



**2007 ASCO Meeting – Breast Cancer**

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**Breast Cancer**

Breast cancer is the leading cause of cancer death in women worldwide. Research on the prevention, screening, diagnosis and treatment of breast cancer was presented at the 2007 ASCO Annual Meeting held in Chicago from June 1 to 4. Several topics, felt to be of clinical importance, are presented below.

**1) What is the role of taxanes in the treatment of early stage breast cancer and in the metastatic setting?**

While taxanes clearly play an important role in the treatment of women with both early and advanced breast cancer, they are associated with significant toxicities including myelosuppression, neuropathy, myalgia, nail changes, fluid retention, febrile neutropenia (mainly for docetaxel) and hypersensitivity reactions. These toxicities are generally manageable with supportive care measures, but can lead to limitations in the duration of therapy or in combining taxanes with other agents with overlapping toxicity profiles. At ASCO 2007, the updates of two clinical trials examining the role of taxanes in both early and metastatic breast cancer were presented.

(Abstract #516) - The final results of the Phase III Intergroup trial E1199 were presented at ASCO, updating the fourth interim analysis presented at the 2006 San Antonio Breast Cancer Symposium (SABCS). This study randomized 4950 women with lymph node-positive or high-



risk ( $\geq 2$  cm), lymph node-negative breast cancer to 4 treatments arms, following 4 cycles of AC chemotherapy (doxorubicin  $60 \text{ mg/m}^2$  + cyclophosphamide  $600 \text{ mg/m}^2$  q 3 w):

P3: paclitaxel  $175 \text{ mg/m}^2$  for q 3 w for 4 cycles (n = 1253)

P1: paclitaxel  $80 \text{ mg/m}^2$  q w for 12 weeks (n = 1231)

D3: docetaxel  $100 \text{ mg/m}^2$  q 3 w for 4 cycles (n = 1236)

D1: docetaxel  $35 \text{ mg/m}^2$  q w for 12 weeks (n = 1230)

Primary comparisons were made of paclitaxel vs. docetaxel and of the 3-weekly vs weekly schedules. Secondary comparisons were made between the P3 and other treatment arms. Neither disease-free survival (DFS), the primary endpoint, nor overall survival (OS), the secondary endpoint, differed significantly in the primary comparisons. Secondary comparisons showed an approximately 5% absolute improvement in DFS for the P1 and D3 regimens and a 3% absolute improvement in OS for the P1 regimen (**Table 1**). More frequent neutropenia, febrile neutropenia and infectious complications were seen in the D3 arm, and more neuropathy in the P1 arm (**Table 1**).

**Table 1. Selected outcomes, final results of the E1199 trial comparing weekly vs 3-weekly doses of paclitaxel and docetaxel**

	<b>P3: paclitaxel 3-weekly</b>	<b>P1: paclitaxel weekly</b>	<b>D3: docetaxel 3-weekly</b>	<b>D1: docetaxel weekly</b>
disease-free survival	76.9%	81.5%	81.2%	77.6%
overall survival	86.5%	89.7%	87.3%	86.2%



Grade 3–4 neutrophils	4%	2%	47%	3%
febrile neutropenia	< 0.5%	1%	16%	1%
Grade 3–4 neuropathy	5%	8%	4%	6%

For the adjuvant treatment of women with early-stage breast cancer, the final results of this study suggest that paclitaxel given weekly and docetaxel given every 3 weeks are both reasonable treatment options for women with early-stage breast cancer, with weekly paclitaxel perhaps offering a better toxicity profile — with the exception of peripheral neuropathy.

(Abstract #1032) – Gradishar presented the results of the fourth interim analysis of a randomized phase II study, which compared the efficacy and safety of 3 regimens of nab-paclitaxel with docetaxel. This study randomized 300 women with metastatic breast cancer to 4 treatment arms:

- A: nab-paclitaxel 300 mg/m<sup>2</sup> every 3 weeks (q 3 w) (n = 76)
- B: nab-paclitaxel 100 mg/m<sup>2</sup> Days 1, 8 and 15, every 28 days (q 3/4 w) (n = 76)
- C: nab-paclitaxel 150 mg/m<sup>2</sup> Days 1, 8 and 15, every 28 days (q 3/4 w) (n = 74)
- D: docetaxel 100 mg/m<sup>2</sup> every 3 weeks (q 3 w) (n = 74)

Primary endpoints were overall response rate and toxicity. Results presented at this ASCO annual meeting were from the fourth planned interim analysis. The current analysis included response assessments made by an Independent Radiology Review (IRR) as well as investigators. Correlation between the investigator and IRR assessments was good, with Pearson Correlation Coefficient of 0.507 for response rates, and 0.852 for progression-free survival (PFS).



**Table 2** shows response rates as assessed by study investigators and the independent radiology assessment. Highest response rates were seen with the 150 mg/m<sup>2</sup> q 3/4 w dose of nab-paclitaxel (arm C), while the lowest response rates were with docetaxel 100 mg/m<sup>2</sup> q 3 w (arm D). Women receiving both the 150 mg/m<sup>2</sup> q 3/4 w dose (arm C) and 300 mg/m<sup>2</sup> q 3 w dose of nab-paclitaxel (arm A) had improved PFS compared to docetaxel 100 mg/m<sup>2</sup> q 3 w, with hazard ratios respectively of 0.46 (p = 0.002) and 0.63 (p = 0.046).

**TABLE 2. Selected outcomes, fourth interim analysis of a phase II trial comparing 3 dose regimens of nab-paclitaxel vs docetaxel<sup>2</sup>**

	A: nab-paclitaxel 300 mg/m <sup>2</sup> q 3 w	B: nab-paclitaxel 100 mg/m <sup>2</sup> q 3/4 w	C: nab-paclitaxel 150 mg/m <sup>2</sup> q 3/4 w	D: docetaxel 100 mg/m <sup>2</sup> q 3 w
response rates (investigator)	43%	62%	70%	38%
response rates (IRR)	35%	45%	47%	28%
any Grade 3–4 toxicity	61%	40%	62%	92%
febrile neutropenia	1%	1%	1%	8%
Grade 3 peripheral neuropathy	17%	9%	16%	11%

In the treatment of metastatic disease, the interim results of Gradishar et al's Phase II trial suggest that weekly nab-paclitaxel is efficacious, with a favourable toxicity profile compared to docetaxel, although final results are needed to draw conclusions from this trial. One has to be cautious in the interpretation of differences seen between treatment arms in interim analysis as these studies are usually not powered to do so. An international Phase III trial (ABIDE) of nab-paclitaxel q 3/4 weeks vs q 3-weekly docetaxel in women with MBC will serve to confirm these Phase II results and will clarify the clinical role of nab-paclitaxel in Canada, where docetaxel has traditionally been the taxane of choice. Based on these interim Phase II results and an earlier Phase III study which showed superior efficacy of nab-paclitaxel (260 mg/m<sup>2</sup> q 3 weeks) vs paclitaxel (175 mg/m<sup>2</sup> q 3 weeks), it is reasonable to offer nab-paclitaxel as first- or second-line therapy in women with MBC who are being considered for single-agent treatment.

## 2) Adjuvant trastuzumab in Her-2 over-expressing breast cancer. What about the heart?



Several randomized trials (NSABP B-31, NCCTG N9831, NSABP B-31, HERA , FinHer) <sup>1,2,3,4</sup>, have shown clinical benefit from the addition of trastuzumab to systemic chemotherapy ( 50% reduction in disease recurrence and 30% improvement in overall survival) in women with HER-2 over-expressing early stage breast cancers. The potential cardiotoxicity of trastuzumab led to close cardiac monitoring of women who participated in the adjuvant studies. Updates on the clinical efficacy of trastuzumab and cardiac safety data were presented at ASCO 2007.

(Abstract 512) - Dr. E. Perez presented the updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in 3968 women with Her2-positive early-stage breast cancer. With the median follow-up of 2.9 years, the improvement in outcomes with the addition of trastuzumab to chemotherapy persisted showing HR=0.48, p<0.00001 for DFS and HR=0.65, p=0.0007 for OS. More importantly, the cumulative incidence of cardiac events – CHF and cardiac death, remained stable at 2.5 % from one to three years of follow-up.

(Abstract LBA513) - Dr. P. Rastogi also reported the five year update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC)→paclitaxel (T) vs. AC→T with trastuzumab(H). The cumulative incidence of cardiac events at 5 years was 3.8% and remained unchanged since the 3 year follow-up. Risk factors for increasing cardiac events were identified to be age>50, being on hypertensive medications and baseline LVEF < 54%. A predictive model for cardiac risk score was postulated using these risk factors. Cardiac risk score = {7.4 + (0.03xAGE)-0.01xLVEF+0.68 if on BP Meds} x100/4.82. This model could help clinicians to predict patients' risk for cardiac dysfunction, allowing one to monitor or treat those patients at higher cardiac risk with more caution.

As we try to maximize treatment efficacy and minimize therapeutic toxicity for our patients, there are still many unanswered questions about the optimal duration and scheduling of adjuvant trastuzumab. While the early results suggest no significant cardiotoxicity, longer cardiac follow-up is needed. Dr. Sharon Hunt, a cardiologist from Stanford University, described the morbidity and mortality associated with congestive heart failure with median overall survival rates of 12 – 18 months (Oral discussion 2007 ASCO). Cardiac dysfunction can develop “slowly and silently”. As we move forward in the discovery and implementation of new promising agents in the treatment of breast cancer it is important to not lose sight of potential long term toxicities which may have a detrimental impact on women's health. Longer follow-up and cardiac monitoring of these women are warranted.

### **3) What is the significance of brain metastases in women with Her2 over-expressing breast cancer?**



The main goals of treatment for metastatic breast cancer are to optimize quality of life, extend survival and palliate symptoms. Women with Her2 over-expressing breast cancer are at an increased risk for developing brain metastases.<sup>5</sup> Several abstracts the 2007 ASCO meeting reported on the clinical implications of the development and treatment of brain metastases on overall survival in this population.

(Abstract 1018) - Dr. M. Pinder from MD Anderson Cancer Centre, US, presented on a study on trastuzumab treatment and the risk of central nervous system metastases. Pinder evaluated time to CNS metastases, death and death subsequent to brain metastases in relation to trastuzumab treatment. In this series of 750 patients, patients with Her2-positive metastatic breast cancer treated with first-line trastuzumab were at 2.84 times higher risk for developing CNS metastases compared to patients who did not receive trastuzumab. The baseline differences among the groups and improved survival of those patients received trastuzumab could explain the increased incidence of brain metastases in trastuzumab treated patients. Those patients treated with trastuzumab had better control of their systemic disease, thus living long enough to develop brain metastases.

(Abstract 1015) - Dr. A. Niwinska from the Maria Sklodowska-Curie Memorial Cancer Centre, Poland presented the effect of early detection of occult brain metastases in Her2-positive breast cancer patients on overall survival. This study compared DFS and OS from two patient groups with metastatic Her2-positive cancer, one with occult brain metastases and the other with symptomatic brain metastases. MRI screening of the brain was performed in 80 patients and 29 patients were found to have occult brain metastases. Whole brain radiotherapy was given to the 29 patients with occult brain metastases during the asymptomatic period. Whole brain radiotherapy reduced the rate of cerebral deaths and improved quality of life, but did not prolong overall survival as compared to those who presented with symptomatic brain metastases.

(Abstract 1017) - A Canadian study presented by Dr. S. Verma from Ottawa examined central nervous system metastases in Her2-positive metastatic breast cancer patients: patterns of relapse and impact on survival. This retrospective cohort study examined patients with Her2-positive metastatic breast cancer who had received trastuzumab. Fifty patients with brain metastases were compared with 50 without brain metastases. The study concluded that brain metastases did not have an adverse effect on overall survival. Patients with brain metastases treated with both surgery and radiation had better overall survival compared to those who received radiation alone or no local-regional treatment. This better-than-expected outcome for patients with brain metastases was postulated to be due to aggressive management of CNS metastases and control of extra-cranial disease.



(Abstract 1019) - Dr. Y. Tham presented a gene expression signature for patients with breast cancer who eventually developed brain metastases. The study hypothesized that gene expression patterns of primary breast cancers may provide a specific metastatic signature for eventual brain metastases. Results showed that patients who developed brain metastases had tumours with expression of genes related to the neurological development pathways and several kinase pathways. These genes will be validated in future studies. The identification of genes which may predict for future development of brain metastases have implications in terms of screening or prophylactic treatment, especially in the high risk group, such as those with Her2-positive breast cancer.

#### **4) Should women with metastatic breast cancer have their disease re-biopsied?**

The phenomenon of ER/PR and Her2 status discordance between the primary tumor and metastatic disease has previously been reported.<sup>6,7,8</sup> ER/PR and Her2 status are important predictors of risk for disease recurrence and treatment response. These markers are usually measured at the time of initial breast cancer diagnosis. This leads to the questions: should we always re-evaluate the ER/PR and Her2 status at the time of diagnosis of metastatic disease and secondly what is the biological mechanism for the development of discordance in ER/PR and Her2 status.

(Abstract 1023) - Dr. U. Wilking from Karolinska Institute, Sweden presented the results of Her2 gene amplification and hormone receptor expression in early and metastatic breast cancer in the same patients. This study compared Her2/ER/PR status from metastatic disease to Her2/ER/PR from initial breast cancer diagnosis and concluded that breast cancer tumor characteristics were not always constant. In this series, 7% of patient's tumours changed their Her2 status (2% from positive to negative, 5% from negative to positive) and 28% (21% from positive to negative, 7% from negative to positive) had a change in their ER/PR expression. Verification of the Her2/ER/PR status in metastatic disease was recommended.

(Abstract 1024) - Dr. R. Broom, from Toronto Mount Sinai Hospital, Canada presented their findings on the changes in ER, PR and Her2 status with time: discordance rates between primary and metastatic breast pathology samples. Of the 100 patients analyzed, a significant discordance rate was shown for ER in 17.7% (9.7% from positive to negative, 8.0% from negative to positive) and for PR in 37% (all from positive to negative). No significant discordance for Her2 status was found, however the sample size was small (only 18 paired samples were examined, one changed from Her2-positive to Her2-negative).

These two studies address an interesting clinical question; however the practical implications of these discordance rates remain unclear.



## **5) What role does pharmacogenomics play in selecting hormone therapy or chemotherapy regimens and how does this affect the way we practice?**

The future of cancer treatment will rely heavily on pharmacogenomics. The optimal therapy for individual patient will be selected based on individual genotype to ensure maximum efficacy of systemic treatment with minimal toxicity.

(Abstract 500) - Dr. J. Mortimer presented the abstract on tamoxifen, hot flashes and breast cancer recurrence: support from pharmacogenetics. Knowledge of the pharmacogenetics of the CYP2D6 has been shown to correlate with the efficacy of adjuvant tamoxifen. Tamoxifen is metabolized by CYP2D6 to the end product of endoxifen. The study hypothesized that the development of hot flashes on adjuvant tamoxifen was an indicator of drug metabolism and would correlate with a more favorable outcome than women who did not experience hot flashes. In the study, 78% of the 864 patients reported hot flashes and a hazard ratio for recurrence of 0.51 (95% CI 0.32-0.79) was reported for those with reported hot flashes. This was more predictive of outcome than age, grade, hormone receptor status or stage II cancer for tamoxifen treated patients.

(Abstract 502) - Dr. R. Punglia from Dana-Farber Cancer institute, US presented a modeling analysis to compare tamoxifen to aromatase inhibitors in early-stage breast cancer after pharmacogenomic testing. Modeling results suggests that initial treatment with tamoxifen could be superior to treatment with aromatase inhibitors for those patients without CYP2D6 mutation.

(Abstract 523) - Cyclin D1 expression in breast cancer patients and tamoxifen therapy was presented by Dr. Filipits. Cyclin D1 plays a central role in cell cycle regulation, directly affects the estrogen receptor, and may predict outcome of tamoxifen therapy. In this study, cyclin D1 expression was determined from surgical tumor specimen by immunohistochemistry. Women with early-stage hormone receptor-positive breast cancer and cyclin D1 negative tumors benefited more from adjuvant tamoxifen therapy than women with cyclin D1 positive tumors.

(Abstract 590) - CYP2D6\*4 polymorphism as blood predictive biomarker of breast cancer relapse in patients receiving adjuvant tamoxifen. Dr. S. Gonzalez-Santiago concluded that breast cancer patients with the CYP2D6 \*4/\*4 or wt/\*4 genotype would benefit less from treatment with adjuvant tamoxifen and would have a higher risk of disease relapse. Pre-treatment CYP2D6 genotype determination could help oncologists in treatment decisions, particularly in regard to the choice of endocrine therapy..



(Abstract 525) - BCIRG 001 molecular analysis: identification of prognostic factors in patients receiving adjuvant therapy for node-positive breast cancer, presented by Dr C. Dumontet. At 55 months median follow-up, TAC (docetaxel/doxorubicin/cyclophosphamide) provided better DFS and OS over FAC (fluorouracil/doxorubicin/cyclophosphamide) chemotherapy in women with early-stage breast cancer. Secondary endpoints in this study evaluated the prognostic value of biomarkers. Data from this group of patients suggested that Tau and p53 were independent markers of DFS and OS in patient receiving adjuvant chemotherapy and identification of these markers by immunohistochemistry may help us to guide patients in therapy decisions and the development of novel regimens.

(Abstract 524) - Dr. M. Press presented the association between topoisomerase II-alpha (TOP2A) gene and responsiveness to anthracycline-based chemotherapy. His group found that metastatic breast cancer patients who had TOP2A gene co-amplification and were treated with AC alone, had a statistically significant improvement in duration of survival compared to those without TOP2A gene amplification ( $p = 0.004$ ). To validate this observation, breast cancer tissue from two large randomized studies of anthracycline-based chemotherapy; one with Her-2 amplification and trastuzumab-based therapy (BCIRG006,  $n = 3,222$ ) and one without Her-2 amplification and combination-based chemotherapy (BCIRG005,  $n = 3,298$ ) were analyzed, comparing TOP2A status with clinical outcome. From both trials, women whose breast cancers showed TOP2A gene co-amplification had a significantly longer disease-free ( $p < 0.001$ ), recurrence-free ( $p < 0.001$ ) and overall survival ( $p = 0.01$ ) compared to women whose breast cancers lacked TOP2A amplification. Interestingly, the added benefit of trastuzumab was not seen among TOP2A co-amplified breast cancer patients in the larger BCIRG006 trial. He concluded that for patients treated with chemotherapy alone, TOP2A gene co-amplification is a useful predictive marker of responsiveness to anthracycline-containing chemotherapy.

Although it would be pre-mature to apply these study results to clinical practice, the concept of using pharmacogenomics to determine the optimal treatment for each individual patient takes us perhaps somewhat closer to the hope of personalized medicine.

## **6) Targeted Therapies: Do biologics add to current treatment practices?**

The use of trastuzumab has led to significant improvement in patient outcomes in both the adjuvant and metastatic settings. Many ongoing studies are looking at novel targeted agents in the treatment of breast cancer.

(Abstract 1004) - Pertuzumab, a Her2 dimerization inhibiting monoclonal antibody, has been studied in a phase II multicenter trial in combination with trastuzumab in patients with Her2-positive metastatic breast cancer who had progressed during treatment with trastuzumab. Dr. J.



Baselga from Vall d'Hebron University Hospital, Spain reported the study results which showed a clinical benefit of 21% PR and 50% SD. The combination of pertuzumab and trastuzumab was well tolerated in patients with pre-treated Her2-positive breast cancer which has progressed during treatment with trastuzumab.

(Abstract 509) - Inflammatory breast cancer is an aggressive disease. Neoadjuvant systemic chemotherapy is the standard clinical approach. Dr. S. Swain, from the National Cancer Institute, presented the molecular pathways and gene ontology categories in association with response to combination chemotherapy plus bevacizumab in inflammatory and locally advanced breast cancer. Bevacizumab therapy alone resulted in decreased p-VEGFR2 and increased apoptosis in tumors suggesting a direct tumor effect. When bevacizumab was combined with chemotherapy, two pathways that regulate microtubule stability and cell cycle and 16 gene ontology categories were associated with the response to combination therapy. Since pathological response to neoadjuvant therapy is an important predictor of outcome, the addition of newer biologics to combination chemotherapy would perhaps lead to higher rates of pathological complete response with minimal added toxicities.

(Abstract 1035) - Dr. C. Geyer updated the results on lapatinab, a dual tyrosine kinase inhibitor of EGFR and Her2, in combination with capecitabine in Her2-positive metastatic breast cancer previously treated with trastuzumab. The overall response rate in 399 patients was 23.7% versus 13.9% (odds ratio 1.9,  $p=0.017$ ) for the combination arm versus capecitabine alone. The TTP was longer in the combination arm, 6.2 months vs. 4.3 months,  $HR=0.57$ ,  $p<0.0001$ . Lapatinib did increase the frequency of grade 1 and 2 diarrhea by 21%.

(Abstract 1006) - Dr. Vahdat from Weill Cornell Medical College reported results on a phase III trial of ixabepilone plus capecitabine compared to capecitabine alone in patients with metastatic breast cancer previously treated or resistant to an anthracycline and resistant to taxanes. He concluded that the ixabepilone and capecitabine combination showed superior efficacy compared to capecitabine alone, PFS was 5.8 months vs. 4.2 months,  $p=0.0003$ , and ORR of 35% vs. 14%,  $p<0.0001$ . The combination has a manageable safety profile in this heavily pretreated population.

(Abstract 1003) - Dr. Rugo from the University of California presented a randomized, double-blind phase II study of the oral tyrosine kinase inhibitor (TKI) axitinib (AG-013736) in combination with docetaxel (DOC) compared with DOC plus placebo (PL) in metastatic breast cancer (MBC). 168 patients were randomized, median TTP was 8.2 months with DOC+AG and 7 months with DOC+PL,  $HR=0.73$ , one-sided  $p=0.052$ . ORR was 40% and 23%,  $p=0.038$ . Common toxicity in the DOC+AG arm included diarrhea (60%), nausea (53%), alopecia (51%), fatigue (49%), stomatitis (44%), vomiting (40%) and febrile neutropenia (16%).



(Abstract1013) - Dr. G. Sledge presented the results on the safety and efficacy of capecitabine plus bevacizumab as first-line in metastatic breast cancer. Results showed median TTP was 5.7 months (95% CI 4.9-8.4), ORR 38%. Most common grade 3 adverse events were hand-foot syndrome (13%) and pain (10%).

Several studies looked at other novel biological agents and showed promising anti-tumor activity, superior efficacy and an acceptable safety profile when compared to chemotherapy alone.

Many other interesting topics were presented at the 2007 annual meeting, as scientists and clinicians continue to make small steps towards a cure for breast cancer

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