

# EDUCATIONAL CONCEPTS GROUP



**Translating Today's Science into Tomorrow's Practice:**  
Highlights from the ECCO 15th/34th ESMO Multidisciplinary Congress

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### **Target Audience**

The target audience for the program includes medical, surgical, and radiation oncologists, oncology pharmacy specialists, and other healthcare professionals involved in the care of patients with breast cancer who are unable to attend the ECCO 15th and the 34th ESMO Multidisciplinary Congress.

### **Learning Objectives**

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

- Incorporate clinical data describing new therapeutic agents or strategies into clinical practice to improve pathologic response rates in patients in the neoadjuvant therapy setting
- Discuss updated efficacy and toxicity data for adjuvant therapy options used in the early breast cancer setting
- Describe the strengths and weaknesses of significant clinical trials of agents designed to improve response and survival rates in the metastatic breast cancer setting
- Explain the implications of genetic analysis and biomarkers on treatment selection and response as they currently relate to patients with breast cancer

### **Statement of Need**

The treatment of breast cancer has evolved rapidly as surgical and radiologic techniques have been refined and more active chemotherapeutic and biologic strategies are investigated and becoming available. A number of new agents have recently demonstrated promising benefits in both the early stage and advanced disease settings. In addition, research efforts now focus on exploring predictive and prognostic markers as well as exploring novel combinations and dosing schedules of new and existing agents in an effort to optimize patient outcomes.

Results from recently reported clinical trials have the potential to change the clinical practice of treating breast cancer. While great strides in our understanding of the disease have been made, many questions remain to be answered. In order for healthcare professionals caring for breast cancer patients to select the most appropriate treatment regimen, knowledge of the clinical data in addition to thorough understanding of the biology of disease, mechanisms of resistance, therapy options, and toxicity profiles is necessary. Recognizing the complexity of today's treatment decisions, this program has been developed to provide a comprehensive overview of recent advances in the treatment of breast cancer.

### **Media: Newsletter**

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## Introduction

The 15th European Cancer Organisation (ECCO) and 34th European Society for Medical Oncology (ESMO) Congress held September 20-24, 2009 in Berlin, Germany marked the first joint Congress endeavor between the two cancer organizations. The unified approach highlights how ECCO president Alexander M. M. Eggermont and ESMO president José Baselga foresee the organizations will meet the increasing complexity of cancer challenges in the next decade. Highlights of newly reported data from the multidisciplinary meeting further disseminate scientific advancement, knowledge, and insight gained from this historic collaboration.

### Featured Content

- ECCO 15th/34th ESMO Best Abstracts
- Insights Into Advanced Disease
- Improving Patient Outcomes in Early Disease
- Late Breaking Abstracts

## ECCO-15/34th ESMO Best Abstracts

### ABCSG-24 Neoadjuvant Trial

One of the major strategies advocated at the Congress to further the effort towards personalized medicine in breast cancer was to optimize use of patient and tumor response data obtainable in the neoadjuvant therapy setting. Pathological complete response (pCR) following primary medical therapy has been associated with improved patient outcome and is therefore considered a surrogate marker for eradication of micrometastatic disease. Current chemotherapy regimens result in a pCR in approximately 15%-20% of patients.

Dr Gunther Steger from the Medical University of Vienna, Vienna, Austria reported the first results of the Austrian Breast and Colorectal Cancer Study Group-Trial 24 (ABCSG-24).<sup>1</sup> This phase III study compared epirubicin 75 mg/m<sup>2</sup>, docetaxel 75 mg/m<sup>2</sup>, and capecitabine 1000 mg/m<sup>2</sup> PO bid days 1-14 (EDC) vs epirubicin 75 mg/m<sup>2</sup> and docetaxel 75 mg/m<sup>2</sup> (ED) as neoadjuvant treatment for early breast cancer. Patients with HER2-positive tumors (approximately 25% of the study population) were further randomized to receive neoadjuvant trastuzumab or not. The primary endpoint was the pCR rate at surgery after 6 cycles of chemotherapy.

Five hundred twelve of 536 enrolled patients were eligible for evaluation. The median age in both study groups was 49 years, 75% of patients had tumors ≤ 5 cm, and 45% were lymph node positive. The EDC regimen produced a pCR rate of 24% vs 16% with ED, HR = 0.58 (95% CI 0.38-0.92), *P* = 0.02. Breast conserving surgery was possible in 75% on the ED arm and 78% on the EDC arm. Logistic regression analysis identified the EDC regimen, tumor size < 5 cm, hormone receptor-negative status, and high tumor grade as predictive of pCR.

While there was no significant difference in the incidence of serious adverse events (SAE) (26% vs 21%) only 75% of patients in the EDC arm received 6 total cycles of treatment vs 97% in the ED arm mostly due to capecitabine-related adverse events.

Dr Steger concluded that the EDC regimen appears both efficacious and feasible in the neoadjuvant setting. Additional data from this trial on the subgroup of HER2-positive patients randomized to receive trastuzumab or not will be presented this December at the 2009 San Antonio Breast Cancer Symposium (SABCS). Additional information for the SABCS can be found at <http://www.sabcs.org/>.

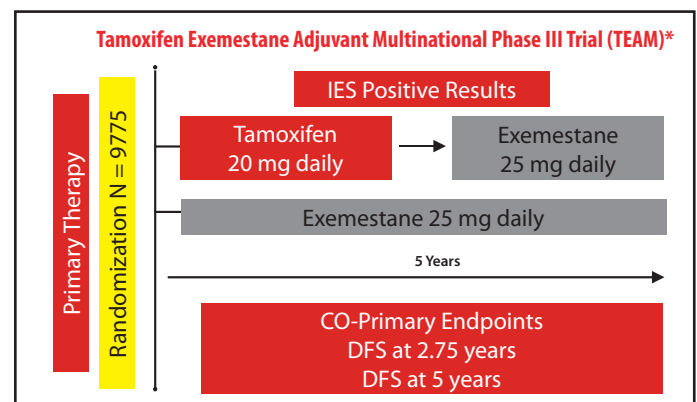
### TEAM Trial Results

Dr Cornelius van de Velde from Leiden University Medical Center, Leiden, The Netherlands presented the results of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) prospective randomized phase III trial in hormone sensitive (HS) postmenopausal early breast cancer. The TEAM study is the largest international trial conducted to assess the efficacy of sequential therapy with an aromatase inhibitor (AI) vs tamoxifen as initial endocrine therapy for HS disease.<sup>2</sup> Nineteen translational and observational sub-studies have been generated from this trial.

Patients with hormone receptor positive disease were randomized to receive either tamoxifen 20 mg daily or exemestane 25 mg daily. The primary endpoint was disease-free survival (DFS). Based on the results of the Intergroup Exemestane Study (IES), the protocol was amended in 2004 so that patients initiated on the tamoxifen arm were switched to exemestane at 2.5-3 years rather than 5 years of tamoxifen administration as in the original protocol.

**Figures 1 and 2.** Nine thousand seven hundred seventy nine patients were enrolled and 740 DFS events were reported at a median 2.75 years follow-up. **Table 1.**

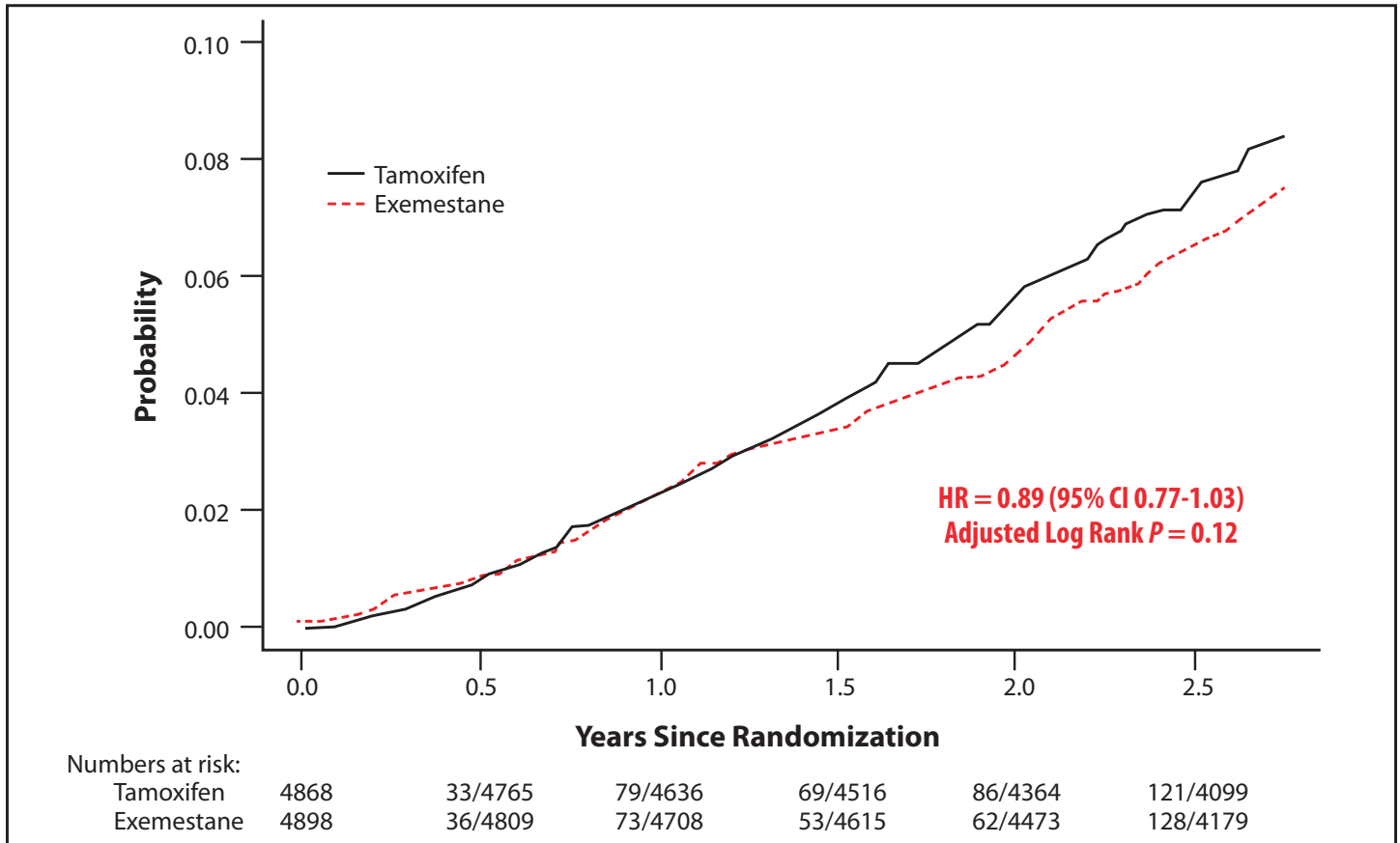
Figure 1. TEAM Trial Schema



\*2004 study design. Bartlett JMS, et al. Presented at the 31st Annual San Antonio Breast Cancer Symposium. 2008; Abstract 81.



**Figure 2. DFS at 2.75 Years**



Bartlett JMS, et al. Presented at the 31st Annual San Antonio Breast Cancer Symposium. 2008; Abstract 81.

**Table 1. TEAM Trial Outcomes at 2.75 Years Median Follow-Up**

	Hazard Ratio	95% Confidence Interval	P Value
Disease-Free Survival on Study Drug	0.83	0.71-0.97	0.02
Relapse-Free Survival	0.85	0.72-1.00	0.06
Time to First Distant Metastasis	0.81	0.67-0.98	0.03

Discontinuation rates were 30% in the tamoxifen arm and 19% in the exemestane arm, emphasizing the importance of educating patients on adherence, which may have confounded the study results. No unexpected safety issues were reported. Patients on the AI arm were more likely to experience arthralgia, diarrhea, and hypercholesterolemia whereas patients on tamoxifen were more likely to experience hot flashes, vaginal bleeding and discharge, as well as thromboembolism. There were no differences

between groups for cardiovascular endpoints including cardiac ischemia/infarction.

At 2.75 years of follow-up, patients treated with exemestane experienced improved DFS and time to distant metastasis. Additional exploration into subgroups that may benefit most from up-front exemestane therapy is needed. The 5-year efficacy results of TEAM will be reported this December at the 2009 San Antonio Breast Cancer Symposium. Results from phase III trials that include direct comparisons of AI's: letrozole vs anastrozole (FACE), anastrozole, letrozole or exemestane, upfront or sequentially (GIM-3-FATA), and exemestane vs anastrozole (MA-27) are eagerly awaited.

Results of two TEAM sub-studies investigating cognitive function and predictive markers were reported at the ECCO/ESMO meeting. The cognitive sub-study led by Dr Christina Schilder from The Netherlands Cancer Institute, Amsterdam examined changes in attention, concentration, learning, memory, and executive function in Dutch women

enrolled in the TEAM trial as compared to healthy controls.<sup>3</sup> Dr Schilder noted although estrogen is known to have both neuroprotective and neurotrophic actions on the brain, there is a paucity of data as to the effect of estrogen deprivation on cognition.<sup>4</sup> A baseline measurement before treatment and a 1-year follow-up evaluation were performed and consisted of 18 neuropsychological tests covering 8 cognitive domains. The 80 women included from the TEAM tamoxifen arm and 99 women from the TEAM exemestane arm had not received adjuvant chemotherapy.

Women receiving tamoxifen performed less well compared to healthy controls on verbal memory and executive functions while no such differences were observed in women receiving exemestane. These data confirm the previously reported Breast International Group (BIG-1-98) experience with letrozole vs tamoxifen and the International Breast Intervention Study (IBIS-II) data suggesting that AI administration does not result in measurable cognitive decline during the early years of therapy.<sup>5,6</sup> Long-term cognitive effects of estrogen deprivation require further study.

A second TEAM sub-study of predictive biomarkers of response to endocrine therapy was reported by Dr John Bartlett from the Edinburgh Cancer Research Center, Edinburgh, United Kingdom.<sup>7</sup> It was hypothesized that estrogen receptor (ER)-positive/progesterone receptor (PgR)-negative patients would benefit from an early switch to AI therapy from tamoxifen. The planned prospective pathology sub-study tested the predictive value of PgR expression on outcome for ER-positive patients enrolled in the TEAM trial. Pathology blocks from 4781 patients were collected and microarrays constructed from 4598 cases and subjected to quantitative analyses of hormone receptors.

The hazard ratio for DFS did not differ according to PgR status, suggesting that it is not a predictive marker for AI benefit. **Table 2.**

**Table 2. Exemestane vs Tamoxifen DFS by PgR Expression**

Marker	Definition	Sub-Study Population (%) N = 4325	Results
PgR-“Rich”	Allred* ≥ 5	77%	HR = 0.81 (95% CI 0.63-1.03)
PgR-“Poor”	Allred* ≤ 4	23%	HR = 0.84 (95% CI 0.60-1.17)

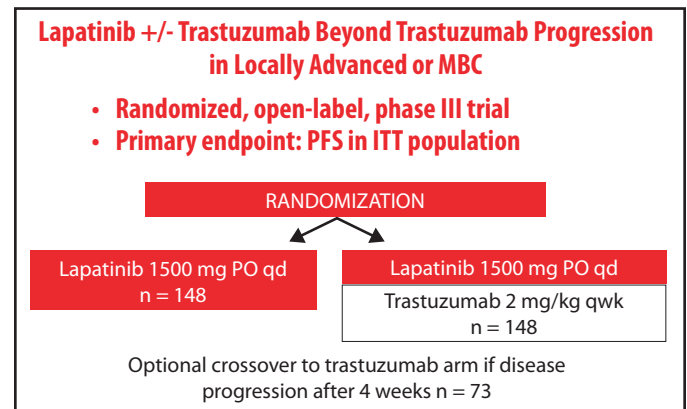
\*Scoring system that combines the proportion of cells staining with the intensity of staining to give a single overall rating.

Dr Bartlett concluded that integrating quantitative measures of hormone receptor status may provide additional prognostic information but preferential treatment effect of exemestane versus tamoxifen based on PgR was not demonstrated.

**Best Abstract: Gene Expression Profiles and Response to HER2 Therapy**

Dr Sunil Badve from the Indiana University Simon Cancer Center, Indianapolis, Indiana presented research on identification of a gene expression profile that may predict response to HER2-targeted therapy.<sup>8</sup> Tumor samples from the phase III EGF104900 study presented by Joyce O’Shaughnessy at the American Society of Clinical Oncology 2008 Annual Meeting were used for gene expression analysis.<sup>9</sup> **Figures 3 and 4.** EGF104900 compared the outcomes of heavily pre-treated metastatic breast cancer (MBC) patients who had progressed on trastuzumab now randomized to receive either single-agent lapatinib or the combination of trastuzumab plus lapatinib.

**Figure 3. EGF104900 Trial Schema**

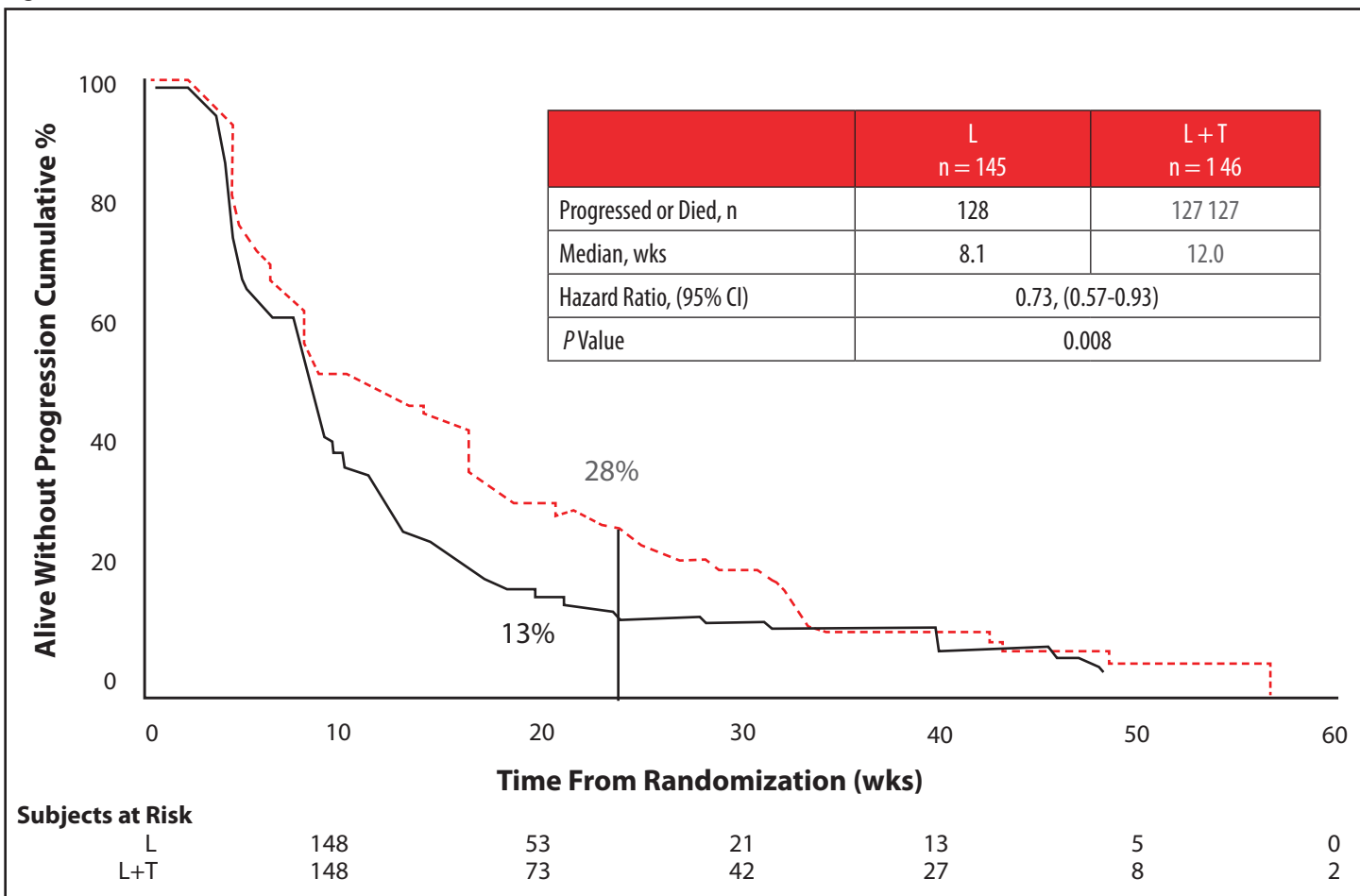


O’Shaughnessy J, et al. *J Clin Oncol.* 2008;26(15S). Abstract 1015.

DNA-mediated annealing, selection, extension, and ligation (DASL) assay gene expression analyses were possible on 133 patient tumor samples from the trial (68 lapatinib and 65 lapatinib plus trastuzumab). Results revealed gene expression differences in HER2-positive tumors that correlated with response to lapatinib or lapatinib plus trastuzumab therapies. **Table 3.** When the study arms were examined as a combined population, 34/502 genes examined were associated with PFS at a < 0.05 significance level. When next examined at a 0.01 significance level, 2/34 genes emerged as associated with PFS; HER2 and MMP7. Increased HER2 RNA expression was associated with increased PFS while increased MMP7 expression was associated with decreased PFS. Gene pathway analysis



**Figure 4. DFS at 2.75 Years**



O'Shaughnessy J, et al. *J Clin Oncol.* 2008;26(15S). Abstract 1015.

suggested higher expression of genes mapping to extracellular matrix and adhesion pathways were associated with worse PFS. PTEN over-expression was associated with a 10-fold risk of adverse prognosis in the combined group, although Dr Badve cautioned that it is premature to draw definitive conclusions as the sample size was small.

**Table 3. Selection of Genes Associated With Improved PFS**

	Increased Gene Expression
Lapatinib	HER2, GRB7, FLI1, PNU TL1
Lapatinib Plus Trastuzumab	COL4A3, PTCH, ESR1, PGR, TGFB R2

These data confirm the feasibility of evaluating gene expression as a potential predictor of treatment utility but a larger series and subsequent validation of such markers

is clearly required. Prospective evaluation of prognostic/predictive gene signatures with respect to adjuvant chemotherapy is ongoing in randomized clinical trials including MINDACT and TAILORx.<sup>10</sup>

### Insights Into Advanced Disease

#### First-Line Therapy: Oral Monotherapy

Single agent oral chemotherapy as a first-line strategy in MBC may be considered in patients with slowly progressing disease and may be a particularly attractive option for elderly patients. Dr Manfred Kaufmann from the Universitätsklinik der J. Wolfgang Goethe-Universität Frankfurt Main, Frankfurt, Germany reported the results of the Mono Efficacy of Capecitabine (MoniCa) German Breast Group (GBG)-39 trial. This was a phase II study of the efficacy of capecitabine as first-line therapy in patients with HER2-negative, "medium-risk", MBC.<sup>11</sup>

Capecitabine was administered as commonly employed in clinical practice at 1000 mg/m<sup>2</sup> PO bid days 1-14 of a 3-week cycle. The primary endpoint was time to progression (TTP). A total of 200 patients were required to meet the pre-specified end-point of a 30-week median TTP, although 165 patients from 35 centers were enrolled. Over half of the patients (54%) had received adjuvant chemotherapy including an anthracycline (36%) and/or a taxane (25%).

Complete response (CR) was achieved in 8%, partial response (PR) in 18%, stable disease (SD) in 38%, and progressive disease (PD) in 28%. The median TTP was 32 weeks (95% CI 27-36). Patients who were > 65 years old had a prolonged TTP, *P* = 0.01 compared to younger patients. The dose was reduced or interrupted in 56% of patients. Three fatal adverse events included myocardial infarction, cerebral bleeding, and liver failure. Hand-foot syndrome (HFS) was experienced in 30-40% of patients although grade 3/4 HFS was experienced in just 8%. Subgroup analysis demonstrated that patients who experienced HFS had a prolonged TTP and OS, vs those who did not, *P* = 0.037 and *P* = 0.025. This is an intriguing pharmacodynamic end-point that warrants further investigation.

Dr Kaufmann concluded that capecitabine 1000 mg/m<sup>2</sup> PO bid as first-line monotherapy demonstrated acceptable efficacy and safety profiles. The benefit seen in the elderly patient subgroup may be of particular interest as an up-front oral therapy option for older patients and could be considered for a phase III trial design.

**First-Line Therapy: An All-Oral Combination Regimen**

As no single standard-of-care regimen exists in the advanced disease setting, continued exploration of agents and regimens with desirable safety and efficacy profiles is needed. The optimal use of agents be it in sequence or combination remains unclear. A study led by Dr Mario Campone from the Centre René Gauducheau, Nantes, France reported the feasibility of an all-oral first-line regimen in MBC.<sup>12</sup> Vinorelbine and capecitabine were selected for combination based on their differing mechanisms of action, single-agent activity in the MBC setting, and oral bioavailability. The randomized phase II assigned MBC patients previously treated with anthracyclines into 1 of 3 study arms:

- **Arm A:** Concurrent vinorelbine (V) 80 mg PO days 1, 8 (first cycle 60 mg) plus capecitabine (X) 1000 mg/m<sup>2</sup> PO bid days 1-14 q3wk
- **Arm B:** V 80 mg PO days 1, 8, and 15 (first cycle 60 mg) x 3 cycles alternating with X 1000 mg/m<sup>2</sup> PO bid days 1-14 x 3 cycles
- **Arm C:** Docetaxel (D) 75 mg/m<sup>2</sup> IV day 1 plus X 1000 mg/m<sup>2</sup> PO bid days 1-14 q3wk

The median age, disease-free interval, and proportions of patients with measurable disease were similar among groups. More patients in arm B had visceral disease (91%) than arms A (66%) or C (65%). The primary endpoint was overall disease control rate (DCR) defined as CR, PR, or SD for ≥ 3 months. **Table 4.** Progression-free survival (PFS) and OS data continue to mature.

**Table 4. Disease Control Rate**

	V + X n = 44	V alternating X n = 47	D + X n = 48
DCR Independent Review	71%	37%	71%
Median Number of Cycles Administered (Range)	8 (1-25)	4 (1-15)	6 (1-18)
Dose of Capecitabine Reduced	41%	7%	52%

The incidence of febrile neutropenia was 2% in arm A, 0% in arm B, and 6% in arm C with neutropenic infection in 0%, 0%, and 12%, respectively. Non-hematologic toxicity included 9% grade 3 diarrhea in arm A, and 19% grade 3 HFS in arm C as compared to 5% in arm A and 2% in arm B. No grade 4 adverse events were reported.

The investigators concluded that the combination arm of V + X appeared to offer a higher DCR than the sequential schedule in this group of patients and showed similar efficacy to the combination of D + X. The higher prevalence of visceral disease in arm B (V alternating with X) may have influenced the response rate. Additional efficacy outcome data is awaited to see if the differences in response translate into a potential disease-free or overall survival advantage. Toxicity was deemed “acceptable”. These data suggest that this oral first-line regimen in MBC is feasible in HER2-negative patients with prior anthracycline exposure and should be further investigated in larger studies.

**First-Line Therapy: Paclitaxel and Oral VEGF Inhibition**

In the Eastern Cooperative Oncology Group trial E2100, the combination of paclitaxel and the vascular endothelial growth factor (VEGF) inhibitor bevacizumab demonstrated increased PFS vs paclitaxel alone in the first-line MBC setting.<sup>13</sup> Motesanib is an oral multiple tyrosine kinase (TK) inhibitor of VEGFR<sub>1-3</sub>, platelet-derived growth factor receptor (PDGR), and KIT. Dr Miguel Martin from the Hospital Clinico San Carlos, Madrid, Spain reported the first efficacy results of the CIRG/TORI 010 trial, a randomized phase II investigation of motesanib plus weekly paclitaxel as first-line therapy of HER2-negative MBC.<sup>14</sup> Patients were randomized into 1 of 3 treatment arms and treated until progressive disease or intolerable toxicity.



- **Arm A:** Paclitaxel 90 mg/m<sup>2</sup> IV qwk x 3 plus placebo
- **Arm B:** Paclitaxel 90 mg/m<sup>2</sup> IV qwk x 3 plus motesanib 125 mg PO daily
- **Arm C:** Paclitaxel 90 mg/m<sup>2</sup> IV qwk x 3 plus open-label bevacizumab 10 mg/kg q2wk

Two hundred eighty two patients from 12 countries were enrolled in the trial. The primary endpoint was the difference in independent review of overall response rates (ORR) between arms A and B. **Table 5.** One-third of patients remained on therapy at the November 2008 cut-off date. While the ORR favored the combination of paclitaxel + motesanib vs single-agent paclitaxel, the response difference was not statically significant,  $P = 0.09$ . The response rate to paclitaxel + motesanib was similar to paclitaxel and open label bevacizumab though formal comparison was not prescribed. Similarly, the trial was not powered to detect differences in PFS between arms.

**Table 5. Efficacy Outcomes**

	Paclitaxel + Placebo n = 94	Paclitaxel + Motesanib n = 91	Paclitaxel + Bevacizumab n = 97
ORR	35% (26-46)	48% (38-59)	45% (35-56)
PFS	8.0 months (6.6-9.6)	9.1 months (8.1-11.6)	10.1 months (9.0-15.3)

Hepatobiliary toxicity seen with motesanib emerged as a unique toxicity with an unknown etiology. Three patients experienced grade 3/4 cholecystitis and 1 patient experienced grade 3/4 gall bladder enlargement. Most other toxicity was gastrointestinal (GI) in nature including nausea, diarrhea, vomiting, and abdominal pain.

Dr Martin concluded that the efficacy of paclitaxel plus motesanib seems to be comparable to paclitaxel plus bevacizumab in terms of ORR. However, the addition of motesanib did not seem to offer an obvious advantage over paclitaxel + bevacizumab particularly when toxicity concerns are considered. The origins of grade 3/4 hepatobiliary toxicity would need to be further defined and prevention/management strategy proposed before continuing development of the compound in the MBC setting.

#### **Pre-Treated MBC: Benefit of Oral VEGF and IV HER2 Inhibition**

Dr Jean-Yves Blay from Centre Leon Berard & University Claude Bernard, Lyon, France reported the phase II study of sunitinib in combination with trastuzumab for the treatment of MBC.<sup>15</sup> Sunitinib is an oral, multiple kinase

inhibitor of VEGFR<sub>1-3</sub>, PDGFR<sub>α,β</sub>, KIT, RET, FLT-3, and CSF-1R. While best known for its efficacy in renal cell carcinoma and gastrointestinal stromal tumors, sunitinib 50 mg PO daily has also shown activity in heavily pre-treated MBC patients.<sup>16</sup> Exploring the concept of combined targeted therapy, sunitinib 37.5 mg PO was combined with trastuzumab at either 2 mg/kg qwk or 6 mg/kg q3wk dosing. After a protocol amendment, the reported trial population of 54 included women who had received prior therapy in the MBC setting including prior trastuzumab or lapatinib exposure.

The primary endpoint was ORR, which was 33% and the CBR was 50%. The majority of responses occurred in patients who were either entirely breast cancer treatment naïve or had not received prior therapy for MBC. Median PFS was 25.3 weeks (95% CI 19.3-29.1).

Grade 3 non-hematological toxicity included asthenia (17%) and hypertension (11%), epistaxis (4%) and diarrhea (6%) with grade 4 pulmonary embolism and pancreatitis also noted. Grade 3/4 neutropenia occurred in 10 patients. Left ventricular ejection fraction (LVEF) decline was documented in 21/54 (39%) of patients; 14/21 (26%) were asymptomatic and 7/21 (13%) symptomatic. Dose reduction to sunitinib 25 mg was required in 43% of patients overall. One death due to cardiogenic shock was also recorded.

Though the response rate for the combination was encouraging, the benefit of sunitinib in addition to trastuzumab needs to be tested formally and Dr Blay stressed that despite modest results, the data should be the basis of a randomized clinical trial.

#### **Pre-Treated MBC: Overcoming Trastuzumab Resistance With mTOR**

Mechanisms of primary and acquired resistance to anti-HER2 therapy are still being understood. It is currently believed resistance to trastuzumab may be associated with loss/deregulation of PTEN or activation of mutations in the PI3K/AKT pathway. Mammalian target of rapamycin (mTOR) is a downstream signal of the PI3K/AKT pathway. Combining everolimus, an oral inhibitor of mTOR, with trastuzumab may reverse resistance and restore clinical activity. A phase I dose finding investigation reported by Dr Fatima Cardoso from the Jules Bordet Institut, Brussels, Belgium combined daily and weekly everolimus with vinorelbine and trastuzumab in patients with HER2-positive MBC with prior resistance to trastuzumab.<sup>17</sup>

Fifty patients were enrolled in the phase I trial. In addition to trastuzumab resistance, patients also exhibited taxane (40%-50%) and lapatinib resistance (20%-25%). Grade 1/2 stomatitis and fatigue were the most common adverse events reported. Grade 3 fatigue was a dose-limiting toxicity. Neuropathy was noted in 43% of patients at the 5 mg

dosing arm and 60% in the 20/30 mg arms. Although such endpoints are not the primary aim of a phase I multicentric trial, efficacy was suggested by a CBR of 37% in the 5 mg daily arm and 58% in the weekly dosing arms. **Table 6.**

**Table 6. Efficacy Outcomes by Everolimus Dose**

	5 mg/day n = 25	20 mg/wk n = 6	30 mg/wk n = 13
CR	4%	-	
PR	16%	17%	15%
SD	60%	50%	60%
PD	20%	33%	15%
Median TTP (wks)	32	33	29

Everolimus in combination with vinorelbine and trastuzumab was well tolerated with promising activity observed in patients who were heavily pretreated. Both a 5 mg/day and 30 mg/week regimens will be further developed.

Dr Cardoso also led a phase I study evaluating sunitinib in combination with docetaxel and trastuzumab as first-line treatment in patients with locally recurrent or metastatic HER2-positive disease.<sup>18</sup> The data suggested the combination was feasible, showed promising efficacy (ORR 78% in 18 evaluable patients), and adverse events were able to be managed through dose delay or reduction. Preliminary evidence of antitumor activity of the combination warrants further evaluation.

## Improving Patient Outcomes in Early Disease

### IES 6-Year Follow-Up

The Intergroup Exemestane Study (IES) demonstrated a DFS benefit when postmenopausal patients with early breast cancer were switched to exemestane after 2-3 years of tamoxifen to complete a total of 5 years therapy vs 5 years of tamoxifen alone.<sup>19</sup> Professor Charles Coombes from the Imperial College London, London, United Kingdom presented an updated analysis of the IES with 6-year follow-up data available as of June 2009. The trial enrolled 4724 patients from 366 sites in 37 countries. The primary endpoint was DFS. **Table 7.** Eighty six percent of patients had ER-positive tumours; however, 12% had tumours in which ER status was unknown.

Disease-free survival in the intention-to-treat (ITT) population was significantly better in the exemestane arm compared to tamoxifen, HR = 0.84 (95% CI 0.75-0.94),  $P = 0.002$ . When restricted to the ER-positive/ER-unknown

population, HR was 0.82 (95% CI 0.73-0.92),  $P = 0.0009$ . There was no subset that did not appear to benefit from exemestane compared with tamoxifen. The OS in the ER-positive/ER-unknown population also favored exemestane HR = 0.86 (0.75-0.99),  $P = 0.04$  representing a 2.4% absolute difference at 8 years.

**Table 7. Outcomes at Median 56 and 91 Months Follow-Up**

	Outcome	Hazard Ratio	95% CI	P Value
Median Follow-Up 56 Months	DFS (ITT)	0.76	0.66-0.88	0.0001
	OS (ER+/ER?)	0.83	0.69-1.00	0.05
Median Follow-Up 91 Months	DFS (ITT)	0.84	0.75-0.94	0.002
	OS (ER+/ER?)	0.86	0.75-0.99	0.04

There were no unexpected safety findings, which included cardiovascular, musculoskeletal, and gynecologic events and bone fractures consistent with similar studies of AI vs tamoxifen. It was noted that carpal tunnel was more common on exemestane (2.8% vs 0.6%,  $P < 0.001$ ), which returned to normal when treatment completed. A cardiovascular endpoint that did not return to normal at completion was hypertension, for which Prof Coombes had, "no explanation whatsoever."

The updated findings confirm that the protective effect of exemestane in postmenopausal women is maintained > 5 years post treatment. Prof Coombes concluded the tamoxifen/exemestane switching strategy appears advantageous in early stage breast cancer and may lessen the serious adverse events seen when individual agents are used for longer periods of time.

### Preventing Premature Ovarian Failure

Depending on the patient age and chemotherapy regimen used, 40%-60% of pre-menopausal women receiving adjuvant chemotherapy will experience premature ovarian failure (POF).<sup>20</sup> Chemotherapy-induced POF leads to infertility, menopausal symptoms, and decreased quality of life. Mechanisms thought to protect ovarian function based on observational studies in premenopausal women undergoing chemotherapy include use of a gonadotropin releasing hormone (GnRH) agonist. Dr Bernd Gerber from the University of Rostock, Rostock, Germany presented the results of the GBG-37 goserelin acetate (Zoladex®) Rescue of Ovarian Function (ZORO) phase II trial, a prospective randomized multicenter study of the ability of goserelin to prevent chemotherapy-induced POF in young hormone-insensitive breast cancer patients receiving anthracycline-containing adjuvant chemotherapy.<sup>21</sup>



Patients between the ages of 18 and 45 with premenopausal follicle stimulating hormone levels (< 15 mIU/mL in the follicular phase) and no evidence of distant metastasis were randomized to receive an anthracycline-containing chemotherapy regimen with goserelin 3.6 mg SC q4wks until the last chemotherapy cycle completed vs chemotherapy alone. The primary endpoint was normal ovarian function defined as 2 consecutive menstrual periods within 21-35 days; 5-8 months after last application of goserelin.

Sixty seven patients were enrolled and 60 evaluable, 30 in each treatment arm. The median age was 35 years in the goserelin arm and 38.5 years in the observation arm. A taxane-free chemotherapy regimen (FEC/FAC) was used in 15 patients on goserelin and 14 patients not receiving goserelin. Seven patients never stopped menses, 2 on goserelin and 5 in the observation arm. By 24 months, all patients had resumed menses. **Table 8.** The median time to restoration of menstruation was 6.25 months on goserelin vs 7.13 months observation only, *P* = non-significant (NS).

**Table 8. Restoration of Menses by Time**

	Goserelin (n)	Observation (n)	P Value
6 months	21	17	0.42
12 months	4	7	

No serious adverse events related to goserelin administration were reported. One woman in each group became pregnant. There was a non-significant trend towards a slightly shortened median time to restoration of menses with goserelin after about 6 months off therapy, although by 1 year the majority of women had resumed menses. The administration of goserelin to protect premenopausal women from chemotherapy-induced POF cannot be supported by this data. The phase III IBCSG 43-05/SWOG 0203 Prevention of Early Menopause Study (POEMS) is ongoing. Additional information is available at [http://www.ibcsg.org/Public/PatientsandPublic/Clinical\\_Trials/Open\\_Trials/IBCSG\\_34-05/Pages/IBCSG34-05\(POEMS\).aspx](http://www.ibcsg.org/Public/PatientsandPublic/Clinical_Trials/Open_Trials/IBCSG_34-05/Pages/IBCSG34-05(POEMS).aspx).

## Late Breaking Abstracts

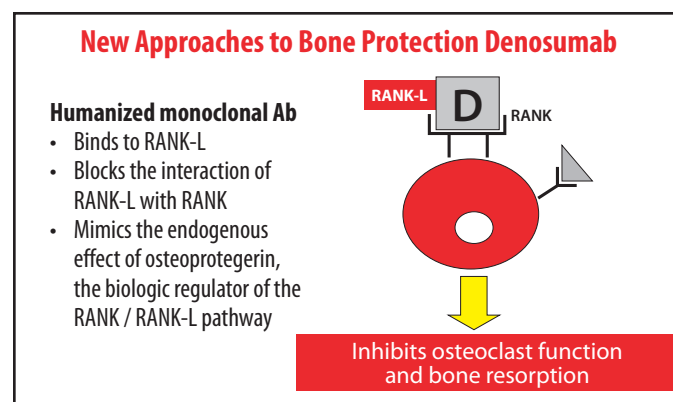
### Denosumab vs Zoledronic Acid in MBC

Bone is the most frequent site of distant relapse, accounting for approximately 40% of all first recurrences.<sup>22</sup> The consequences of bone metastases may include pain, pathologic fracture, or hypercalcemia of malignancy. The monoclonal antibody denosumab, a first-in-class receptor activator of nuclear factor  $\kappa$ B ligand (RANK-L) inhibitor, has been identified as a key mediator of osteoclast activity.

**Figure 5.** It has also been discovered that RANK-L is a central mediator of bone destruction in MBC.<sup>23</sup> Dr Alison Stopeck

from the University of Arizona, Tucson, Arizona presented results of a randomized phase III study of the impact of denosumab vs zoledronic acid (ZA) on the incidence of skeletal-related events (SRE) in MBC patients with bone metastases.<sup>24</sup>

**Figure 5. Denosumab Mechanism**



RANK = receptor activator of nuclear factor  $\kappa$ B; RANK-L = receptor activator of nuclear factor  $\kappa$ B ligand; Ab = antibody. 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 SC and IV placebo or SC placebo 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. 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* = NS.

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 palliation of patients with breast cancer.

### SOLTI-0701: Capecitabine +/- Sorafenib in MBC

Sorafenib is an oral multiple kinase inhibitor with activity against VEGFR<sub>1-3</sub>, PDGFR<sub>α</sub>, KIT, FLT-3, RAF, and RET widely known for its efficacy in hepatocellular and renal cell carcinomas. Phase II data indicated MBC single-agent activity and early investigation indicated safety and potential for efficacy for the combination of capecitabine and sorafenib.<sup>25</sup> Dr José Baselga presented results of SOLTI-0701, a randomized, double-blind, phase IIb trial that compared the efficacy and safety of capecitabine 1000 mg/m<sup>2</sup> PO bid days 1-14 q3wk plus continuous sorafenib 400 mg PO bid (SC) vs capecitabine plus placebo (PC) in women with locally advanced or MBC.<sup>26</sup> Eligibility criteria included HER2-negative status and ≤ 1 prior chemotherapy regimen for advanced disease.

The primary endpoint was PFS. The trial accrued 229 patients over 15 months. Prior chemotherapy was administered to 77% of patients in the SC arm and 68% of patients in the PC arm that included anthracyclines (89%) and taxanes (60%). **Table 9.**

**Table 9. Prior Line(s) of Therapy**

	Sorafenib + Capecitabine (SC)	Placebo + Capecitabine (PC)
First-Line Treatment	43%	54%
Second-Line Treatment	57%	45%

Median PFS was significantly longer in the capecitabine plus sorafenib arm. **Table 10.** This represents a 42% reduction in risk of disease progression. The benefit was seen in patients receiving both first-line (HR = 0.50, *P* = 0.002) and second-line (HR = 0.65, *P* = 0.034) therapy. The ORR was 38% for SC and 31% for PC. Overall survival data is maturing.

**Table 10. PFS Outcome Results**

	Sorafenib + Capecitabine n = 115	Placebo + Capecitabine n = 114	HR (95% CI)	<i>P</i> Value
PFS	6.4 months	4.1 months	0.58 (0.41-0.81)	0.0006

The most common grade 3/4 toxicity included diarrhea, dyspnea, neutropenia, and mucositis with grade 3/4 HFS (reported as hand-foot skin reaction) experienced in 13% of patients on PC but 45% of patients on SC. Seven percent of patients on the PC arm discontinued therapy due to AE vs 15% on SC, the most common reasons being HFS and diarrhea.

The all-oral regimen of capecitabine plus sorafenib demonstrated improvement in PFS in patients with advanced breast cancer as compared to capecitabine plus placebo. The regimen was tolerable although patients will need to be monitored closely for HFS and counseled appropriately. No new or unexpected SAE emerged from the data.

These results represent the first randomized study to demonstrate the value of sorafenib administered in combination with cytotoxic therapy in advanced breast cancer. Current randomized phase II studies of the Trials to Investigate the Effects of Sorafenib in Breast Cancer (TIES) program in locally advanced or MBC include an evaluation of sorafenib plus paclitaxel in the first-line setting, sorafenib plus gemcitabine in the first- or second-line setting following progression on bevacizumab, and sorafenib plus docetaxel and/or letrozole in the first-line setting. According to recent reports, the sorafenib plus paclitaxel trial led by Dr Bill Gradishar from Northwestern University, Chicago, Illinois did not show a statistically significant PFS advantage for the combination of sorafenib plus paclitaxel vs paclitaxel alone. These data remain to be formally presented and published.<sup>27</sup>

Dr Baselga indicated potential areas of future development include defining a supportive care strategy for HFS, documenting the impact on QOL, and exploring potential activity in triple-negative breast cancer. Whether or not sorafenib-containing combinations move forward into phase III breast cancer trials remains to be determined.

### Conclusion

There was a wealth of state-of-the-art information presented at the ECCO 15th/34th ESMO Multidisciplinary Congress for cancer researchers, clinicians, policy makers, and patients to take back and translate into practice. The 35th ESMO Congress will be held October 8-12, 2010 in Milan, Italy. The next joint ECCO 16th/36th ESMO Multidisciplinary Congress will take place September 23-27, 2011 in Stockholm, Sweden. Additional information can be obtained at <http://www.esmo.org> or <http://www.ecco-org.eu>.



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