5 Minute JournalClub

Key SABCS Presentations

Issue 8, 2011

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CME Information

LEARNING OBJECTIVES

- Recognize the rate of discordance in ER and HER2 status between primary breast cancer and sites of tumor relapse.
- Counsel patients with recurrent breast cancer about the clinical implications of biomarker discordance and the role of repeat biopsy, when feasible.
- Compare and contrast the time to onset of ONJ and subsequent dental outcomes in patients with BC who received bisphosphonates either alone or in combination with bevacizumab.
- Counsel patients with BC and bone metastases about the benefits and risks of treatment with denosumab relative to zoledronic acid.
- Recall the efficacy and tolerability of tamoxifen with or without everolimus in hormone receptor-positive breast cancer previously treated with an AI.
- Recall the efficacy of fulvestrant with lapatinib in AI-refractory hormone receptor-positive breast cancer.
- Educate patients with metastatic breast cancer about the relative risk of clinically significant cardiac toxicity with the combination of bevacizumab and chemotherapy.
- Assess the efficacy and safety of the combination of bevacizumab and 75-mg/m^2 docetaxel with or without trastuzumab for the first-line treatment of HER2-negative and HER2-positive metastatic breast cancer.

CME Information

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FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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No real or apparent conflicts of interest to disclose.

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Advisory Committee: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc, EMD Serono Inc, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi-Aventis.

Discordance in Hormone Receptor and HER2 Status in Breast Cancer during Tumor Progression

Lindstrom LS et al.

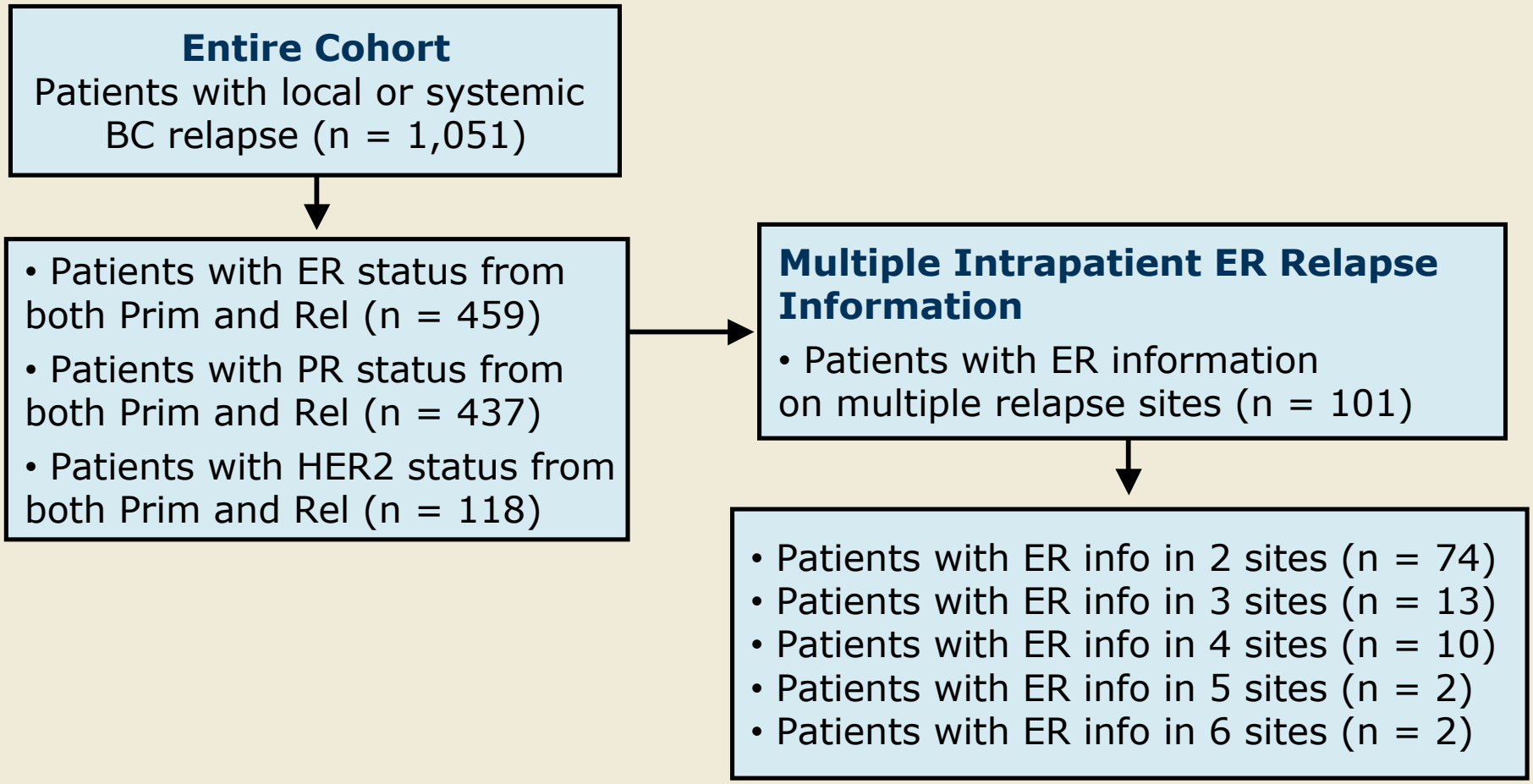
Proc SABCS 2010;Abstract S3-5.

Background and Methods

- Management of metastatic breast cancer (mBC) is routinely based on primary tumor ER/PR and HER2 status.
  - Alterations in these predictive factors for therapy may lead to altered management.
- **Methods:**
  - Patients (n = 1,051) with breast cancer experiencing relapse from 1997-2007 and reported to the Stockholm-Gotland Breast Cancer Registry were investigated.
  - Biochemical, IHC or immunocytochemical (ICC) methods were used for determination of ER and PR.
  - Primary tumor HER2 status investigated using IHC with two or three monoclonal antibodies, confirmed by FISH for IHC 2+ and 3+ and recurrences using ICC or FISH.
- **Aim:**
  - To determine if hormone receptors and HER2 expression profiles change between primary breast tumor (Prim) and relapse (Rel).

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

Hormone Receptor and HER2 Cohort



Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

Intraindividual ER and HER2 Status in Primary Tumor and Relapse

ER status	Local and systemic relapse n = 459	Systemic relapse only n = 335
Prim(+)/Rel(+)	44.0%	39.1%
Prim(+)/Rel(-)	26.4%	30.7%
Prim(-)/Rel(+)	6.7%	6.3%
Prim(-)/Rel(-)	22.9%	23.9%
HER2 status	**n = 118**	**n = 98**
Prim(+)/Rel(+)	21.2%	18.4%
Prim(+)/Rel(-)	6.8%	6.1%
Prim(-)/Rel(+)	3.4%	4.1%
Prim(-)/Rel(-)	68.6%	71.4%

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

ER Status Change between First and Subsequent Relapses*

ER status change	n	%
Stable positive	34	33.7%
Stable negative	38	37.6%
Positive to negative	11	10.9%
Negative to positive	12	11.9%
Heterogeneity†	6	5.9%
Total	101	100%

* ER status between different relapse sites in the same patient were assessed, using the ER status of the first relapse site as the basis of comparison.

† Includes patients who had discordant ER status between subsequent relapse sites.

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

Risk of Death Depending on Intraindividual ER Status in Primary Tumor and Systemic Relapse

Intraindividual primary tumor and metastasis ER status	Patients (n)	Deaths overall	OS from BC diagnosis to death or censoring HR (95% CI)	OS from mBC diagnosis to death or censoring HR (95% CI)
Prim(+)/Met(+)	131	54	Reference	Reference
Prim(+)/Met(-)	103	61	1.40 (1.00-1.98)	1.33 (0.90-1.98)
Prim(-)/Met(+)	21	9	0.87 (0.44-1.72)	1.06 (0.49-2.28)
Prim(-)/Met(-)	80	44	1.27 (0.79-2.05)	1.21 (0.69-2.12)

* Adjusted for age and calendar year of diagnosis, PR, tumor classification, tumor stage, lymph node metastasis, hormonal therapy and chemotherapy

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

Author Conclusions

- Every third patient experienced a change in hormonal receptor status, and one patient in 10 experienced a change in HER2 status during tumor progression.
- Intraindividual primary and relapse ER and PR status were significantly associated with differential survival (data not shown).
- Patients losing ER positivity had an increased risk of dying compared to patients with stable ER-positive disease.
- Our data combined with the data from other groups demonstrate that morphological verification of biomarker profiles of suspected metastatic breast cancer lesions will improve diagnostic precision and personalized management.

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

Investigator Commentary: Discordance in Hormone Receptor and HER2 Status between the Primary Breast Cancer Tumor and Metastases

One of the themes that emerged in 2010 was the question: Does the cancer change over time? And of course we want to focus on changes that are clinically meaningful.

Data presented at ASCO 2010 in addition to a presentation by Lindstrom and colleagues at San Antonio evaluated changes in clinically relevant markers between the primary tumor and metastatic disease. If you evaluate these data — again, Dr Lindstrom's data set focused on ER and HER2 — you find small but real and consistent changes in relevant markers between the primary breast tumor and metastatic disease. I believe rebiopsying at the time of relapse is a reasonable approach. The main reason to rebiopsy is to ensure you're treating what you think you're treating, as a number of conditions can masquerade as metastatic breast cancer.

I also believe rephenotyping to be of value, but you have to be cautious in using it to guide therapy. For example, a hormone receptor-positive breast tumor that's negative on rebiopsy may or may not reflect endocrine-insensitive disease.

Presentation by Lisa A Carey, MD, SABCS December 12, 2010

Effect of Denosumab versus Zoledronic Acid Treatment in Patients with Breast Cancer and Bone Metastases: Results from the Extended Blinded Treatment Phase

Stopeck A et al.

Proc SABCS 2010;Abstract P6-14-01.

Phase III Study Design

Accrual: 2,046 (Closed)

Eligibility

Advanced breast cancer

Bone metastasis

No prior bisphosphonates

R

Denosumab + Placebo IV
q 4 weeks
(n = 1,026)

Supplemental calcium and vitamin D in both arms

Zoledronic acid + Placebo SC
q 4 weeks
(n = 1,020)

Denosumab 120 mg subcutaneously (SC)
Zoledronic acid (ZA) 4 mg intravenously (IV)

Primary Endpoint: Time to first on-study skeletal related event (SRE) (predefined as pathologic fracture, radiation or surgery to bone, or spinal cord compression) – Noninferiority
Secondary Endpoints: Time to first and subsequent on-study SRE (superiority), safety

Stopeck A et al. *Proc SABCS* 2010;Abstract P6-14-01.

Primary Endpoint: Estimated Time to First On-Study SRE (Noninferiority)

Denosumab n = 1,026	Zoledronic acid n = 1,020	Hazard ratio (HR) (95% CI)	*p*-value*
32.4 months	27.4 months	0.82 (0.71 – 0.95)	< 0.0001

- Denosumab therapy resulted in an 18% reduction in risk of time to first on-study SRE in comparison to treatment with zoledronic acid

* Superiority analysis, $p = 0.0096$

Stopeck A et al. *Proc SABCS* 2010;Abstract P6-14-01.

Secondary Endpoints

	Denosumab	ZA	HR, *p*-value	Risk reduction
Time to first on-study SRE or hypercalcemia (superiority)	32.4 mos	25.1 mos	0.82; 0.0076	18%
Time to first and subsequent on-study SREs*, events	526 events	669 events	0.76; 0.0008	22%
Skeletal morbidity rate	0.46	0.58	—; 0.0039	—
Overall survival	NR	NR	0.96; 0.5605	—
Time to overall disease progression	NR	NR	0.98; 0.7295	—

* Multiple event analysis

NR, not reported

Stopeck A et al. *Proc SABCS* 2010;Abstract P6-14-01.

SRE Types and Adverse Events

Types of SREs by Treatment Group			
	Denosumab	**ZA**	***p*-value**
Pathologic fracture	23.5%	28.1%	0.0354
Radiation to bone	13.5%	17.2%	0.0184
Surgery to bone	2.9%	2.8%	NR
Spinal cord compression	1.4%	1.4%	NR
Adverse Events, n (%)			
	Denosumab (n = 1,020)	**ZA (n = 1,013)**	***p*-value**
Serious adverse events	489 (47.9%)	509 (50.2%)	NR
AEs related to renal toxicity	55 (5.4%)	95 (9.4%)	NR
Osteonecrosis of the jaw (ONJ)	26 (2.5%)	18 (1.8%)	0.2861
Hypocalcemia (any; Grade 3/4)	62 (6.1%); 18 (1.8%)	37 (3.7%); 12 (1.2%)	NR
Acute-phase reactions	109 (10.7%)	286 (28.2%)	NR

Stopeck A et al. *Proc SABCS* 2010;Abstract P6-14-01.

Hypocalcemia and ONJ

Hypocalcemia

- Approximately half of the events occurred within the first 6 months after the first dose (denosumab 57%, ZA 46%).
- The majority of patients who experienced hypocalcemia had a single hypocalcemia event (denosumab 71%, ZA 70%).

ONJ

- Most patients had a history of tooth extraction, poor oral hygiene and/or use of a dental appliance (denosumab, 24/26 patients [92%]; ZA, 15/18 patients [83%]).
- Most patients were current or past recipients of chemotherapy (denosumab, 19/26 patients [73%]; ZA, 14/18 patients [78%]).
- 69% of patients in the denosumab group and 44% in the ZA group discontinued treatment due to ONJ.
- As of data cutoff (October 1, 2010), ONJ was considered resolved by the investigator for 12/26 (46%) patients in the denosumab group and 9/18 (50%) patients in the ZA group.

Stopeck A et al. *Proc SABCS* 2010;Abstract P6-14-01.

Author Conclusions

- In this extended data analysis of denosumab in patients with breast cancer and bone metastases, denosumab was superior to ZA in preventing SREs.
- Continued denosumab treatment resulted in a median time to first SRE that was 5 months longer than treatment with ZA.
- Continued denosumab treatment significantly reduced the proportion of patients who experienced pathologic fractures or radiation to bone compared with ZA.
- Patients treated with denosumab had a higher incidence of hypocalcemia.
- Patients treated with ZA had a higher incidence of renal adverse events and acute-phase reactions.
- Incidence of ONJ was low and similar in both groups.
- Denosumab represents a new treatment option for patients with breast cancer and bone metastases without the need for dose adjustment or renal monitoring.

Stopeck A et al. *Proc SABCS* 2010;Abstract P6-14-01.

Osteonecrosis of the Jaw: Dental Outcomes in Metastatic Breast Cancer Patients Treated with Bisphosphonates with/without Bevacizumab at Roswell Park Cancer Institute

Ngamphaiboon N et al.

Proc SABCS 2010;Abstract P2-13-03.

Methods

- All cases of osteonecrosis of the jaw (ONJ) in metastatic breast cancer, while receiving bevacizumab (Bev) + bisphosphonates (BP) or bisphosphonates alone, and diagnosed between October 2002 and April 2010 were reviewed.

- ONJ was diagnosed and staged in the department of dentistry according to the American Association of Oral and Maxillofacial Surgeons position paper (*J Oral Maxillofac Surg* 2009;67(5 Suppl):2-12).

Ngamphaiboon N et al. *Proc SABCS* 2010;Abstract P2-13-03.

Clinical Manifestations, Time and Dose of Bisphosphonates Prior to Diagnosis of ONJ

Presentations	All (n = 27)	Bev + BP (n = 7)	BP (n = 20)
Necrotic bone	85%	86%	85%
Purulence	48%	57%	45%
Swelling	33%	29%	35%
Pain	67%	86%	60%
Paraesthesia	15%	0%	20%
Tooth mobility	33%	57%	25%
Edentulous	19%	14%	20%
Treatments	**(n = 27)**	**(n = 7)**	**(n = 20)**
Median time to ONJ	34.0 mo	32.6 mo	34.6 mo
Median number of BP doses	32.0	32.0	36.5

Ngamphaiboon N et al. *Proc SABCS* 2010;Abstract P2-13-03.

Dental Outcomes of Treatments for ONJ

Dental responses*	All (n = 27*)	Bev + BP (n = 7)	BP (n = 20)	Year of diagnosis 2007-2010 (n = 13)	Year of diagnosis <2007 (n = 14)
Complete resolution	24%	33%	21%	33%	15%
Partial resolution	28%	50%	21%	33%	23%
Stable disease	28%	0%	37%	25%	31%
Progressive disease	20%	17%	21%	8%	31%

* n = 25; Two patients (one from each arm) lost to follow-up were excluded from response analysis

Ngamphaiboon N et al. *Proc SABCS* 2010;Abstract P2-13-03.

Author Conclusions

- The addition of bevacizumab to bisphosphonates does not appear to alter the time to development of ONJ.
  - 32.6 months versus 34.6 months
- The number of bisphosphonate treatments administered prior to the diagnosis of ONJ was similar between bevacizumab + bisphosphonates and bisphosphonates.
- Patients who were diagnosed with ONJ in 2007-2010 presented with lower stages and had improved outcomes.
- Since dental management of ONJ has not changed over time, early recognition and screening may account for the improvement in dental outcomes.

Ngamphaiboon N et al. *Proc SABCS* 2010;Abstract P2-13-03.

Investigator Commentary:

Effect of Bevacizumab on the Development of Rare Adverse Events

Osteonecrosis of the jaw (ONJ) is a real phenomenon but a relatively rare consequence of bisphosphonate therapy and denosumab. The Roswell Park study demonstrated that the risk of ONJ did not appear to increase for patients receiving bisphosphonates and bevacizumab, nor did the consequences of ONJ appear to increase when it did develop.

Interview with William J Gradishar, MD, January 4, 2011

Impact of Bisphosphonates on Skeletal-Related Events in Patients with Breast Cancer and Bone Metastases

The randomized, placebo-controlled study of denosumab versus zoledronic acid for patients with advanced breast cancer and bone metastasis reported an 18 percent reduction in risk with the primary study endpoint of time to first on-study SRE with denosumab compared to zoledronic acid.

Tolerability was favorable with this agent. Denosumab appears to be at least as well tolerated and more effective at preventing SREs than monthly zoledronic acid and can be used in patients with renal insufficiency, which was an area in which we previously had no options to offer patients.

Presentation by Lisa A Carey, MD, SABCS December 12, 2010

TAMRAD: A GINECO Randomized Phase II Trial of Everolimus in Combination with Tamoxifen versus Tamoxifen Alone in Patients with Hormone-Receptor Positive, HER2 Negative Metastatic Breast Cancer with Prior Exposure to Aromatase Inhibitors

Bachelot T et al.

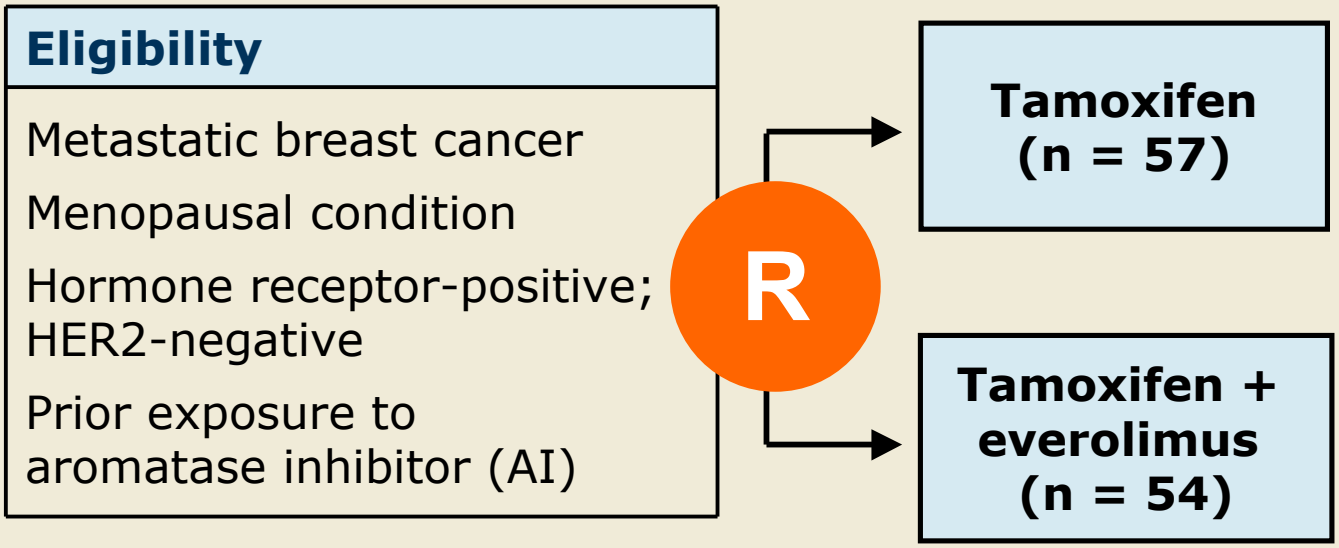
Proc SABCS 2010;Abstract S1-6.

Background

- Everolimus is an mTOR inhibitor shown to increase the antitumor activity of letrozole in the neoadjuvant setting (*JCO* 2009;27:2630).
- Randomized trials of first-line hormone therapy with mTOR inhibition in metastatic breast cancer (mBC) have been disappointing (*Proc SABCS* 2006;Abstract 6091).
- Selection of patients with aromatase inhibitor-pretreated mBC may enrich the study population for tumors that are driven by activation of the PI3K/AKT/mTOR pathway.

Bachelot T et al. *Proc SABCS* 2010;Abstract S1-6.

TAMRAD Phase II Study Schema



Primary endpoint:

Clinical benefit rate (CBR) at 6 months; a gain of 20% in CBR required to warrant further study of tamoxifen/everolimus combination.

Secondary endpoints: Time to progression (TTP), overall survival, objective response rate, toxicity.

Bachelot T et al. *Proc SABCS* 2010;Abstract S1-6.

Efficacy Outcomes

	Tamoxifen	Tamoxifen + Everolimus	Hazard Ratio (95% CI)	*p*-value
CBR (n = 57; 54)	42.1%	61.1%	—	—
Median TTP (n = 57; 54)	4.5 mos	8.6 mos	0.53 (0.35-0.81)	0.0026
TTP, all pts with primary hormone resistance[1] (n = 54)	3.9 mos	5.4 mos	0.74 (0.42-1.3)	—
TTP, all pts with secondary hormone resistance[2] (n = 56)	5.0 mos	17.4 mos	0.38 (0.21-0.71)	—
Overall survival (n = 57; 54)	—	—	0.32 (0.15-0.68)	0.0019

[1] Patients who received no benefit from hormone therapy, experiencing either relapse during adjuvant AI or progression within six months of starting AI in the metastatic setting

[2] Patients who relapsed later, either after AI discontinuation in the adjuvant setting or after responding, experiencing progression later in the metastatic setting

Bachelot T et al. *Proc SABCS* 2010;Abstract S1-6.

Select Adverse Events

Adverse event (AE)	Tamoxifen (n = 57)		Tamoxifen + everolimus (n = 54)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Fatigue	52.6%	10.5%	74.1%	5.6%
Stomatitis	7.0%	0	51.9%	11.1%
Rash	5.3%	1.8%	38.9%	5.6%
Anorexia	17.5%	3.5%	44.4%	9.3%
Diarrhea	8.8%	0	38.9%	1.9%
Dose reduction due to AE	0		28%	
Treatment discontinuation due to AE	7.0%		5.6%	

Bachelot T et al. *Proc SABCS* 2010;Abstract S1-6.

Author Conclusions

- Everolimus combined with tamoxifen allowed for a 61% CBR compared to 42% with tamoxifen alone.
- Time to progression and overall survival increased with the addition of everolimus to tamoxifen compared to tamoxifen alone.
- Toxicity was manageable and consistent with previous studies.
- Clinical benefit may favor patients with secondary hormone resistance.
- Based on these promising results, this combination warrants further study in hormone-receptor positive/HER2-negative mBC after progression on aromatase inhibitors.

Bachelot T et al. *Proc SABCS* 2010;Abstract S1-6.

CALGB 40302: Fulvestrant with or without Lapatinib as Therapy for Hormone Receptor Positive Advanced Breast Cancer: A Double-Blinded, Placebo-Controlled, Randomized Phase III Study

Burstein HJ et al.

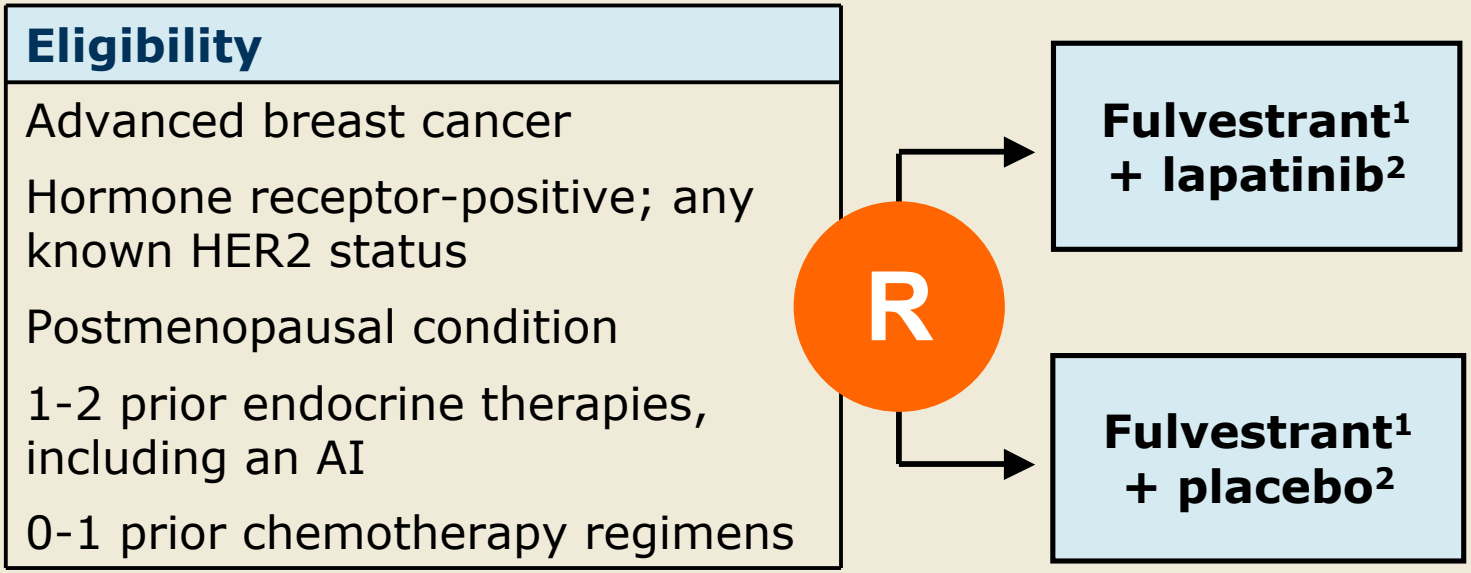
Proc SABCS 2010;Abstract PD05-01.

Background

- Preclinical studies have suggested important interactions between ER and HER2 signaling pathways.
- Addition of EGFR and/or HER2 targeted therapies can improve rates of tumor control compared to endocrine therapy alone in laboratory models of ER-positive breast cancer.
- CALGB 40302 was designed to determine whether the addition of the dual-kinase inhibitor lapatinib would improve progression-free survival among women with hormone receptor-positive metastatic breast cancer treated with the antiestrogen agent fulvestrant.

Burstein HJ et al. *Proc SABCS* 2010;Abstract PD05-01.

CALGB-40302: Study Schema



Primary endpoint:
Progression-free survival (PFS)

[1] 500 mg IM day 1, followed by 250 mg day 15 and day 28, and every 4 weeks thereafter
[2] 1,500 mg PO QD

Burstein HJ et al. *Proc SABCS* 2010;Abstract PD05-01.

Efficacy Outcomes

	Fulvestrant + lapatinib	Fulvestrant + placebo	*p*-value
Median PFS All patients (n = 131; 133) HER2-negative (n = 93; 85) HER2-positive (n = 23; 28)	 5.2 mo 4.1 mo 5.9 mo	 4.0 mo 4.0 mo 2.8 mo	 0.94 0.53 0.29
Median overall survival (n = 131; 133)	22.3 mo	21.9 mo	0.64

At the recommendation of the Data Safety and Monitoring Board, the study was closed and treatment unblinded on 7/14/2010 having accrued 267 patients.

Burstein HJ et al. *Proc SABCS* 2010;Abstract PD05-01.

Author Conclusions

- Among women with hormone receptor-positive breast cancer previously treated with an AI, adding lapatinib to fulvestrant does not improve PFS.
- While generally well tolerated, the addition of lapatinib to fulvestrant led to a higher rate of Grade 3 adverse events including fatigue, diarrhea, rash, and liver function enzyme abnormalities compared to placebo (data not shown).
- Planned exploratory subset analyses suggest improvement in PFS with lapatinib compared to placebo in women with HER2-positive tumors.
- At present, the addition of EGFR/HER2 inhibition does not enhance outcomes seen with fulvestrant therapy in ER-positive advanced breast cancer.
  - Patients with HER2-positive tumors may benefit from anti-HER2 treatments in combination with endocrine therapy.

Burstein HJ et al. *Proc SABCS* 2010;Abstract PD05-01.

Investigator Commentary: Combining Biologic and Endocrine Therapy in Advanced ER-Positive Breast Cancer

The TAMRAD study was interesting in that the outcome was better than expected with the addition of everolimus to tamoxifen. The caveat is that this is a Phase II trial with approximately 100 patients, but the investigators demonstrated an improvement in clinical benefit rate, time to disease progression and survival with the addition of everolimus. The suggestion also arose that patients with secondary, as opposed to primary, endocrine resistance may have derived the most benefit from the combination. Of course, more side effects — fatigue, stomatitis, rash, et cetera — were observed with the doublet. The presenters' conclusion was appropriately cautious in stating that the doublet should not be considered as standard treatment and further research is warranted.

In the CALGB trial 40302, the addition of lapatinib to fulvestrant did not enhance progression-free or overall survival for the overall population or in patients with HER2-normal advanced breast cancer. A suggestion of improvement was observed in the HER2-positive population, but it was not statistically significant. Whether a subset of patients with ER-positive or HER2-positive disease can be teased out who will benefit from the combination — as was observed with letrozole/lapatinib and anastrozole/trastuzumab — remains to be seen.

Interview with William J Gradishar, MD, January 4, 2011

A Meta Analysis of Risk of Cardiovascular Events in Patients with Metastatic Breast Cancer (MBC) Treated with Anti Vascular Endothelial Growth Factor (VEGF) Therapy — Bevacizumab

Nasim S et al.

Proc SABCS 2010;Abstract P6-12-01.

Methods

- Randomized Phase III trials that evaluated chemotherapy with or without bevacizumab in MBC as first- or second-line therapy were identified.
- Data extraction was carried out from results published in the literature or from conference proceedings of the selected studies.
  - ECOG-E2100, AVADO, RIBBON 1, RIBBON 2 and a Phase III trial of capecitabine with or without bevacizumab in MBC (*JCO* 2005;23:792)
- All Grade 3 and 4 cardiovascular events in these trials were collected.
  - Hypertension, left ventricular dysfunction, congestive heart failure, cardiomyopathy, venous and arterial thromboembolic events

Nasim S et al. *Proc SABCS* 2010;Abstract P6-12-01.

Relative Risk with Bevacizumab-Containing Regimens

Grade 3-4 events	Relative risk	*p*-value
Hypertension	10.32	<0.0001
Left ventricular dysfunction	2.58	0.04
Venous/arterial thromboembolism	1.71	0.16

Nasim S et al. *Proc SABCS* 2010;Abstract P6-12-01.

Author Conclusions

- Bevacizumab administered in combination with chemotherapy for patients with MBC is associated with significant cardiotoxicity:
  - Hypertension
  - Left ventricular dysfunction
- Careful monitoring of cardiac function is warranted in trials combining chemotherapy with bevacizumab:
  - To assess long-term cardiac sequelae
  - To better understand the mechanism underlying bevacizumab-induced cardiac damage

Nasim S et al. *Proc SABCS* 2010;Abstract P6-12-01.

Phase II Multicenter Study of Docetaxel and Bevacizumab (Bev) +/- Trastuzumab as First-Line Treatment of Patients with Metastatic Breast Cancer (MBC)

Schwartzberg LS et al.

Proc SABCS 2010;Abstract P6-12-08.

Background

- Progression-free survival (PFS) is improved with the addition of Bev to docetaxel or paclitaxel for first-line treatment of HER2-negative MBC.
- There are limited data on Bev combined with docetaxel at the dosage of 75 mg/m^2 in patients with HER2-negative MBC, and no data on Bev plus docetaxel at any dosage in patients with HER2-positive MBC.
- **Primary objective:** Evaluate PFS with docetaxel (D) and Bev plus trastuzumab (T) for the first-line treatment of patients with MBC.
- **Secondary objectives:** Response; overall survival (OS); safety and toxicity

Schwartzberg LS et al. *Proc SABCS* 2010;Abstract P6-12-08.

Study Design

Phase II, nonrandomized, parallel-group, prospective, multicenter study

Accrual: 73 (Closed)

Eligibility

Stage IV breast adenocarcinoma with ≥1 measurable lesion

No brain metastasis

No prior chemotherapy for MBC

No prior treatment with Bev or other anti-VEGF therapy

Normal LVEF

ECOG PS 0-1

→ **Stratum 1: HER2-negative (n = 52)**

Bev, 15 mg/kg prior to D, 75 mg/m^2, q3wk

→ **Stratum 2: HER2-positive (n = 21)**

Bev, 15 mg/kg prior to D, 75 mg/m^2 + T, 8 mg/kg cycle 1 (6 mg/kg subsequent cycles, administered after D infusion on all treatment days) q3wk

G-CSF prophylaxis was administered to all patients
Treatment until unacceptable toxicity, progression or death

Schwartzberg LS et al. *Proc SABCS* 2010;Abstract P6-12-08.

Efficacy Results (Intent to Treat)

Outcome	Stratum1, HER2-neg Bev+D (n = 52)	Stratum2, HER2-pos Bev+D+T (n = 21)
Median PFS	8.5 mos	13.43 mos
Overall response rate	57.7%	81.0%
- Complete response	5.8%	28.6%
- Partial response	51.9%	52.4%
- Stable disease	26.9%	4.8%
- Progressive disease	11.5%	4.8%
Median response duration	8.57 mos	12.2 mos
Overall survival (OS)	61.5%	76.2%

OS measured at the time of data cutoff (patient accrual August 2006 to March 2009; data cutoff April 5, 2010)

Schwartzberg LS et al. *Proc SABCS* 2010;Abstract P6-12-08.

Selected Adverse Events (AE)

All Grades; Grade 3/4 AEs	Stratum1, HER2-neg Bev+D (n = 52)	Stratum2, HER2-pos Bev+D+T (n = 20)
Fatigue	71.2%; 11.5%	65.0%; 10.0%
Alopecia	67.3%; 0%	75.0%; 0%
Nausea	53.8%; 0%	55.0%; 0%
Diarrhea	44.2%; 1.9%	35.0%; 0%
Dysgeusia	40.4%; 0%	40.0%; 5.0%
Headache	30.8%; 0%	40.0%; 0%
Epistaxis	28.8%; 0%	40.0%; 0%
Arthralgia	28.8%; 3.8%	25.0%; 0%
Vomiting	23.1%; 1.9%	25.0%; 0%
Hypertension	15.4%; 3.8%	35.0%; 0%

Schwartzberg LS et al. *Proc SABCS* 2010;Abstract P6-12-08.

Author Conclusions

- In first-line treatment of MBC, docetaxel at 75 mg/m^2 plus Bev in HER2-negative disease or docetaxel at 75 mg/m^2 plus trastuzumab plus Bev in HER2-positive disease was safe and feasible.
- Response and PFS for patients with HER2-negative disease were similar to previous reports, confirming the benefit of adding Bev to docetaxel.
- Overall toxicity was less with Bev combined with docetaxel at 75 mg/m^2, compared to higher doses.
- Response rates with docetaxel/trastuzumab/Bev are among the highest reported for HER2-positive disease, and median PFS of 13.4 months with low incidence of Grade 3/4 toxicity suggest the addition of Bev is a promising strategy for patients with HER2-positive disease.

Schwartzberg LS et al. *Proc SABCS* 2010;Abstract P6-12-08.

Investigator Commentary: Effect of Bevacizumab on the Development of Rare Adverse Events

Evidence from multiple trials indicates that bevacizumab is associated with a higher risk of hypertension, although serious hypertension is relatively rare.

In the pooled analysis of several trials — ECOG-E2100, AVADO, RIBBON 1, RIBBON 2 and an earlier study of capecitabine with or without bevacizumab — an increased incidence was observed, predictably, of hypertension and more left ventricular dysfunction.

These findings underscore the prudence of carefully monitoring patients receiving bevacizumab for hypertension and overall cardiac function.

Interview with William J Gradishar, MD, January 4, 2011