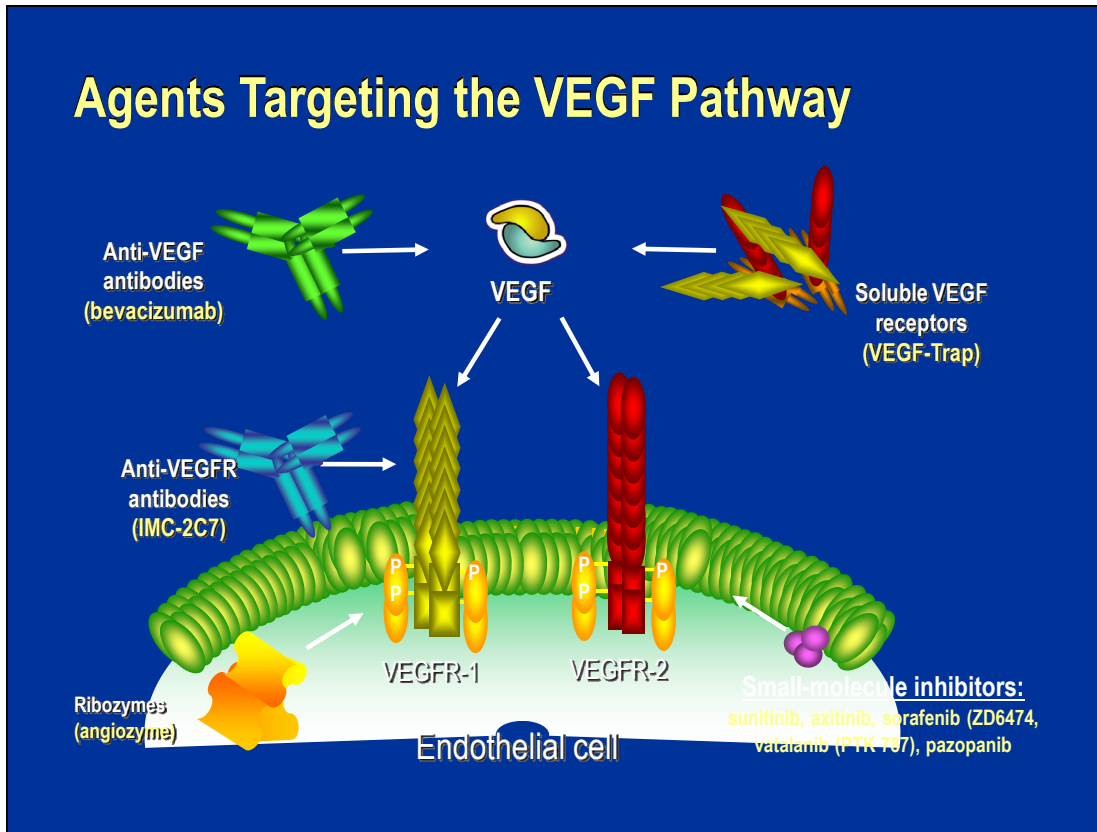
CASE STUDY 3:

Antiangiogenesis Agents in Metastatic Breast Cancer

- 53-year-old woman initially diagnosed with T2N0M0 ER/PR/HER2-negative grade III infiltrating ductal carcinoma of the breast
- She underwent surgery, followed by dose dense AC→T
- 16 month later, she presents with mild cough
- PET/CT scan: several 1.5-2cm nodules in the right and left lung and a 1.5cm mass in the right adrenal gland.
- FNA and immunochemistry consistent with triple negative disease
- Blood work: normal
- ECOG performance score: 1.

In the third case, approaches for triple-negative disease and questions surrounding the use of antiangiogenic agents will be discussed. This is a 53-year-old woman who was initially diagnosed with T2/N0/M0 ER/PR/HER2-negative, grade III infiltrating ductal carcinoma of the breast. She underwent surgery followed by dose-dense AC, followed by paclitaxel. Sixteen months later she presents with a mild cough. A PET/CT scan is done in this case to stage her and she is found to have several roughly 1.5 to 2.0-centimeter nodules in the right and left lung, and a 1.5-centimeter mass in the right adrenal gland. She has a fine-needle aspirate of the adrenal mass and that confirms carcinoma with immunohistochemistry consistent with triple-negative disease. Her blood work is normal and her ECOG performance score is 1.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.



There are a variety of agents now targeting the VEGF angiogenesis pathway. Bevacizumab is a recombinant VEGF antibody derived from a humanized murine monoclonal antibody that can recognize all known isoforms of VEGF-A and prevents receptor binding, thereby inhibiting angiogenesis and tumor growth. *In vitro* bevacizumab inhibits VEGF-induced endothelial cell proliferation and migration, and in xenograft models of a range of tumor types (including breast cancer) tumor growth is significantly decreased by bevacizumab. IMC-2C7 is an anti-VEGF receptor antibody under investigation.¹

Inhibition of the VEGFR mRNA has been attempted both with ribozyme (catalytic RNA molecules), which specifically cleave the mRNAs for the primary VEGFRs, and antisense VEGF. Angiozyme is a synthetic ribosome that cleaves the mRNA for the receptor VEGFR1/Flt-1. Preclinical studies confirmed inhibition of both primary tumor growth and metastasis.¹

Several receptor tyrosine kinase inhibitors (TKIs) that target the tyrosine kinase portion of VEGFR1 and VEGFR2 have been developed and are being investigated. The orally administered VEGFR2 inhibitor ZD6474 was generally well tolerated but exhibited little activity in patients with refractory metastatic breast cancer. A multireceptor targeting agent is PTK787, which is a pan-VEGF, PDGFR, c-kit and c-Fos receptor TKI. It inhibited the growth of a broad panel of carcinomas in rodent models, with histological examination revealing inhibition of microvessel formation.¹

VEGF-Trap is a fully human soluble decoy receptor protein that consists of a fusion of the second immunoglobulin (Ig) domain of human VEGFR1 and the third Ig domain of human VEGFR2 with the constant region (Fc) of human IgG1. VEGF trap has a high affinity for all isoforms of VEGFA, as well as PlGF.²

References:

- Fox SB, Generali DG, Harris AL. Breast tumour angiogenesis. *Breast Cancer Res.* 2007;9:216.
 Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer.* 2008 Aug;8:579-91.

E2100: First-Line Paclitaxel + Bevacizumab

Summary of Outcome

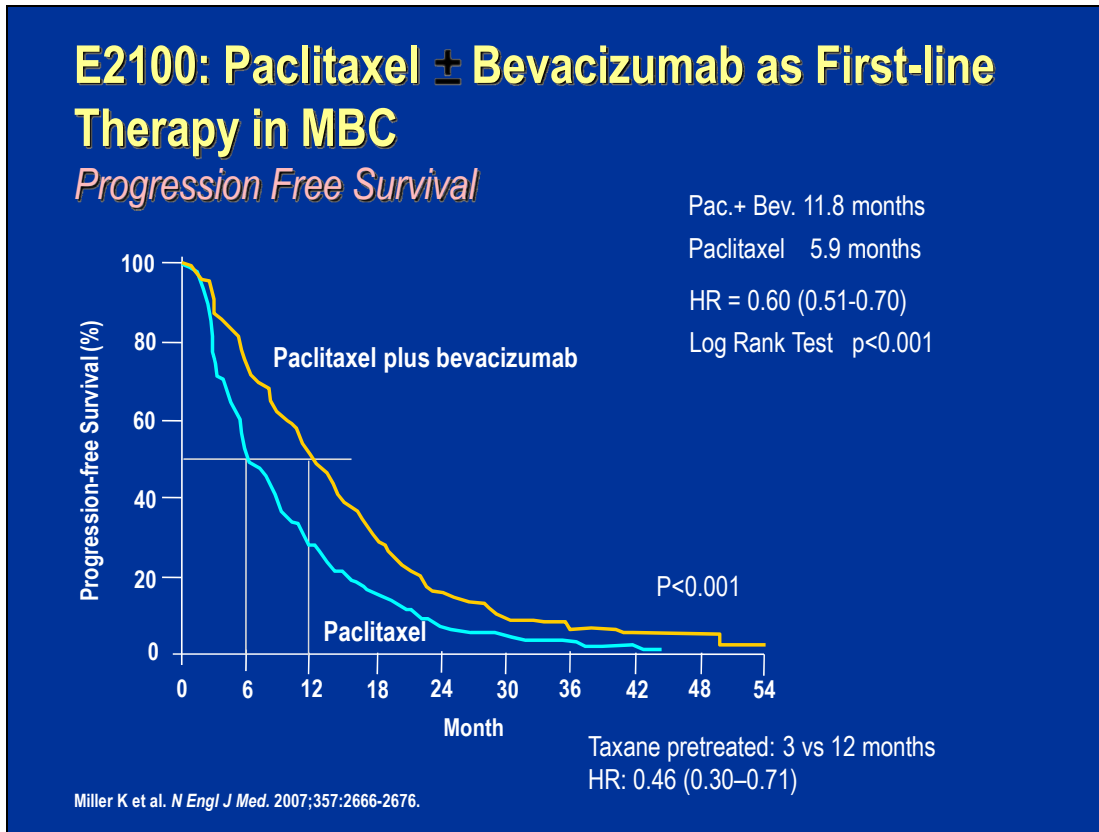
	Paclitaxel	Paclitaxel/ Bevacizumab	HR	P-Value
Progression-Free Survival	5.9 mo	11.8 mo	0.60	<0.001
Response Rate (All Patients)	21.2%	36.9%	-	<0.001
Response Rate (Measurable Disease)	25.2%	49.2%	-	<0.001
Median Survival	25.3 mo	26.7 mo	0.88	0.16
1-Year Survival	73.4%	81.2%	-	<0.001

Miller K et al. *N Engl J Med.* 2007;357:2666-2676.

E2100 was an open label, phase 3 trial where randomly assigned patients received 90 mg of paclitaxel per square meter of body-surface area on days 1, 8, and 15 every 4 weeks, either alone or with 10 mg of bevacizumab per kilogram of body weight on days 1 and 15. Paclitaxel plus bevacizumab significantly prolonged progression-free survival as compared with paclitaxel alone (median, 11.8 vs. 5.9 months; hazard ratio for progression, 0.60; $P < 0.001$) and increased the objective response rate (36.9% vs. 21.2%, $P < 0.001$). The overall survival rate, however, was similar in the two groups (median, 26.7 vs. 25.2 months; hazard ratio, 0.88; $P = 0.16$).

Reference: Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007 Dec;357:2666-76.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.



This figure shows the difference in progression-free survival between these two groups of patients. Paclitaxel plus bevacizumab significantly prolonged progression-free survival as compared with paclitaxel alone (median, 11.8 vs. 5.9 months; hazard ratio for disease progression, 0.60; $P < 0.001$). At 6 to 12 months there is an approximate 40% relative benefit. Despite a striking improvement in progression-free survival, the addition of bevacizumab did not prolong overall survival in this study. Researchers found that treatment with bevacizumab early in the course of metastatic breast cancer, when angiogenic pathways are less redundant, improved progression-free survival and the objective response rate.

References: Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007 Dec;357:2666-76.

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Bevacizumab Toxicity

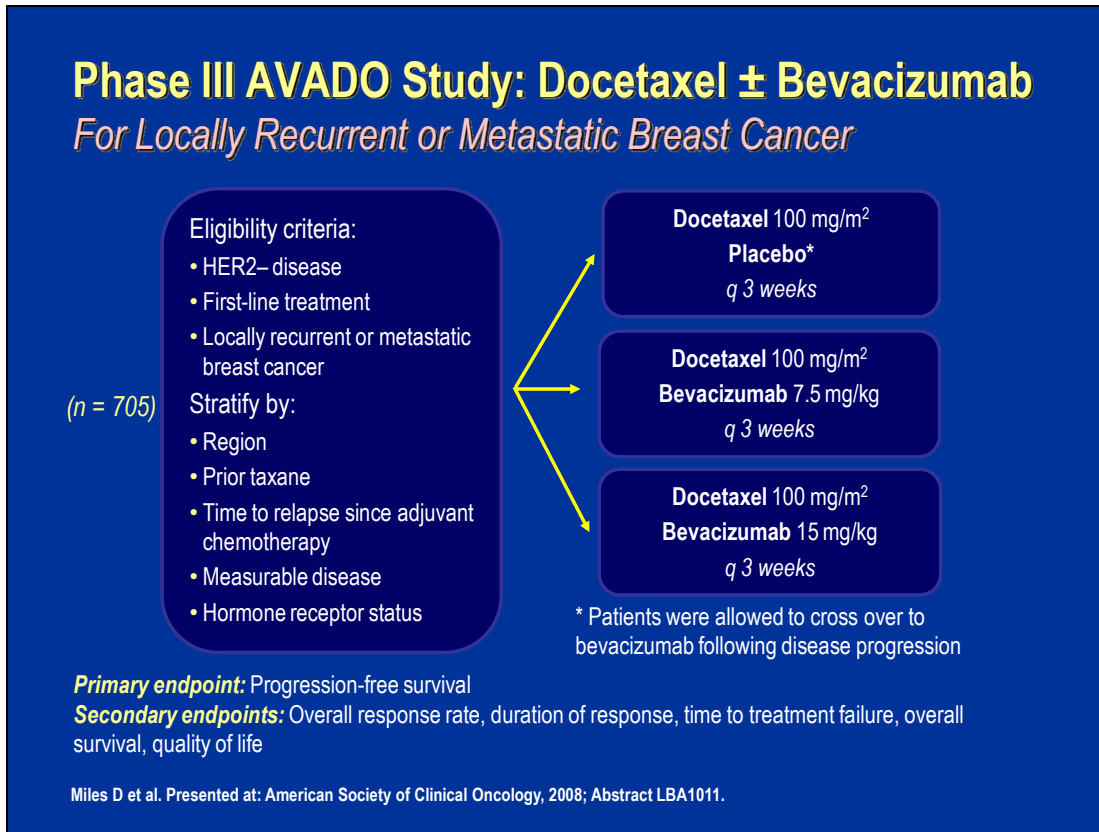
NCI-CTC Grade 3 and 4

	Paclitaxel (n=332)		Pac.+ Bev. (n=350)		P Value
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)	
Hypertension	0	0	14.4	0.3	<0.001
Thromboembolic	0.6	0.9	1.6	0.5	NS
Bleeding	0	0	0.5	0	NS
Infection	2.9	0	8.8	0.5	<0.001
Fatigue	4.6	0.3	8.8	0.3	0.04
Cerebrovascular ischemia	0	0	0.8	1.1	0.02
Proteinuria	0	0	2.7	0.8	<0.01
Sensory neuropathy	17.1	0.6	23.0	0.5	0.05
Headache	0	0	2.2	0	0.008

Miller K et al. *N Engl J Med.* 2007;357:2666-2676.

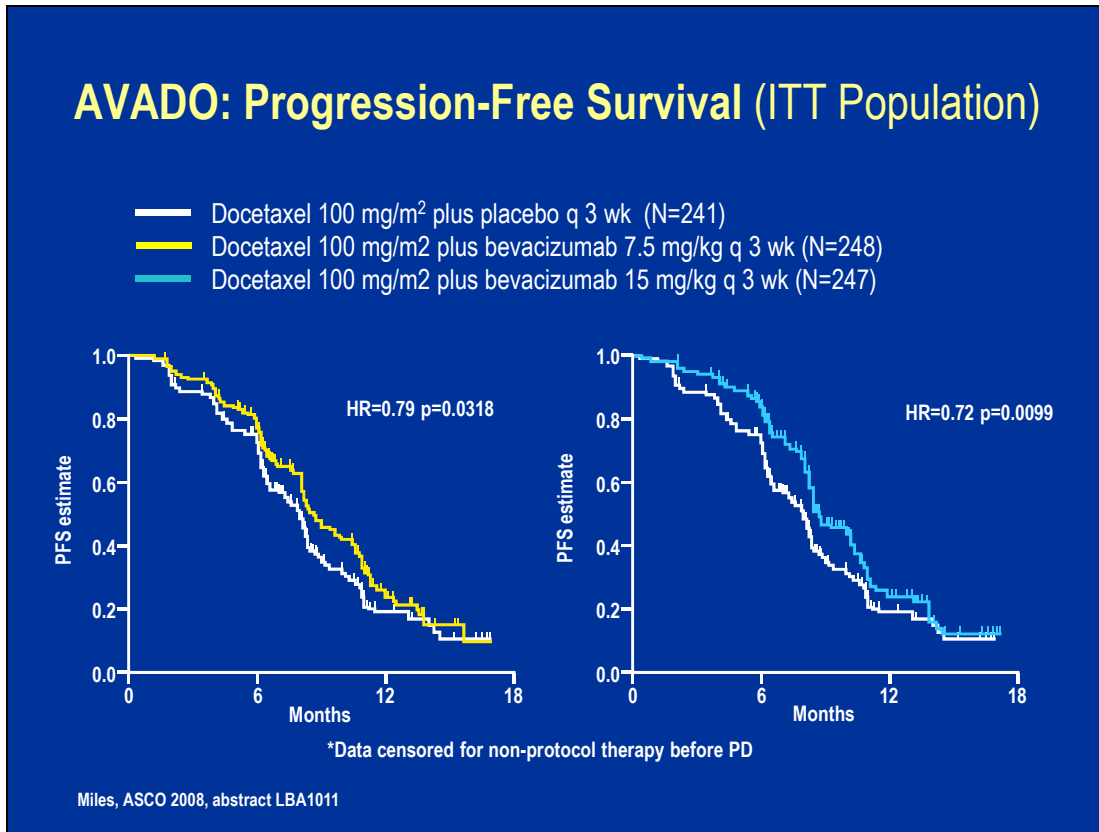
The addition of bevacizumab had little effect on the frequency or severity of expected paclitaxel-related toxic effects. Hematologic, gastrointestinal, and musculoskeletal toxic effects were minimal and similar in both groups. Grade 3 or 4 neuropathy (23.6% vs. 17.6%, $P=0.03$), infection (9.3% vs. 2.9%, $P<0.001$) and fatigue (8.5% vs. 4.9%, $P=0.04$) were more frequent in the combination group. Hypertension was increased in patients receiving paclitaxel and bevacizumab, but was easily managed with additional medications. Physicians need to closely monitor patients at risk for hypertension who receive bevacizumab. There was a slight increase in proteinuria, which should also be monitored in patients due to its association with hypertension. The dose limiting toxicity for bevacizumab is headache, however, this side effect generally improves over time.

Reference: Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007;357:2666-76.



The AVADO study investigated the combination of bevacizumab (full dose at 15 mg/kg versus half dose at 7.5 mg/kg) and docetaxel as first-line therapy in patients with untreated metastatic HER2 normal disease. In this randomised, double-blind phase III study docetaxel was administered q3 weeks for up to 9 cycles and bevacizumab/docetaxel was administered q3 weeks until disease progression or unacceptable toxicity.

References: Miles D, Chan A, Romieu G, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol*. 2008;26 (May 20 suppl):abstr LBA1011. *Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents*. Medscape CME Spotlight. Oct 2008.



Bevacizumab at two doses (7.5 or 15 mg/kg every three weeks) in combination with docetaxel in both arms significantly improved progression free survival compared to docetaxel alone, although a similar effect was observed with docetaxel plus placebo. Objective response rate was superior in both bevacizumab-containing arms relative to docetaxel alone.

Reference: Miles D, Chan A, Romieu G, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol*. 2008;26 (May 20 suppl):abstr LBA1011.

AVADO Summary of Response

		Placebo (n=207)	Bev 7.5† (n=201)	Bev 15† (n=206)	
ITT population	TTP	8mos	8.7mos	8.8mos	
	HR	--	0.79	0.72	
	p value (vs placebo)	--	0.0318	0.0099	
Patients with measurable disease	ORR	44	55	63	
	p value (vs placebo)	--	0.0295	0.0001	
	Best response				
	CR	1	3	1	
	PR	44	52	62	
SD	39	35	25		
PD	12	5	4		

Miles D et al. Presented at: American Society of Clinical Oncology, 2008; Abstract LBA1011.

The overall response rate (ORR) increased progressively with the addition and increased dosing of bevacizumab. The difference between the AVADO trial and E2100 is that AVADO was designed to give patients the maximum number of cycles of docetaxel. Bevacizumab is essentially being studied as a single agent. While progression free survival did not improve by a large amount with the addition of bevacizumab, it did improve the response of patients to docetaxel. Therefore, bevacizumab may have a primary role in combination chemotherapy, but not as a maintenance single agent. More data is needed to confirm this role.

References:

Miles D, Chan A, Romieu G, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol*. 2008;26 (May 20 suppl):abstr LBA1011.

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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

Miles D et al. Presented at: American Society of Clinical Oncology, 2008; Abstract LBA1011.

This study was not powered to assess differences in survival and no difference in overall survival between arms was seen. Of note, there was no observed increase in treatment-related deaths in the bevacizumab arm secondary to mortal-type toxicities.

Reference: Miles D, Chan A, Romieu G, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol*. 2008;26 (May 20 suppl):abstr LBA1011.

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AVADO Study: Grade \geq 3 Adverse Events

	Docetaxel/Placebo (n = 233)	Docetaxel/Bevacizumab 7.5 mg/kg (n = 250)	Docetaxel/Bevacizumab 15 mg/kg (n = 247)
Any Grade \geq 3 AE	67%	75%	74%
AE-related Death	2.6%	1.6%	1.6%
Neutropenia	17%	19%	20%
Febrile Neutropenia	12%	15%	17%
Diarrhea	3%	7%	7%
Fatigue	5%	8%	6.5%
PPE	0.9%	5%	6%
Mucosal Inflammation	0.4%	4%	5%
Sensory Neuropathy	2%	3%	4.5%
Anemia	3%	0.4%	1%
Infection	3%	0.8%	0.4%
Venous Thromboembolic Event	3%	1%	1%
Hypertension	1%	0.4%	3%
Bleeding	0.9%	1%	1%

Grade 3/4 events occurring in < 1% in each arm: Wound-healing complications, GI perforation, CHF, arterial thromboembolic event, proteinuria

Miles D et al. Presented at: American Society of Clinical Oncology, 2008; Abstract LBA1011.

Toxicities were modest and mainly docetaxel related. PPE and mucosal inflammation were increased in the bevacizumab arms (0.9% vs 5% vs 6%; 0.4% vs 4% vs 5%). There was a slight increase in sensory neuropathy in the higher dose of bevacizumab (2% vs 3% vs 4.5%) suggesting a dose relationship where bevacizumab could potentiate some taxane related and docetaxel specific toxicities. Overall, adverse events were very modest and well managed.

References:

Miles D, Chan A, Romieu G, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol*. 2008;26 (May 20 suppl):abstr LBA1011.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Selected Agents Targeting the VEGF Pathway

Class	Examples	Targets	Stage of Development	Company
AGENTS TARGETING THE VEGF LIGAND				
Antibodies	Bevacizumab 1121b	VEGF	Approved Phase III	Genentech Im-clone
Soluble receptors	Aflibercept	VEGF Trap	Phase II	Regeneron/Sanofi Aventis
AGENTS TARGETING THE VEGF RECEPTORS				
Small molecule inhibitors	Sunitinib	VEGFR-2, PDGFR, c-Kit	Phase III	Pfizer
	Axitinib	VEGFR-2, PDGFR	Phase II	Pfizer
	SU014813	VEGFR1,2; c-Kit	Phase II	Pfizer
	Pazopanib	VEGFR1,2;PDGFR, c-Kit	Phase II	GSK
	Sorafenib	Raf, VEGFR1,2; c-Kit	Phase II	Bayer/Onyx
	Vatalanib	VEGFR-1/2 PDGFR, c-Kit	Phase II/III	Novartis
	AEE788	VEGFR1,2; ErbB1,2	Phase I	Novartis
	Vandetanib	VEGFR-2/EGFR	Phase II/III	AstraZeneca
	Cediranib	VEGFR, c-Kit	Phase II/III	AstraZeneca
Motesanib diphosphate	VEGFR1,2; PDGFR, c-Kit	Phase II/III	Amgen	

Other agents that target the VEGF pathway that are the focus of on-going clinical trials. These agents include antibodies, soluble receptors, and small molecule inhibitors. Some of these small molecule agents target other receptors, such as platelet-derived growth factor receptor (PDGFR), which are also critical to the process of angiogenesis.

References: www.clinicaltrials.gov

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

TKI for Advanced Breast Cancer

Phase II Results

Sunitinib single agent – 64 pts

- 7 (11%) partial response; 3 (5%) stable disease for 6mos
- Median TTP 10 weeks; OS 38 weeks

Adverse events

- Anorexia, mucosal inflammation, headache (grade 3)
- Neutropenia, thrombocytopenia (grade 4)

Burstein HJ et al. *J Clin Oncol.* 2008;26:1810-1816.

Sunitinib is an oral tyrosine kinase inhibitor (TKI) that targets several receptor tyrosine kinases, including VEGFR (VEGFR-1, VEGFR-2 and VEGFR-3), PDGFR (PDGFR-alpha and PDGFR-beta), KIT, and colony-stimulating factor-1 receptor. In a Phase II trial in heavily pretreated patients, the primary objective was to determine the antitumor activity of sunitinib at a starting dose of 50 mg administered once daily for 4 weeks, followed by 2 weeks off treatment, in repeated 6-week cycle. Eleven percent (11%) had a partial response to single-agent sunitinib and 3 patients had stable disease for 6 months. There were significant adverse events, such as grade 3 headache, mucosal inflammation, and decreased oral intake or anorexia. Patients also had grade 4 neutropenia and thrombocytopenia that resulted in dose delays and reduction. Studies are now trying to determine how to modulate these issues.

References: Burstein HJ, Elias AD, Rugo HS, et al. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol.* 2008;26:1810-6.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

TKI for Advanced Breast Cancer

Axitinib-docetaxel vs docetaxel – 168 pts

- Median TTP: 8.2 mo vs 7 mo; HR 0.73; ORR: 40% vs 23% ($p=0.038$)
- Adverse events axitinib>docetaxel
 - Grade 3-4
 - febrile neutropenia (16 vs 7%)
 - fatigue (13 vs 5%)
 - stomatitis (13 vs 2%)
 - diarrhea (11 vs 0%)
 - hypertension (5 vs 2%).

Rugo HS. Presented at: American Society of Clinical Oncology, 2007; Poster 1003.

The primary objective was to determine whether the time to progression (TTP) of axitinib (VEGF specific) + docetaxel is superior to docetaxel +placebo. This was a Phase II randomized trial at 80 mg/m² q 3 weeks of docetaxel in combination with 5 mg BID of axitinib. Improvement in TTP as well as overall response rate (ORR) was markedly increased in those who had prior adjuvant chemotherapy. This indicates that anti-angiogenic agents may help in reversing resistance. There was an enhancement of several toxicities in the axitinib + docetaxel arm. Axitinib is now being tested against other agents that do not have the same toxicity profile, such as gemcitabine.

References: Rugo HS, Stopeck A, Joy AA, et al. A randomized, double-blind phase II study of the oral tyrosine kinase inhibitor (TKI) axitinib (AG-013736) in combination with docetaxel (DOC) compared to DOC plus placebo (PL) in metastatic breast cancer (MBC). *J Clin Oncol*. 2007;25 (18S): abstract 1003.

Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

CASE STUDY 3: ***Clinical Management***

- 53-year-old woman with ER/PR/HER2-negative breast cancer, prior treatment dose dense AC→T
- Recurrence at 16 month in lung and adrenal glands
- Very mild symptoms
- Option for management:
 - Taxane-bevacizumab
 - Single agent CT
 - Combination CT
 - Paclitaxel- bevacizumab preferred
 - Prior exposure to taxane
 - Visceral, poor prognosis disease

This 53-year-old woman with triple negative breast cancer, who received prior treatment with dose dense AC → T adjuvant therapy and whose disease recurred at 16 months in the lung and adrenal glands. Her symptoms are mild at this point in time with no signs of hypoxia or shortness of breath. Options for management include taxane/bevacizumab combination, single agent chemotherapy without bevacizumab, or a combination chemotherapy. The preferred choice of treatment would be paclitaxel and bevacizumab because this patients fits into the subgroup analysis from two different trials; exposure to prior taxane in the adjuvant setting and visceral poor prognosis disease, even though her symptoms are mild. The goal here is to get the best response rate and the longest response rate in the first-line setting.

Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Conclusions

- Postmenopausal hormone positive MBC
 - Tamoxifen, AI, fulvestrant are all options
 - Initial therapy with AI preferred
 - Individualize therapy based on safety and patient compliance as well as tumor burden and prior responses
 - Use chemotherapy-based treatment for rapidly progressing or hormonal therapy-refractory disease
- HER2+ MBC
 - Trastuzumab, single agent or in combination with chemotherapy, as first-line therapy
 - Upon progression, switch to lapatinib plus capecitabine or change chemotherapy (eg. capecitabine) with continuation of trastuzumab
 - Newer HER2 targeted approaches including immunoconjugates and other agents under investigation

In summary, for hormone receptor-positive metastatic breast cancer, use of aromatase inhibitors in postmenopausal patients as first line therapy and other options, such as fulvestrant and even tamoxifen in certain patients are all treatment options. Therapy should be individualized to the patient based on safety and compliance as well as tumor burden and response to prior therapy. Chemotherapy based treatment should be used for disease that is rapidly progressing or is refractive to hormonal therapy.

In HER2-positive disease, HER2-targeted agents, like trastuzumab, should be used in the first-line setting. With progression on trastuzumab, which will start to become more prevalent, the different options are to switch out the chemotherapy and continuing trastuzumab versus switching to lapatinib and capecitabine, which is an FDA-approved option. Both options are viable and different characteristics may influence that treatment decision. The possibility of new HER2 targeted agents as well as the new tyrosine kinase inhibitors may be possible treatment options when they become available.

Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.

Conclusions *(cont.)*

- Targeted therapy for triple negative MBC
 - Taxane plus bevacizumab - improves RR, TTP over taxane alone
 - Other agents targeting the VEGF pathway under investigation

Finally, not only in triple-negative disease, but in any metastatic disease, the options for antiangiogenic therapy is now primarily studies in the HER2/neu-negative population. Taxane therapy with bevacizumab can improve response rate and time to progression. Other agents targeting the VEGF pathway that are now under investigation will build on and expand the treatment tools for treating triple negative disease.

Reference: Advances in the Management of Metastatic Breast Cancer: Hormonal Therapy and Targeted Agents. Medscape CME Spotlight. Oct 2008.