

# EDUCATIONAL CONCEPTS GROUP



## Translating Today's Science into Tomorrow's Practice: Highlights from the 2009 Breast Cancer Symposium

### **Editors**

#### **Terry P. Mamounas, MD, MPH, FACS**

Professor of Surgery  
Northeastern Ohio Universities College of Medicine  
Medical Director  
Aultman Cancer Center  
Canton, Ohio

#### **Eric P. Winer, MD**

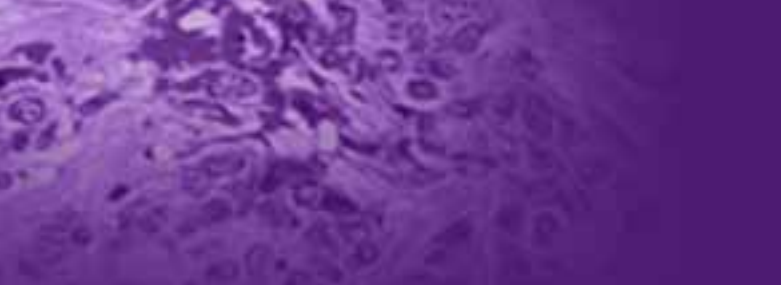
Chief, Division of Women's Cancers  
Dana-Farber Cancer Institute  
Professor of Medicine  
Harvard Medical School  
Boston, Massachusetts

This activity is sponsored by

EDUCATIONAL  
CONCEPTS GROUP

This activity is supported by an educational grant from

**Genentech**  
BIOONCOLOGY™



**Table of Contents** *(click the section you wish to view)*

<b>Introduction .....</b>	<b>1</b>
<b>Incorporation of Translational Science Into Clinical Trials .....</b>	<b>1</b>
<b>Supercharging Hormonal Therapy.....</b>	<b>2</b>
<b>PARP Inhibitors in MBC .....</b>	<b>4</b>
<b>End of the Anthracycline Era? .....</b>	<b>8</b>
<b>Cardiovascular Health and Breast Cancer .....</b>	<b>10</b>
<b>Bone Health and Breast Cancer .....</b>	<b>13</b>
<b>Conclusion.....</b>	<b>16</b>
<b>References.....</b>	<b>16</b>

## ACCREDITATION INFORMATION

### PHYSICIAN CONTINUING EDUCATION

#### ACCREDITATION STATEMENT

Educational Concepts Group, LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

#### CREDIT DESIGNATION STATEMENT

Educational Concepts Group, LLC designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.

### PHARMACIST CONTINUING EDUCATION



Educational Concepts Group, LLC is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Type of activity: Knowledge-based

Educational Concepts Group, LLC designates this continuing education activity for 1.5 contact hours (0.15 CEUs) (UAN 0199-0000-09-076-H01-P).

### METHOD OF PARTICIPATION

There are no fees for participating and receiving CME/CE credit for this activity. During the period November 20, 2009 through November 19, 2010, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test and activity evaluation form.

### CME/CE CREDIT

Physicians and pharmacists who complete the post-test with a score of 70% or better may view and print their credit letter or statement of credit via the website, [www.educationalconcepts.net](http://www.educationalconcepts.net).

### FACULTY DISCLOSURE STATEMENT

All faculty participating in continuing education activities sponsored by ECG are expected to disclose to the audience any real or apparent commercial financial affiliations related to the content of their presentations/materials.

### ECG HAS DECLARED THE FOLLOWING FINANCIAL RELATIONSHIPS

ECG receives educational grants from pharmaceutical industry and other commercial sources. Planners, managers, and other staff members at ECG have no relevant financial relationships to disclose.

None of the contents may be reproduced in any form without prior written permission from the publisher. This activity may be accessed at [www.educationalconcepts.net](http://www.educationalconcepts.net).

### ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT

This activity is supported by an educational grant from Genentech BioOncology.

## THE FOLLOWING FACULTY MEMBERS HAVE DECLARED RELEVANT FINANCIAL RELATIONSHIPS

### Terry P. Mamounas, MD, MPH, FACS

#### Consultant Fees

Agendia, Genentech BioOncology, Genomic Health, Inc., GlaxoSmithKline, Novartis, Pfizer Inc, sanofi-aventis Group

#### Honorarium

Agendia, Genentech BioOncology, Genomic Health, Inc., GlaxoSmithKline, Novartis, Pfizer Inc, sanofi-aventis Group

#### Speakers' Bureau

Genentech BioOncology, Genomic Health, Inc., sanofi-aventis Group

### Eric P. Winer, MD

#### Grants/Research Support

Genentech BioOncology

## ACKNOWLEDGEMENT

The faculty wish to thank Maureen Haas, PharmD, BCPS, BCOP, a paid employee of ECG, for assistance in writing this document.

## DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Please refer to the official prescribing information for each product or consult the *Physicians' Desk Reference* for discussion of approved indications, contraindications, and warnings.

## DISCLOSURE OF OFF-LABEL USE

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. ECG does not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity do not necessarily represent the views of ECG. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

## CME/CE INQUIRIES

For further information, please contact:  
Educational Concepts Group, LLC  
1300 Parkwood Circle SE, Suite 325, Atlanta, Georgia 30339  
Phone: 1.770.933.1681 | Fax: 1.770.933.1692  
[www.educationalconcepts.net](http://www.educationalconcepts.net)



### **Target Audience**

The target audience for the program includes medical, surgical, and radiation oncologists, as well as allied oncology healthcare professionals charged with the care of patients with breast cancer.

### **Learning Objectives**

Upon completion of this educational activity, participants should be better able to:

- Select appropriate adjuvant treatment regimens based on current understanding of clinical markers, efficacy, and safety profiles
- Explain the rationale behind novel agents and combinations to overcome resistance mechanisms in breast cancer
- Evaluate emerging new therapeutic options for treatment of metastatic breast cancer by reviewing ongoing and planned clinical trials
- Describe ongoing research regarding strategies of incorporating bisphosphonates into breast cancer treatment paradigms

### **Statement of Need**

As many advances have been realized in the treatment of breast cancer, challenges still exist. Therefore, the dissemination of critical research findings to the medical oncology community in a timely manner is critical for clinical trial enrollment and reporting, new treatment adaptation, and potential to impact the long-term outcomes of these patients. Continuing medical education programs are important vehicles to assist in the timely distribution and application of this key information in order to improve patient outcomes.

### **Media: Newsletter**

Estimated time to complete activity: 1.5 hours

Release date: November 20, 2009

Expiration date: November 19, 2010

This activity may be accessed at [www.educationalconcepts.net](http://www.educationalconcepts.net)

## Introduction

The 2009 American Society of Clinical Oncology (ASCO) Breast Cancer Symposium was held October 7-9, in San Francisco, California. The multidisciplinary symposium encouraged engaged participation and collaborative interaction. Educational lectures, discussions, and tumor boards were designed to help clinicians interpret the wealth of information available and translate findings into the larger clinical context. The information exchange highlighted emerging science and the future of breast cancer care.

## Incorporation of Translational Science Into Clinical Trials

Drs Martine Piccart-Gebhart and Christos Sotiriou from the Jules Bordet Institute, Brussels, Belgium gave a tandem keynote address, symbolic of the partnership between medical oncology and functional genomics necessary for advances in breast cancer research. It has been estimated that a compound entering phase I testing has an 8% chance of achieving registration, with an even lower percentage for anticancer agents. Drs Piccart and Sotiriou believe the current development pathway is inefficient. It was suggested that agents fail late in development due to lack of innovation in study design and lack of accurate prognostic and predictive markers leading to poor patient selection.

Dr Piccart emphasized personalized therapy for breast cancer exists more as a myth than current reality and that the inherent slowness of the development process may be improved by rethinking our current paradigm. She contends that progress will be accelerated, in-part, by incorporating translational science into clinical trial design from the inception of the compound development strategy. **Figure 1.**

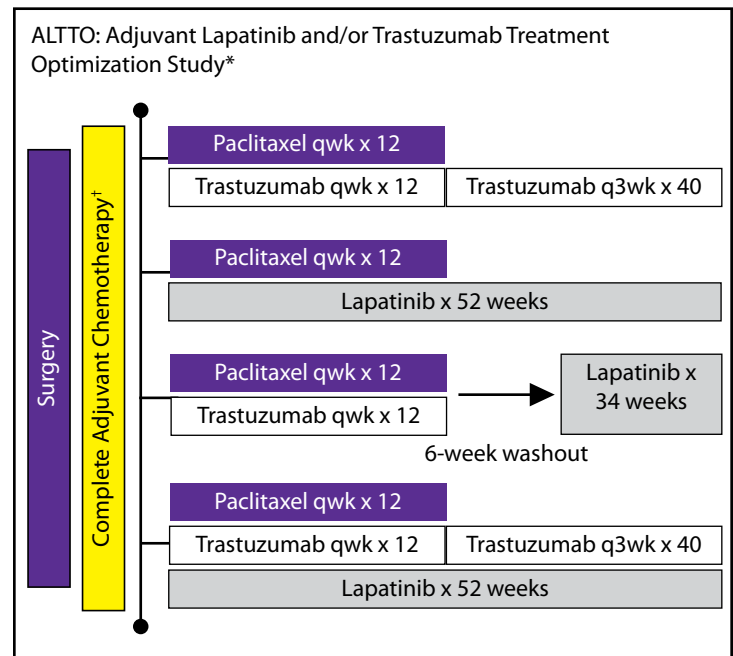
Limitations to progress include previous suboptimal translational research efforts. For example, in the HERA trial for which Dr Piccart served as principal investigator, just 1 in 5 women enrolled had tumor blocks obtained. In fact, the HERA trial reached over

**Figure 1. Progress in Breast Cancer Scientific Collaborations**




50% accrual before translational research was able to be initiated. Dr Piccart believes the strength of future efforts will be effective collaboration. The rapid accrual, "exceeding expectations," of the target 8000 women to the Breast International Group (BIG) adjuvant lapatinib and/or trastuzumab treatment optimization (ALTTO) trial is an example of such collaborative efforts. Additional information on the ALTTO trial can be found at <http://alitto.com/patients.php>. **Figure 2.**

**Figure 2. ALTTO Schema**



\*Study design 2; †Radiotherapy administered as clinically indicated. Available at: [http://www.breastinternationalgroup.org/BIG/Clinical\\_Trials/Active\\_trials/BIG\\_2-06\\_ALTTO\\_N063D\\_EGF\\_106708.aspx](http://www.breastinternationalgroup.org/BIG/Clinical_Trials/Active_trials/BIG_2-06_ALTTO_N063D_EGF_106708.aspx). Accessed September 22, 2008.



It was noted that lapatinib will have been in development for approximately 10 years prior to the completion of the ALTO trial, the results of which may establish feasibility in the adjuvant setting. Dr Piccart stated, "There must be more efficient ways".

The hallmark examples of validated predictive biomarkers in breast cancer include hormone receptor and HER2 expression and the corresponding development of anti-endocrine and anti-HER2 agents. Unfortunately, there has been slow progress in identifying therapeutic strategies efficacious for individual patients. Identifying markers of response for a particular agent remains an unmet need in breast cancer therapy and lack of routine marker testing results in administration of therapy to patients who receive little to no benefit.

One suggested approach to overcome these identified obstacles is to initiate proof-of-concept trials in the neoadjuvant setting that run concordantly with the phase III development of agents in the advanced disease setting. The neoadjuvant setting is an especially attractive evaluation platform for translational research and promising biomarkers identified in this setting could be further validated in adjuvant trials. Using the information gained in the neoadjuvant setting to define the appropriate patient population for future testing should increase the likelihood of clinical success.

In moving towards this model, BIG is launching a series of international neoadjuvant trials based on the evaluation of promising targeted therapies in distinct molecular breast cancer subgroups replacing the prior "one size fits all" model. NEO-BIG trials will evaluate short-term surrogate endpoints such as pathologic complete remission (pCR), proliferation markers such as Ki-67, and/or functional imaging changes. For example, NEO-BIG will soon be initiating a trial comparing 16 weeks of endocrine therapy alone vs endocrine therapy plus an insulin-like growth factor-1 receptor (IGF1-R) monoclonal antibody prior to surgery with routine Ki-67 analysis. The primary outcomes will be cell cycle response defined as day 15 Ki-67 < 2.7% and MRI volume response.

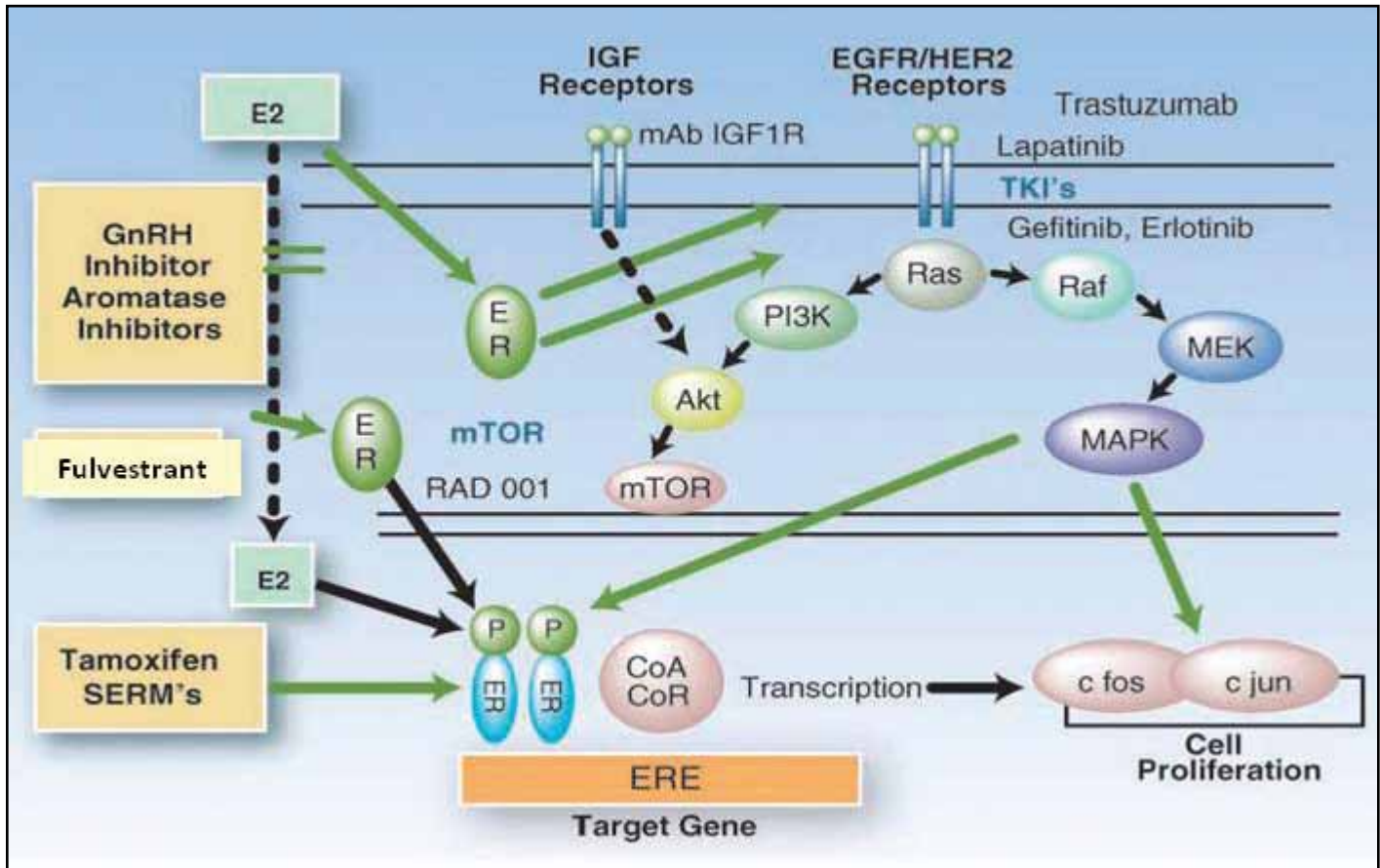
Dr Sotiriou highlighted milestones of recent and ongoing translational research that included identification of gene expression microarray profiles of luminal A, luminal B, HER2, and basal-like subtypes. In addition, results from ongoing phase III prospective validation trials, TAILORx and MINDACT, will provide level I evidence for incorporation of genomic assays into routine clinical practice. Another highlight includes the understanding that quantitative measures of proliferation are significant. The phase III preoperative endocrine therapy individualizing care (POETIC) trial will validate the role of Ki-67. This trial will recruit approximately 4000 postmenopausal, hormone receptor-positive women throughout the United Kingdom. The biological aim is to test whether levels of Ki-67 following two weeks treatment with an aromatase inhibitor before surgery can predict long-term outcome. Additional information can be found at [http://www.icr.ac.uk/research/research\\_sections/clinical\\_trials/clinical\\_trials\\_list/10967.shtml](http://www.icr.ac.uk/research/research_sections/clinical_trials/clinical_trials_list/10967.shtml).

In conclusion, Drs Piccart and Sotiriou emphasized that personalized medicine will become reality once there is a change in vision, research methodology, and culture. These changes may lead to faster access to the right drug for the right patient and decrease the time and cost associated with drug development. A collaborative effort between basic science, bioinformatics, clinicians, regulatory agencies, and pharmaceutical industry is required to effectively and efficiently translate today's science into tomorrow's practice.

### **Supercharging Hormonal Therapy**

Estrogen receptor (ER) expression remains the most powerful predictor of response to hormone therapy to date. Therapy with hormonal agents becomes limited when *de novo* or acquired resistance develops. The mechanisms responsible for the development of resistance remain poorly defined. Suggested mechanisms include loss of ER expression, altered ER function, or enhanced activation. Dr Suzanne Fuqua from Baylor College of Medicine explored future approaches to potentiate the efficacy of hormone therapy.

Figure 3. Cross-Talk Pathways in Endocrine Resistant Breast Cancer




Moy B, Goss P. *Clin Cancer Res.* 2006;12(16):4790-4793.

Estrogen receptor-positive tumors have heterogeneity in genetic make-up that translates into heterogeneity in disease response.<sup>1,2</sup> The upregulation of growth factor signaling pathways in ER-positive tumors has been identified. It has been found that tumors utilize different signaling pathways with luminal ER-positive tumors preferring the PI3K/AKT pathway and basal-like ER-negative tumors utilizing the Src/RAS/RAF pathway.<sup>3</sup> Estrogen receptor expression may change during treatment or at disease progression and hyperactivation of growth factors can lead to the evolution of ER-negative tumors. This phenomenon has been noted in 15-20% of hormone therapy treated tumors and up to 40% of chemotherapy treated tumors when comparing hormone expression profiles between the primary tumor and metastatic

lesion(s). Dr Fuqua posed the question, do ER-positive tumors, which become resistant to hormone therapies, now engage ER-negative pathways?

Tamoxifen resistant cells show an upregulation of growth factor signaling. The consequence of upregulation is growth factor/ER cross-talk where IGF1-R, HER2, and EGFR activate downstream RAS/RAF and PI3K/ATK signaling pathways that phosphorylate the ER receptor, modifying the receptor and how it responds to pharmacotherapy. **Figure 3.** These complex cross-talk pathways suggest that simultaneous blockade of ER, growth factor receptors, and their downstream signals will be required to bypass resistance mechanisms.



Molecular studies of post translational modifications (PTM) at the ER hinge domain have shown corresponding changes in hormone sensitivity, protein stability, and response to tamoxifen. Acetylation, ubiquitination, methylation, and sumoylation of the ER at the K302 position of the hinge domain can subsequently affect phosphorylation at serine (S)305. Clinical studies have shown us that phosphorylation at S305 predicts for poor outcomes in tamoxifen treated patients. Additional research as to the impact of selective modification of post translational events at the hinge domain site and how this information tells us how a cell may evade treatment is ongoing.

When the ER is mutated at a key residue, K303R, there is upregulation of all levels of cross-talk including phosphorylated HER2, AKT, and MAPK. Growth factor signaling decreases effectiveness of anti-estrogen therapy in these mutant cells. From this work it has been theorized that K303R mutated cells may be responsive to HER2 targeted therapies in the absence of documented HER2 amplification as the downstream pathways appear to be activated. Investigation to assess the efficacy and safety of combinations of endocrine therapy and targeted therapy is a fertile area of research. The aromatase inhibitor (AI) resistant phenotype associated with K303R expression is dependent on activation of S305 within the receptor. A potential treatment approach includes blockade of S305 phosphorylation to restore AI sensitivity. One preclinical model being investigated is the use of S305-ER peptide to block growth factor signaling and prevent PTM. Additional study of resistance mechanisms to AI therapy is ongoing. Early work has found mutant AI resistant cells are hypersensitive to PI3K/AKT inhibitors and when the pathway is inhibited, AI sensitivity can be restored.<sup>4</sup> Another pathway being studied is insulin-like growth factor (IGF) as IGF1-R inhibitors also appear to restore sensitivity to AI.<sup>5</sup>

It is widely accepted that androgens and estrogens exert opposite effects on breast cancer cell growth. Dr Fuqua points out androgens can both stimulate or inhibit the proliferation of breast cancer cells. Sixty to seventy percent of ER-positive tumors express androgen receptor (AR) and 40-50% of ER-negative

tumors do as well. Expression of AR is considered to be a marker of good prognosis although overexpression of AR can confer resistance to tamoxifen. Unpublished work also suggests that AR overexpression confers resistance to anastrozole. Microarray analysis of a subset of ER/PR-negative tumors reveals clusters with higher expression of AR regulated genes.<sup>6</sup> Dr Fuqua considers the potential to target the AR “food for thought” for future investigation.

In conclusion, the ER remains a viable clinical target in most hormone-resistant tumors. Mechanisms of hormone resistance are still being discovered and may include loss of ER, mutation of the ER at K303R, activation of growth factor receptors and growth factor signaling pathways, and potentially overexpression of AR. In considering how to supercharge hormonal therapy, approaches include use of growth factor receptor inhibitors, signal transduction inhibitors, and direct or indirect inhibition of the AR. Future drug development may include more selected ER downregulators and/or agents that inhibit novel ER targets such as post translational modifications.

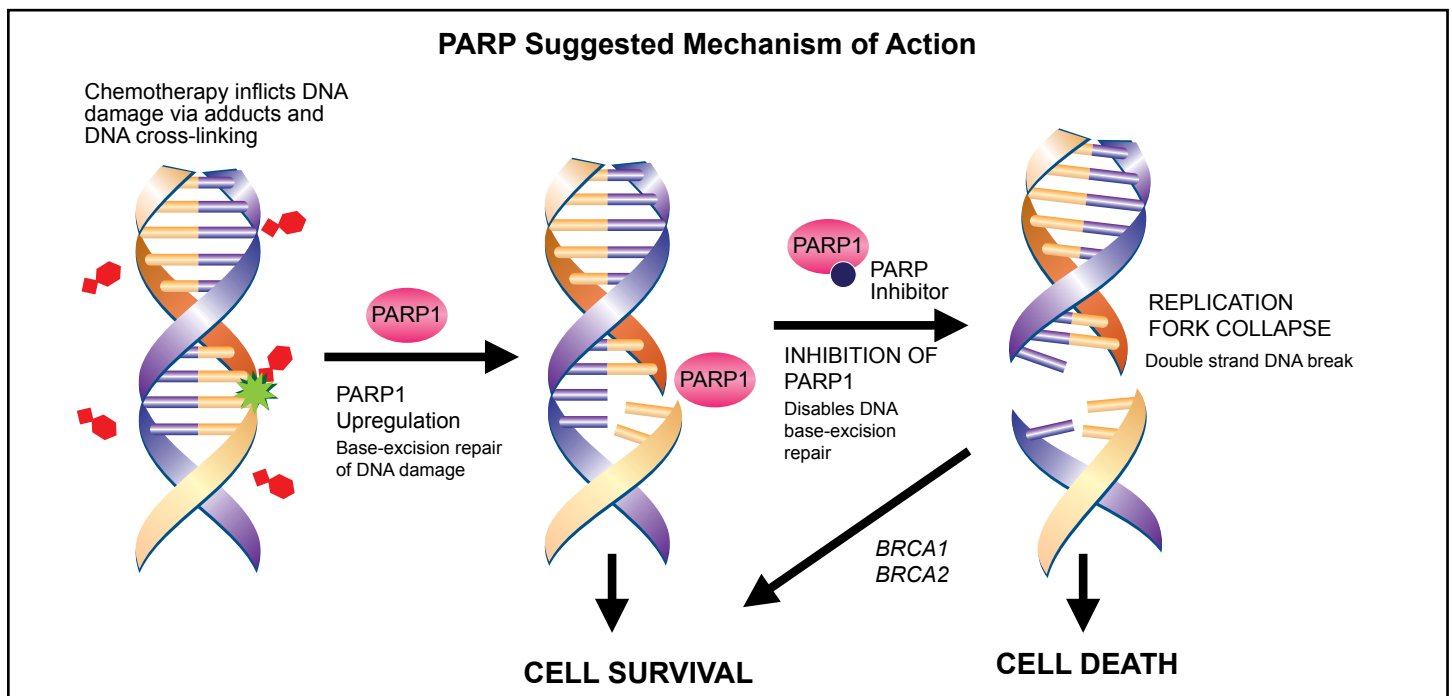
### PARP Inhibitors in MBC

Dr Antoinette Tan from the Cancer Institute of New Jersey gave an update on the clinical status of poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of breast cancer. DNA damage may occur in multiple forms including single- and double-strand DNA breaks. Several mechanisms of DNA repair are employed by cells to maintain genomic integrity essential for cell survival. One such mechanism, the PARP enzyme, represents an expanding research focus in MBC. One of the known functions of PARP is to repair single-strand DNA breaks induced by DNA damaging agents such as chemo- or radiotherapy through base excision repair. *BRCA* repairs double-strand breaks via homologous recombination and non-homologous end joining.<sup>7</sup> In normal cells, *BRCA1/BRCA2* and PARP work in unison to repair DNA damage. Approximately 5% of breast cancer cases in the United States (US) arise in persons with mutated *BRCA1/BRCA2*. In tumor cells with mutated *BRCA1/BRCA2* PARP is the primary means of DNA repair. **Figure 4.**

PARP is an attractive development target as, in theory, agents that inhibit PARP should preferentially damage tumor cells deficient in *BRCA1/BRCA2* while causing minimal damage or disruption to normal cells. In addition, PARP inhibitors may augment the cytotoxicity of DNA-damaging agents and radiation, making them a rational selection for combination therapy. **Table 1.**

Women with triple negative breast cancer (TNBC) defined as tumors that are estrogen receptor (ER) negative, progesterone receptor (PR) negative, and HER2-negative share some clinical and pathologic features in common with *BRCA1* related breast cancers. *BRCA* function may be lost in TNBC and conversely, approximately 80% of *BRCA1* related cancers are triple negative.<sup>8,9</sup> Gene expression studies show PARP-1 to

**Figure 4. PARP Mechanism of Action**



O'Shaughnessy J, et al. *J Clin Oncol.* 2009;27(15S). Abstract 3.

**Table 1. Selection of DNA Damaging Chemotherapy**

Class	DNA Damage	Example
Alkylating Agents	DNA interstrand cross-links resulting in double strand DNA breaks	Cyclophosphamide
Platinum Compounds	Form adducts with DNA	Cisplatin Carboplatin Oxaliplatin
Topoisomerase I Inhibitors	Arrest of DNA replication fork	Etoposide Irinotecan Topotecan Mitoxantrone
Miscellaneous	Directly damages DNA causing double-strand breaks	Bleomycin

be upregulated in triple negative tumors suggesting that PARP may be a rational target in this historically treatment-resistant population. Due to the aggressive nature of TNBC and limited therapeutic options for women with advanced disease, exploration of agents that improve progression-free survival (PFS) and overall survival (OS) is needed. **Table 2.**



**Table 2. Selection of PARP Inhibitors in Clinical Development**

Agent	Route	Phase
BSI-201	IV	I-III
Olaparib	PO	I/II
Veliparib	PO	I/II
AG014699	IV	I/II
CEP-9722	PO	I
MK-4827	PO	I
INO-1001	IV	I

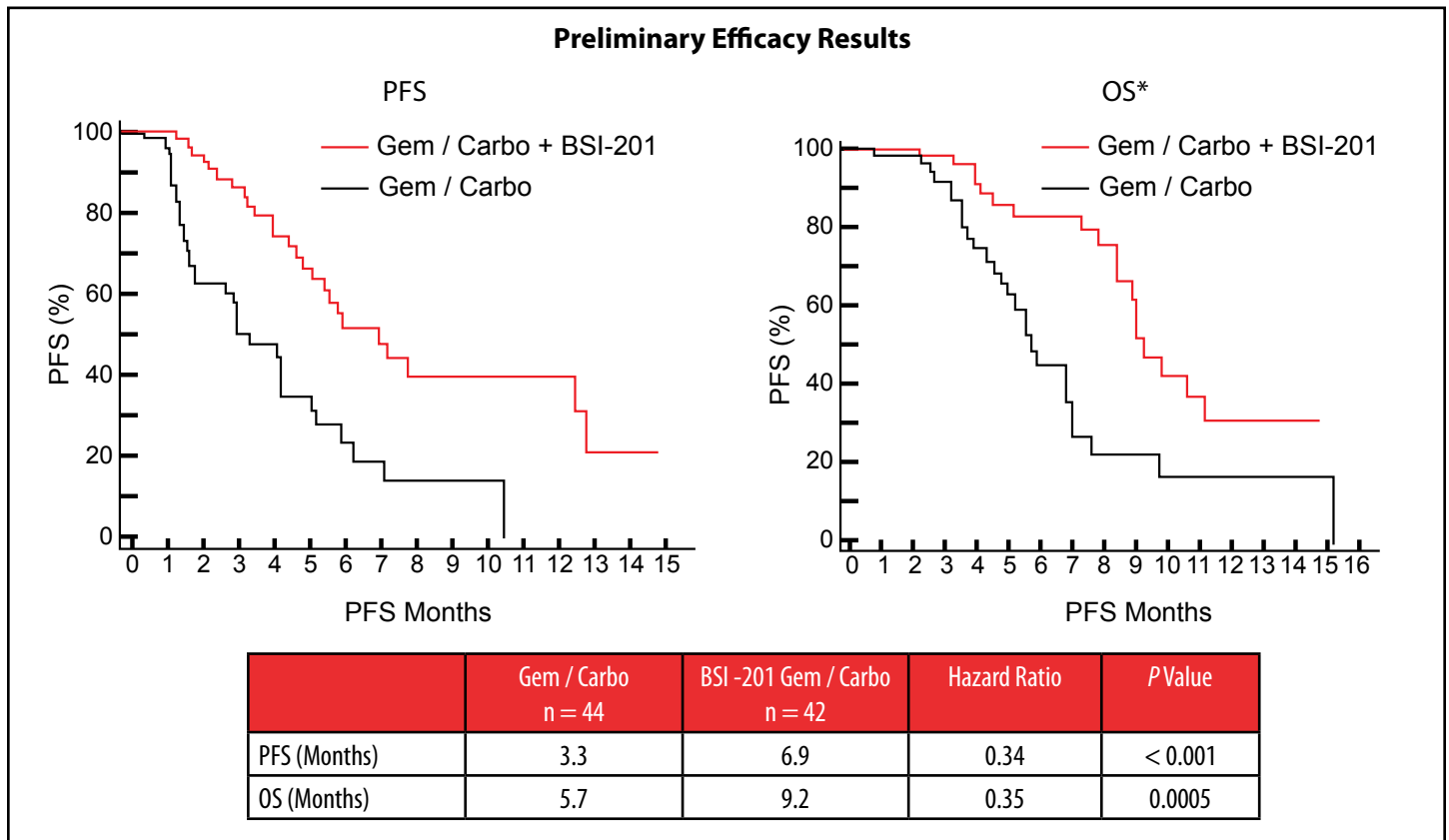
At the 2009 ASCO Annual Meeting Dr Joyce O’Shaughnessy reported improved OS and PFS for women with TNBC when the PARP inhibitor BSI-201 was given in combination with gemcitabine/ carboplatin compared with chemotherapy alone.<sup>10</sup> The

combination of gemcitabine/carboplatin was selected due to previous demonstrated activity in the MBC setting and preclinical evidence of synergy between the agents resulting in double-strand DNA breaks and intrastrand DNA cross-links, which rely on *BRCA1/BRCA2* for repair.

The phase II investigation enrolled 123 patients with metastatic TNBC. Patients were randomized to receive gemcitabine 1000 mg/m<sup>2</sup> IV and carboplatin AUC = 2 IV days 1 and 8 with/without BSI-201 5.6 mg/kg IV days 1, 4, 8, and 11 of a q3wk cycle. More than 50% of patients had received prior adjuvant chemotherapy and approximately 40% received previous therapy for metastatic disease.

The primary endpoint was clinical benefit rate (CBR) defined as CR + PR + SD for 6 months. The combination

**Figure 5. BSI-201 Efficacy**



\*The trial was not powered to detect a difference in OS.  
O’Shaughnessy J, et al. *J Clin Oncol.* 2009;27(15S). Abstract 3.

of BSI-201 and gemcitabine/carboplatin tripled the CBR. **Table 3.** In addition, the PFS increased from 3.3 months to 6.9 months with the addition of BSI-201; HR = 0.34 (95% CI 0.20-0.58),  $P < 0.0001$ . **Figure 5.**

**Table 3. Response Outcomes**

	Gem/Carbo + BSI-201 n = 42	Gem/Carbo n = 44	P Value
ORR	48%	16%	0.002
CBR	62%	21%	0.0002

Gene expression studies performed in 50 patients verified that PARP-1 was upregulated in the majority of patients. The frequency and nature of hematologic and non-hematologic adverse events did not differ between arms, nor was there a difference in the need for dose reduction. The positive findings of this investigation were the basis from which the ongoing phase III trial in metastatic TNBC was designed. Additional information can be found at <http://www.clinicaltrials.gov/ct2/show/NCT00938652?term=BSI-201&rank=7>.

**Table 4. Patient Characteristics**

	400 mg BID n = 27	100 mg BID n = 27
Median age	44 years (32-72)	41 years (28-67)
Ashkenazi Jewish	19%	7%
African American	0%	4%
BRCA1	67%	56%
BRCA2	33%	41%
Both	0%	4%
TNBC	50%	64%
ER+ / HER2-	41%	15%
Median Time From Diagnosis (Range)	62 months (11-253)	66 months (16-344)
Number of Prior Regimens	3 (1-5)	3 (2-4)
Taxane and Anthracycline	96%	70%
Taxane / Anthracycline + Capecitabine	37%	41%
	22%	30%

Tutt A. *J Clin Oncol.* 2009;27(15S). Abstract CRA501.

A separate phase II trial of the oral PARP inhibitor olaparib presented at ASCO demonstrated activity in patients confirmed as *BRCA1/BRCA2* mutation carriers with advanced breast cancer. In this study by Tutt et al, olaparib was administered on a continuous cycle to two sequential dosing cohorts.<sup>11</sup> The first cohort received olaparib at 400 mg PO bid, a previously determined maximally tolerated dose, while the second cohort received 100 mg PO bid.

A total of 27 patients were enrolled into each dose cohort. Over 50% of patients in each cohort had *BRCA1* mutations and more than 50% of tumors were triple negative. **Table 4.** Both groups were previously exposed to a median 3 prior lines of chemotherapy.

The 400 mg dose appeared to be more effective than 100 mg indicating a dose-response relationship. **Table 5.** Progression-free survival was higher in the 400 mg arm, 5.7 months vs 3.8 months in the 100 mg arm.

**Table 5. Olaparib Response Rate**

	ORR	CR	PR
400 mg bid	41%	4%	37%
100 mg bid	22%	0%	22%

Overall, olaparib was well tolerated. Grade 3 fatigue, nausea, and vomiting were reported more often in the 400 mg dosing cohort although no patient stopped therapy due to adverse events in the group. **Table 6.** According to Dr Tutt this study provides proof-of-concept for the activity and tolerability of genetically defined targeted therapy in heavily pre-treated patients with advanced breast cancer.

While the response rates in these trials are encouraging, not all patients with *BRCA1/BRCA2* mutations had a response. Recent preclinical studies suggest that secondary *BRCA2* mutations may restore *BRCA* expression and function causing resistance to PARP inhibition as well as platinum compounds. Future work

**Table 6. Adverse Events**

Patients	Olaparib 400 mg BID, n = 27		Olaparib 100 mg BID, n = 27	
	Grade 1 / 2 (%)	Grade 3 (%)	Grade 1 / 2 (%)	Grade 3 (%)
Fatigue	56	15	56	7
Nausea	41	19	56	0
Vomiting	26	11	22	0
Headache	37	0	19	4
Constipation	22	0	30	0
Diarrhea	60	0	15	0
Cough	15	0	30	0
Dyspnea	4	0	37	4
Insomnia	7	0	26	0
Pain in Extremities	7	0	22	4

Tutt A. *J Clin Oncol*. 2009;27(15S). Abstract CRA501.

includes identification and validation of resistance mechanisms as well as biomarker assays to identify *BRCA* pathway defects. While early results with PARP inhibitors suggest these agents have activity and are well tolerated, confirmatory trials to further define their role are needed. Many questions regarding pharmacokinetic and pharmacodynamic parameters are yet to be explored. These questions include

- What is the optimal dose and frequency?
- How should dosing be timed in relation to combination therapy regimens?
- Will there be a role for chronic/preventive use in patients with *BRCA* mutations?
- How can resistance be avoided/overcome?

Answering these questions as well as the evolution of long-term toxicity data will help expand the influence of PARP inhibition in breast cancer therapy.

### End of the Anthracycline Era?

Dr Hal Burstein discussed the data regarding the appropriate use of anthracycline containing adjuvant regimens. Why is anthracycline use still a controversial issue? Three main reasons Dr Burstein

cited why anthracycline use is still controversial included the emergence of non-anthracycline chemotherapy regimens, the availability of biomarkers that may predict benefit from specific adjuvant chemotherapy regimens, and persistent concerns over late toxicity of anthracyclines.

With decades of treatment advances, where do anthracyclines fit into the treatment paradigm today? Due to the relative convenience of administration and reasonable treatment duration as compared to other regimens, adriamycin/cyclophosphamide (AC) has become the backbone of modern breast cancer chemotherapy in the

US. The combination of AC followed by paclitaxel has been used in conjunction with biologics such as trastuzumab (NSABP B-31/NCCTG N9831) and bevacizumab (E5103 data expected) in the adjuvant setting, investigated prospectively in the elderly and pregnant patient populations, and in molecular diagnostic studies such as SWOG 8814 and ECOG 2197.

Excluding CMF, are non-anthracycline regimens as good as or even better than AC? The US Oncology 9735 adjuvant trial compared AC to docetaxel/cyclophosphamide (TC) q3wk x 4 cycles. Disease-free survival at 84 months showed a HR = 0.74 (95% CI 0.56-0.96) for TC vs AC,  $P = 0.03$  and OS showed an advantage for TC over AC as well; HR 0.69 (95% CI 0.50-0.97);  $P = 0.03$ .<sup>12</sup> Dr Burstein stated that the real issue is not whether taxanes are superior to anthracyclines, rather whether the combination of anthracyclines and taxanes is superior to either alone. Data from a recent review by Gianni et al suggest that the addition of a taxane to an anthracycline regimen substantially reduces the risk of disease recurrence.<sup>13</sup>

Dr Burstein then questions if we are satisfied with the evidence that removing anthracyclines from treatment is acceptable? The NSABP-30 trial, which compared

AC x 4 → docetaxel (T) x 4, vs AT x 4, vs TAC x 4 in node-positive, HER2-negative women suggested a DFS advantage with the AC → T regimen (HR = 0.83 vs TAC,  $P = 0.006$  and 0.80 vs AT,  $P = 0.001$ ) giving caution that a regimen of TC alone would not be sufficient for women with high-risk disease though an OS advantage was not demonstrated.<sup>14</sup>

In HER2-positive disease, data from the NSABP-31/NCCTG N9831 pooled analysis showed the DFS advantage of adding trastuzumab to an AC → paclitaxel regimen.<sup>15</sup> The BCIRG 006 trial offers evidence of the option of a non-anthracycline adjuvant regimen in the HER2-positive, node-positive or high-risk node-negative population comparing the regimens of AC → T, AC→T + trastuzumab (H), and docetaxel, carboplatin, and trastuzumab (TCH) regimens.<sup>16</sup> The second interim analysis showed that both the trastuzumab containing arms had higher DFS rates at 4 years with the AC → TH arm having a slightly more favorable hazard ratio (HR = 0.61 [95% CI 0.48-0.76],  $P < 0.0001$ ) vs TCH (HR = 0.67 [95% CI 0.54-0.83],  $P = 0.0003$ ). These results were consistent among node-negative patients and in the OS analysis. Dr Burstein admits the small difference in HR is not statistically significant and is of limited clinical significance. In truth, the trial was neither powered nor designed to compare efficacy between the AC → TH and TCH arms.

**Table 7. Non-Anthracycline Options Summary**


Population	Efficacy Summary
HER2-Negative	Anthracycline AND taxane regimens ≥ anthracycline OR taxane regimens
HER2-Positive	Lack of sufficient evidence for anthracycline vs non-anthracycline regimen when trastuzumab is administered

Dr Burstein reiterated the following statements by Gianni et al published in the October 1, 2009 edition of the *Journal of Clinical Oncology (JCO)*, which summarizes the current evidence as such;

*Anthracyclines have been shown in numerous randomized trials to be one of the most effective agents for the treatment of breast cancer. Such an established regimen should only be discarded or replaced on the basis of convincing data. So far, there is insufficient evidence to do so. Data generated from a single trial (USON 9735) and retrospective subgroup analyses are intriguing but require substantiation before such a major change in clinical practice can be recommended. In the HER2-positive population, in particular, data from a single unpublished trial that has only reached interim analysis (BCIRG 006) should be interpreted cautiously in the context of published trials that all support treatment in combination with an anthracycline with or without a taxane backbone.<sup>13</sup>*

In light of the evidence, can biomarkers be used to better define who should get anthracyclines? The meta-analysis by Gennari et al suggested the DFS advantage with anthracyclines as compared to CMF is found in the HER2-positive population and to a much lesser extent in the HER2-negative population.<sup>17</sup> Work to identify the predictive and/or prognostic ability of topoisomerase II $\alpha$  (TOP2A), a gene on chromosome 17 continues.<sup>18</sup> A retrospective review of the MA-5 trial by O'Malley et al provided additional evidence that patients with TOP2A amplification/deletion had increased relapse-free survival when treated with CEF vs CMF. The difference was not detected in patients with normal TOP2A.<sup>19</sup> However, this has not been a universal finding. The NSABP B-23 trial compared AC vs CMF in ER-negative, node-negative breast cancer where there was no significant difference in OS by either HER2 or TOP2A. When HER2-positive patients are treated with trastuzumab as in the NSABP B-31 trial TOP2A was not shown to be prognostic of OS.<sup>13</sup> As summarized in recent *JCO* editorials, the jury is still out.<sup>20,21</sup>

In addressing breast cancer and cardiotoxicity, the Von Hoff algorithm and data from clinical trials such as E1199 and CALGB 9741 suggest conventional regimens such as AC or FEC confer a 2-3% or lower risk of congestive heart failure (CHF).<sup>22</sup> In contrast, data from



the SEER registry among women 65 years and older suggests this risk may be higher in patients receiving anthracyclines, although this data was retrospectively extracted from Medicare billing codes.<sup>23</sup> A subsequent review by Pinder et al suggested that nearly one-half of women in the registry developed CHF and there was a greater risk when anthracycline-based therapy was administered to women ages 66-70.<sup>24</sup>

There is discordance between the SEER data, clinical experience, and long-term follow-up from randomized clinical trials. For example, SWOG 8897 showed no significant difference in late cardiac events as measured by left ventricular ejection fraction (EF) at 10-13 years in women receiving CAF vs CMF.<sup>25</sup> The frequency of CHF associated with AC chemotherapy in women age  $\geq 65$  years in the study by Muss et al was 0%.<sup>26</sup> Factors such as patient selection criteria, various anthracycline regimes, length of follow-up, ascertainment and evaluation bias may account for the variation in the rate of cardiotoxicity reported in clinical trials vs registry data.

Cardiotoxicity and trastuzumab therapy has been vigorously investigated in the NCCTG N9831 and NSABP B-31 trials. Data suggest a 3-4% risk of CHF in women treated with AC followed by paclitaxel and trastuzumab therapy compared to 0.5-1% in women receiving AC followed by paclitaxel.<sup>27,28</sup> Risk factors identified in these trials include baseline EF, post AC therapy EF, patient age (especially  $\geq 60$  years), and prior history of antihypertensive medication. Cardiotoxicity updates from the BCIRG 006 trial are awaited though interim data suggest a 1.3% risk of symptomatic CHF with the TCH arm.<sup>16</sup> A trial update is anticipated this December at the 32nd Annual San Antonio Breast Cancer Symposium.

In summary, anthracyclines are associated with a low but real incidence of heart failure. For the majority of women who warrant chemotherapy, the benefit of anthracycline therapy outweighs the potential risk of harm. Dr Burstein concluded that, "rumors of [anthracycline] death are greatly exaggerated."

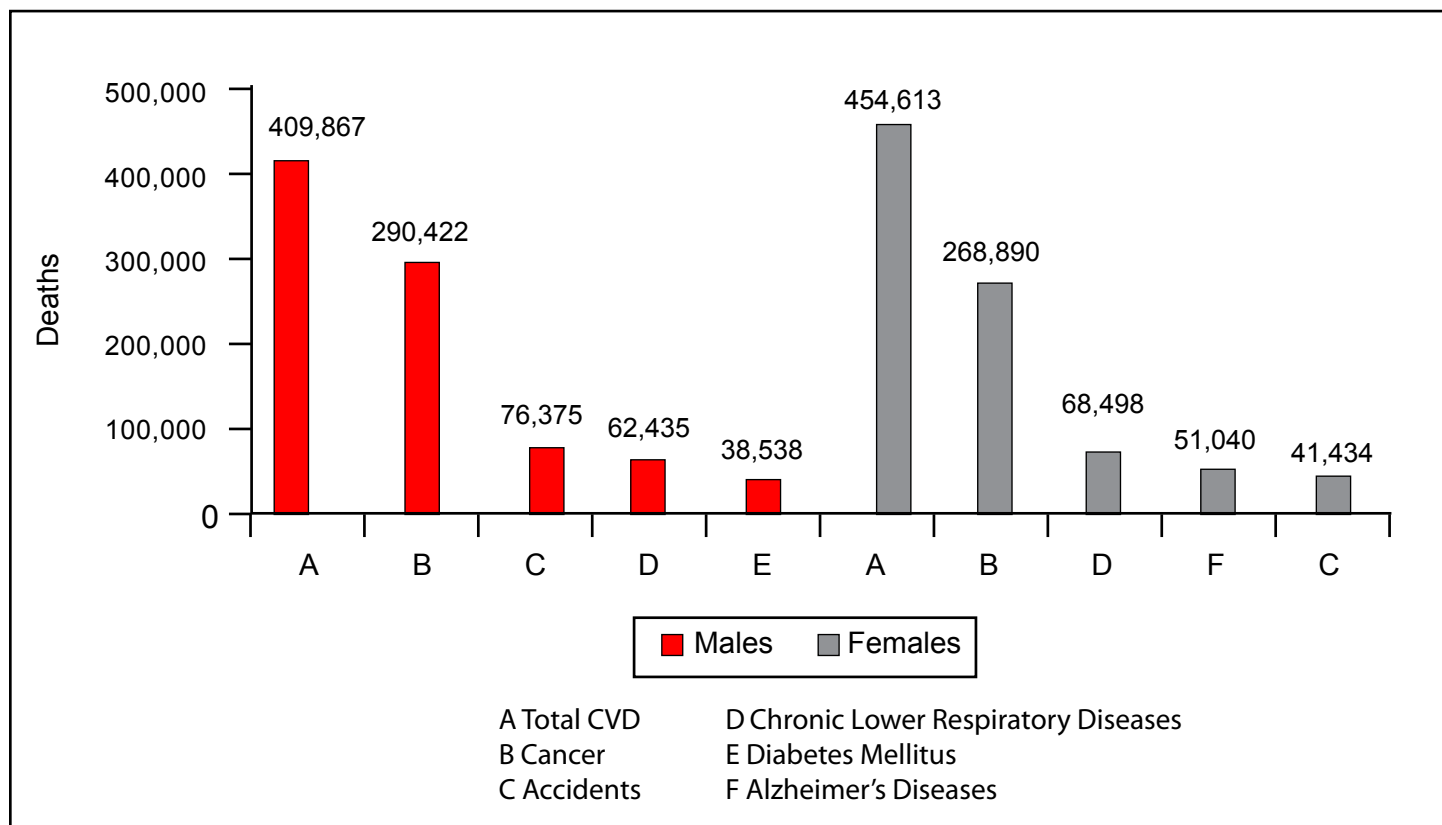
Anthracyclines remain at the core of the most effective, best studied adjuvant treatment regimens to date. Dr Burstein suggests in the future, anthracycline use will diminish as physicians are able to administer less chemotherapy and be more selective as diagnostic tests refine which tumors warrant which regimens. Current markers are not yet sufficient for defining which tumors warrant anthracyclines. Fortunately, non-anthracycline regimes have shown activity and are an option for patients who require a non-anthracycline alternative. Additional data in support of non-anthracycline based regimens may validate the efficacy of this approach.

### Cardiovascular Health and Breast Cancer

Patients with cancer often present at diagnosis with multiple other comorbidities. These conditions may impact treatment decision-making, prognosis, and quality of care assessment. An observational prospective cohort study of 19,268 patients receiving care between 1995-2001 for a new cancer diagnosis examined OS in patients with or without co-morbidities. Kaplan-Meier survival curves revealed that at any point in time the patients with more severe levels of co-morbidity had worse survival ( $P < 0.001$ ) suggesting co-morbidity is an important independent prognostic factor for patients with cancer.<sup>29</sup> While it is easy to "point the finger" at cancer treatments as the cause of cardiovascular endpoints on therapy, we must not forget the contributions of the natural history of ischemic heart disease, hypertension, and diabetes as well.

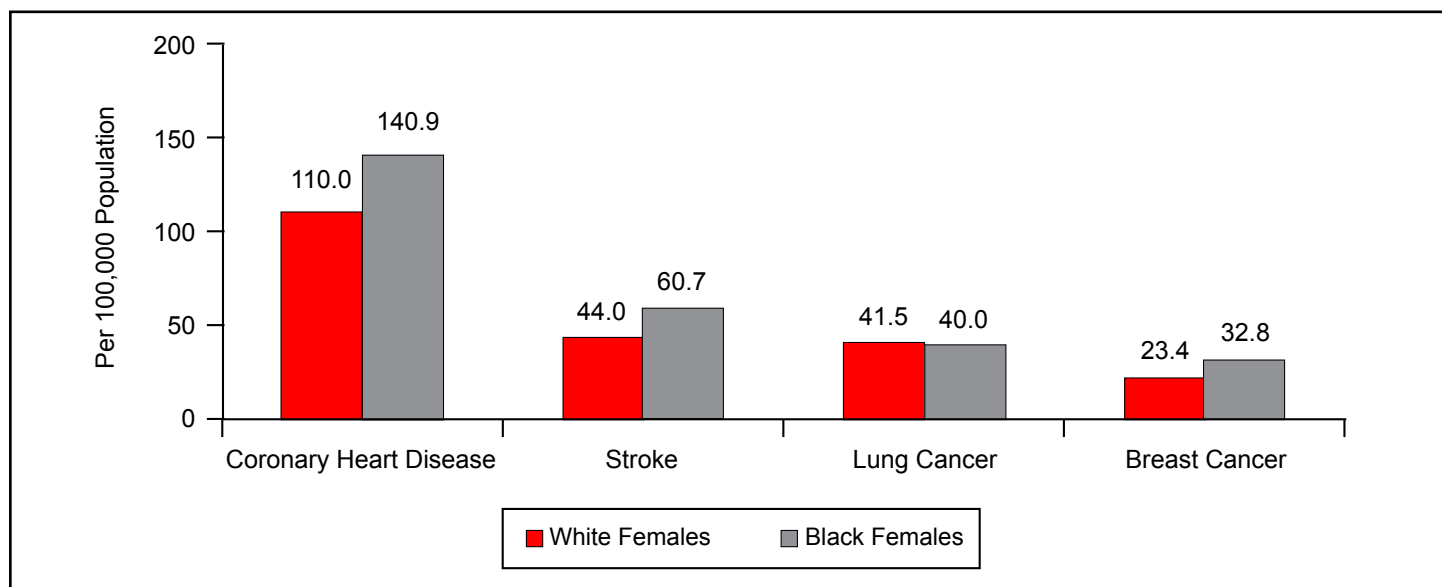
The American Heart Association reports that 1 in 3 adult women in the US have some form of cardiovascular disease. Furthermore, cardiovascular disease and cancer are the leading causes of death in the US. Dr Jean-Bernard Durand medical director of cardiomyopathy services at MD Anderson Cancer Center addressed the topic of maximizing cardiovascular health during and after cancer treatment from a cardiologist point of view. **Figures 6 and 7.**

**Figure 6. Major Causes of Death**



CVD and other major causes of death for all males and females (United States: 2005). Source: NCHS.

**Figure 7. Death Rates in Females**



Age-adjusted death rates for CHD, stroke, lung and breast cancer for white and black females (United States: 2005). Source: NCHS and NHLBI.

There is little published literature on the relationship between cancer and cardiovascular disease and few randomized clinical trials on prevention of cardiotoxicity in cancer patients. The discovery and incorporation of targeted therapies into treatment has brought increased emphasis to understanding the relationship between anticancer agents and cardiovascular effects. Dr Durand emphasized that better understanding is necessary so that the cardiology approach can support, not interrupt treatment.

Dr Durand points out cancer trials have had various definitions of cardiovascular endpoints. The 2009 updated Common Toxicity Criteria for Adverse Events (CTCAE) defines hypertension as a disorder characterized by a pathological increase in blood pressure; measured as a repeated elevation  $\geq 140/90$  mm Hg.<sup>30</sup> The updated criteria align with the Joint Nutrition Council (JNC-VII) guidelines. **Table 8.** The JNC-VII guidelines can be viewed at <http://www.nhlbi.nih.gov/guidelines/hypertension/jncintro.htm>. It has been shown that cardiovascular mortality risk doubles with every 20 mm Hg increase over 115/75 mm Hg for persons age 40-60 years.<sup>31</sup> This is of note as the inclusion criteria for many oncology trials require a blood pressure of  $\leq 160/100$  mm Hg; representing a potential 4-fold increase in risk of a cardiovascular event at study initiation.

**Table 8. CTCAE Version 4.02**

Toxicity Criteria	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Classification	Prehypertension	Stage 1	Stage 2	Life-threatening consequences	Death
JNC-VII Systolic Blood Pressure mm Hg	120-139	140-159	$\geq 160$	-	-
JNC-VII Diastolic Blood Pressure mm Hg	80-89	90-99	$\geq 100$	-	-

Cardiotoxic drug therapy, including chemotherapy, has been incorporated into the criteria for classification into stage A of the American College of Cardiology/American Heart Association heart failure staging system where although patients may be asymptomatic and have a normal left ventricular EF they remain at high risk for developing heart failure.<sup>32</sup> Fortunately, when patients with anthracycline-induced EF decline are treated with the appropriate angiotensin-converting enzyme inhibitors and beta-blockers (carvedilol and metoprolol) the vast majority of patients normalize their EF within 8-12 weeks suggesting that treatment-related cardiac injury is reversible. Work done at MD Anderson also suggests that women who have a decline in EF while on trastuzumab therapy may continue on trastuzumab without detriment when appropriate medical management for HF has been initiated and close monitoring is employed. In terms of stopping HF therapy once an EF has returned to normal, the experience from MD Anderson suggests that once patients are initiated on heart failure therapy, they should remain on therapy indefinitely.

Future approaches to prospectively identify patients at risk for development of heart failure or ischemia include measuring rotational forces of the heart and using 3D imaging to obtain qualitative and quantitative measurements of overall global strain. Dr Durand stated that it is being discovered that

changes in rotational forces of the heart precede changes in EF and may be a better predictor of future cardiovascular events than B-type natriuretic peptide, troponin, or EF.

In conclusion, while there are no guidelines or consensus statements specific to chemotherapy/targeted therapy associated cardiovascular disease, increased understanding of the mechanism of development, early treatment, less dependence on EF, and interdisciplinary collaboration will be the way of the future. Early identification of patients at

risk of a cardiovascular endpoint prior to initiating therapy and diligent cardiovascular monitoring on therapy will improve patient outcomes. Following evidence-based cardiovascular guidelines reduces the mortality of cardiology-associated adverse events in oncology patients. Alignment of goals of clinical and translational research by the disciplines of oncology and cardiology will further maximize the efficacy and safety of future therapies.

### Bone Health and Breast Cancer

A multidisciplinary team composed of endocrinologist Dr Pauline Camacho from Loyola University Medical Center, orthopedic surgeon Dr Joseph Lane from NewYork-Presbyterian Hospital, and medical oncologist Dr Allan Lipton from Milton S. Hershey Medical Center discussed the data surrounding bone health and breast cancer.

Osteoporosis results from an imbalance between bone formation and bone resorption. The subsequent microarchitectural changes in bone lead to an increased risk of bone fracture development. Primary causes of osteoporosis include aging and natural changes in endogenous estrogen levels associated with menopause. Secondary causes include disease states, conditions, or factors that accelerate bone loss. Dr Camacho studied the prevalence of secondary causes of osteoporosis in 64 early-stage breast cancer patients as compared to 174 women with no known breast malignancy. At least one secondary cause was found in 78% of the breast cancer population, which was similar to the 77% found in the non-cancer population. The prevalence of newly diagnosed metabolic bone disorders in the breast cancer population was 58% with the most common source being vitamin D deficiency (38%).<sup>33</sup>

Secondary causes of osteoporosis also include medications such as AI or certain chemotherapies. Data from the ATAC and MA-17 trials suggests that in women receiving AI therapy, changes in lumbar spine bone mineral density (BMD) occur fastest and are most


pronounced. The data also suggest the most significant percentage of bone loss from baseline occurs during the first 1-2 years on AI therapy. This highlights the importance of dual energy x-ray absorptiometry (DEXA) scanning and evaluation for secondary causes of bone loss if patients will be initiated on AI.

The gold standard in diagnosing osteoporosis remains central DEXA scanning with strong evidence supporting the link between fracture risk and bone density. However, data from the national osteoporosis risk assessment (NORA) trial indicates that 50% of fractures occur in women whose t-score is > -2.5 suggesting that there is more to fracture risk assessment than just obtaining BMD and t-scores.<sup>34</sup> The identification of high-risk patients in this BMD range is a clinical priority. Dr Camacho reminded the audience that, "fracture begets fracture" and therefore the primary aim should be to prevent first fracture events.<sup>35</sup> The World Health Organization fracture risk assessment tool (FRAX<sup>®</sup>) is a newer approach based on models that integrate clinical risk factors as well as BMD. **Table 9.**

**Table 9. Clinical Risk Factors**

Bone Fracture Risk Factors <sup>36</sup>
Age
Body mass index < 20 kg/m <sup>2</sup>
Previous low trauma fracture
Family history of hip fracture
Current cigarette smoking
High alcohol intake
Rheumatoid arthritis
Prior or current glucocorticoid use

FRAX algorithms give the 10-year probability of fracture although Dr Camacho cautions the model assumes bone loss is static. The applicability during periods of rapid bone loss (which may or may not be applicable in the breast cancer setting) is unknown. Additional information on the FRAX algorithm can



be found at <http://www.shef.ac.uk/FRAX/>. The FRAX algorithm may help to further determine fracture risk by including individual patient risk factors into the BMD and t-score model. The 2003 ASCO bisphosphonate therapy guidelines are currently under revision. The national osteoporosis foundation guidelines can be found at <http://www.nof.org>.

Dr Lane reminded the audience that in the cancer setting, metastatic bone disease occurs in 4.9 million patients in the US. In fact, breast cancer is one of the top five cancers that most often metastasize to bone. The consequences of metastatic bone disease include risk for pathologic fracture, spinal cord compression, hypercalcemia, and immobility. Furthermore, of those patients with bone disease, 70% experience bone pain. The good news is that longer survival of patients with metastatic disease necessitates development of long-term strategies to prevent and treat bone metastases.

Goals of treatment of pathologic fractures include pain relief, preservation of function, and provision of long-lasting construction. This is challenging as Dr Lane reports fracture healing in breast cancer is approximately 37%. Treatment often includes bone stabilization via polymethylmethacrylate (PMMA) cement +/- zoledronic acid (ZA) or replacement via prosthesis depending, in part, on the weight-bearing capacity of the affected bone.

The prediction of an impending fracture is an inexact science; particularly with the widespread use of bisphosphonate therapy. First published in 1989, the Mirels scoring system is still used today to grade the site, size, tumor character, and pain. A score of 9 or higher suggests prophylactic stabilization is needed as there is a > 90% chance of fracture within three months.<sup>37</sup> Future prediction methods may include finite analysis of bone to determine the force necessary to break the bone at a specified point, evaluation of SUV activity of the tumor via PET, and evaluation of bone repair response.

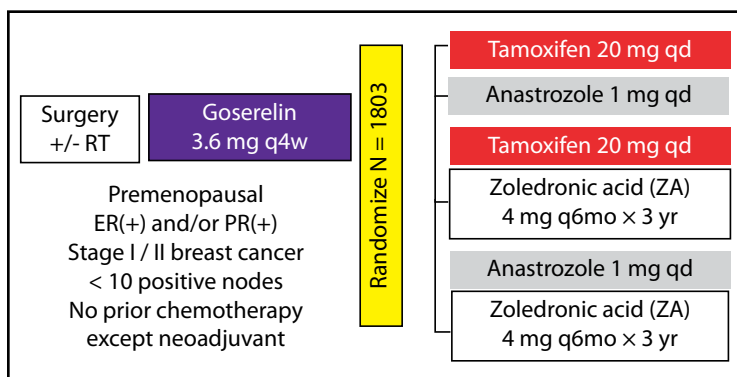
Despite best therapeutic efforts a significant proportion of patients with breast cancer will develop metastatic disease. Bone is the most frequent site

of distant relapse, accounting for approximately 40% of all first recurrences.<sup>38</sup> In clinical trials, a skeletal related event (SRE) occurred within 1 year for ≥ 50% of patients with MBC who did not receive bisphosphonate therapy. According to Dr Lipton, the average breast cancer patient with bone metastasis will experience an SRE every 3 months. The goals of non-surgical intervention for treatment of bone metastases are prevention of SRE and the resulting morbidity, loss in independent functioning, and quality of life change.

Bisphosphonates have been the cornerstone of long-term management of bone metastasis with data showing significant reduction and/or delay in SREs. Retrospective analyses done by Dr Lipton's group suggest a survival advantage for patients with high bone resorption (as indicated by high levels of N-telopeptide of type I collagen [NTx]) who normalize NTx within 3 months after initiation of zoledronic acid (ZA).<sup>39</sup>

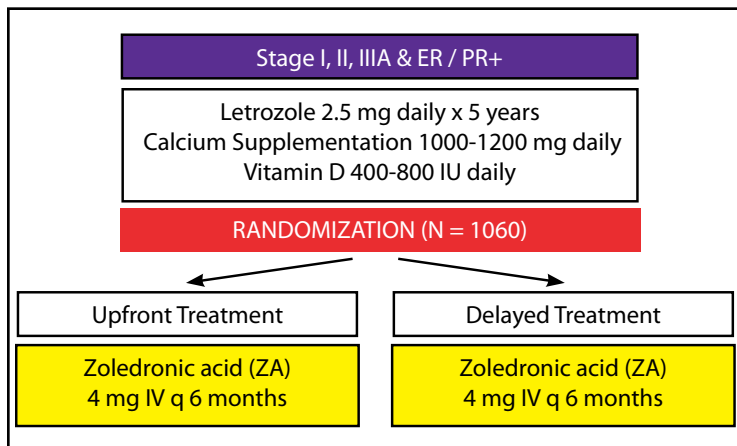
Treatment success has led to the exploration of the potential role of bisphosphonates in the adjuvant setting for prevention of bone metastasis. Preclinical evidence suggests that bisphosphonates have antitumor effects and several trials are examining the efficacy of bisphosphonates in the early disease setting. The Austrian Breast and Colorectal Cancer Study Group Trial (ABCSCG-12) examined the effect of ZA 4 mg IV q6mo in premenopausal breast cancer patients receiving adjuvant endocrine therapy. The addition of ZA significantly reduced disease-free survival events by 36% compared with endocrine therapy alone, HR = 0.65,  $P = 0.01$ . **Figure 8.** In postmenopausal patients, the zoledronic acid-letrozole adjuvant synergy trials (Z-FAST and ZO-FAST) compared the effects of upfront vs delayed ZA on bone loss and SRE. **Figure 9.** At 12 months, a combined analysis showed a lower rate of disease recurrence in the up-front arm (0.84%) vs the delayed arm (1.9%). Several ongoing trials including NSABP B-34, SWOG 0307, and AZURE will provide additional evidence on the usefulness of bisphosphonates in the prevention of metastatic disease.

Figure 8. Austrian Breast Cancer Study Group (ABC SG-12)



Gnant MF, et al. *J Clin Oncol.* 2007;25:820-828.

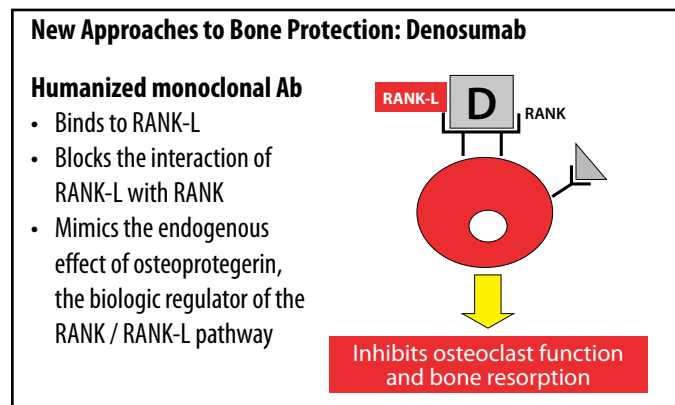
Figure 9. Bone Loss Prevention Trial ZO-FAST



Eidtmann H, et al. Presented at the 31st Annual San Antonio Breast Cancer Symposium 2008. Abstract 44.

Recent advances include the development of the monoclonal antibody denosumab, a first in class receptor activator of nuclear factor  $\kappa\beta$  ligand (RANK-L) inhibitor, identified as a key mediator of osteoclast activity. **Figure 10.** It has been discovered that RANK-L is a central mediator of bone destruction in MBC.<sup>40</sup> The results of a randomized phase III study of the impact of denosumab vs ZA on the incidence of SRE in MBC patients with bone metastases were recently presented.<sup>41</sup>

Figure 10. Denosumab Mechanism



McClung MR, et al. *N Engl J Med.* 2006;354:821-831.

Two thousand forty six patients with documented bone metastases were randomized to receive either denosumab 120 mg subcutaneous (SC) and IV placebo or placebo SC with ZA 4 mg IV q4wk adjusted for creatinine clearance (CrCl). Patients actively receiving IV bisphosphonate infusions or with a CrCl < 30 mL/min were excluded from participation. Patients were counseled to take calcium  $\geq$  500 mg and vitamin D  $\geq$  400 IU daily. The primary endpoint was time to first on-study SRE. Skeletal related events were defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression.

At 34 months, denosumab significantly delayed the time to first on-study SRE compared with ZA, HR = 0.82 (95% CI 0.71-0.95),  $P = 0.01$ . The median time to first on-study SRE was not reached for denosumab while the time to first on-study SRE was a median of 26.5 months for ZA. Time to subsequent on-study SRE was also delayed by denosumab vs ZA with a HR = 0.77, (95% CI 0.66-0.89),  $P = 0.001$ . In a pre-specified exploratory analysis, patients on the denosumab arm reported worsening of pain later than those on the ZA arm (88 days vs 64 days) respectively; HR = 0.87, (95% CI 0.79-0.97),  $P = 0.009$ . Overall survival and TTP of MBC did not differ between arms.

Rates of adverse events and grade 3/4 adverse events were similar across both treatment arms. Renal toxicity occurred in 4.9% of denosumab patients and 8.5% of ZA patients despite dose adjustment for CrCl. Osteonecrosis of the jaw occurred in 2% of patients on denosumab and 1.4% of patients on ZA,  $P =$  non-significant.

The phase III data indicate that denosumab was superior to ZA in delaying or preventing SRE in women with documented bone metastases. Disease-related endpoints such as TTP and OS did not differ. Denosumab represents a novel treatment option for patients with breast cancer bone metastases. Furthermore, this trial highlights the importance of conducting supportive care trials to optimize the spectrum of breast cancer care.

## Conclusion

Save the date for the 2010 ASCO Breast Cancer Symposium to be held September 24-26, 2010 near Washington, DC.

## References

1. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. Aug 17 2000;406(6797):747-752.
2. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguishes tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A*. Sep 11 2001;98(19):10869-10874.
3. Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, et al. An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer. *Cancer Res*. Aug 1 2008;68(15):6084-6091.
4. Barone I, Cui Y, Herynk MH, et al. Expression of the K303R estrogen receptor- $\alpha$  breast cancer mutation induces resistance to an aromatase inhibitor via addiction to the PI3K/Akt kinase pathway. *Cancer Res*. Jun 1 2009;69(11):4724-4732.
5. Barone I. Unpublished work. 2009.
6. Doane AS, Danso M, Lal P, et al. An estrogen receptor-negative breast cancer subset characterized by a hormonally regulated transcriptional program and response to androgen. *Oncogene*. Jun 29 2006;25(28):3994-4008.
7. Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy. *Nat Rev Cancer*. Mar 2008;8(3):193-204.
8. Young SR, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. *BMC Cancer*. 2009;9:86.
9. Anders CK, Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. *Clin Breast Cancer*. Jun 2009;9(suppl 2):S73-S81.
10. O'Shaughnessy J, Osborne C, Pippen JE, et al. Efficacy of BSI-201 a poly(ADP-ribose) polymerase-1 (PARP1) inhibitor in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): results of a randomized phase II trial. *J Clin Oncol*. 2009;18s. Abstract 3.
11. Tutt A, Robson M, Garber J, et al. Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. *J Clin Oncol*. 2009;18S. Abstract CRA501.
12. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology research trial 9735. *J Clin Oncol*. Mar 10 2009;27(8):1177-1183.
13. Gianni L, Norton L, Wolmark N, Suter TM, Bonadonna G, Hortobagyi GN. Role of anthracyclines in the treatment of early breast cancer. *J Clin Oncol*. Oct 1 2009;27(28):4798-4808.
14. Swain S, Henong J, Geyer C, et al. NSABP B-30 definitive analysis of patient outcomes from a randomized trial evaluating different schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel, and cyclophosphamide in women with operable, node-positive breast cancer. Presented at the 31st Annual San Antonio Breast Cancer Symposium. December, 2008. Abstract 75.
15. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. Oct 20 2005;353(16):1673-1684.
16. Slamon D, Eiermann W, Robert NJ, et al. Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: Second interim efficacy analysis. Presented at the 29th Annual San Antonio Breast Cancer Symposium. December, 2006. Abstract 52.
17. Gennari A, Sormani MP, Pronzato P, et al. HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. *J Natl Cancer Inst*. Jan 2 2008;100(1):14-20.
18. Harris LN, Broadwater G, Abu-Khalaf M, et al. Topoisomerase II alpha amplification does not predict benefit from dose-intense cyclophosphamide, doxorubicin, and fluorouracil therapy in HER2-amplified early breast cancer: results of CALGB 8541/150013. *J Clin Oncol*. Jul 20 2009;27(21):3430-3436.

19. O'Malley FP, Chia S, Tu D, et al. Topoisomerase II alpha and responsiveness of breast cancer to adjuvant chemotherapy. *J Natl Cancer Inst.* May 6 2009;101(9):644-650.
20. Esteva FJ, Hortobagyi GN. Topoisomerase II alpha amplification and anthracycline-based chemotherapy: the jury is still out. *J Clin Oncol.* Jul 20 2009;27(21):3416-3417.
21. Pritchard KI. Are HER2 and TOP2A useful as prognostic or predictive biomarkers for anthracycline-based adjuvant chemotherapy for breast cancer? *J Clin Oncol.* Aug 20 2009;27(24):3875-3876.
22. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med.* Nov 1979;91(5):710-717.
23. Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. *J Clin Oncol.* Dec 1 2005;23(34):8597-8605.
24. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol.* Sep 1 2007;25(25):3808-3815.
25. Ganz PA, Hussey MA, Moinpour CM, et al. Late cardiac effects of adjuvant chemotherapy in breast cancer survivors treated on Southwest Oncology Group protocol s8897. *J Clin Oncol.* Mar 10 2008;26(8):1223-1230.
26. Muss HB, Berry DA, Cirincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med.* May 14 2009;360(20):2055-2065.
27. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol.* Mar 10 2008;26(8):1231-1238.
28. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol.* Nov 1 2005;23(31):7811-7819.
29. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL, Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA.* May 26 2004;291(20):2441-2447.
30. National Cancer Institute. Cancer Therapy Evaluation Program v4.0. Available at: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).
31. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* Dec 14 2002;360(9349):1903-1913.
32. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation.* Dec 11 2001;104(24):2996-3007.
33. Camacho PM, Dayal AS, Diaz JL, et al. Prevalence of secondary causes of bone loss among breast cancer patients with osteopenia and osteoporosis. *J Clin Oncol.* Nov 20 2008;26(33):5380-5385.
34. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA.* Dec 12 2001;286(22):2815-2822.
35. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA.* Jan 17 2001;285(3):320-323.
36. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporos Int.* Jun 2005;16(6):581-589.
37. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res.* Dec 1989(249):256-264.
38. Coleman R. Potential use of bisphosphonates in the prevention of metastases in early-stage breast cancer. *Clin Breast Cancer.* Jul 2007;7(suppl 1):S29-S35.
39. Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. *Cancer.* Jul 1 2008;113(1):193-201.
40. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* Apr 15 2004;350(16):1655-1664.
41. Stopeck A, Body J, Fujiwara Y, et al. Denosumab versus zoledronic acid for the treatment of breast cancer patients with bone metastases: results of a randomized phase III study. *European Journal of Cancer.* 2009;7(3). Abstract 2LBA.



**Click here to take  
the post-test**