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*Unless noted below*

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## **Management and Prognosis: How Best to Treat Breast Cancer Patients**

SAN ANTONIO – As therapies for breast cancer continue to emerge, the issues of how to best monitor success and gauge prognosis remain important questions.

At the CTRC-AACR Annual San Antonio Breast Cancer Symposium, researchers will present new data on Herceptin, circulating tumor cells, mucinous breast carcinoma and the role of the Ki67 antigen during a press conference on Saturday, Dec. 12, 2009, at 8:00 a.m. CT, in room 217C of the Henry B. Gonzales Convention Center.

Claudine Isaacs, M.D., will host this press conference. Isaacs is director of the Clinical Breast Cancer Program and medical director of the Cancer Assessment and Risk Evaluation Program at Georgetown's Lombardi Comprehensive Cancer Center.

Reporters who cannot attend in person may call in using the following information:

- U.S. & Canada: (888) 282-7404
- International: (706) 679-5207
- Access Code: 39119499
- Topic: AACR

The following abstracts will be presented at the press conference:

### **80. Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial**

Clinicians can now recommend that trastuzumab, currently sold as Herceptin by Genentech-Roche, be given concurrently with chemotherapy to achieve maximum benefit in terms of disease-free survival.

Researchers, led by Edith Perez, M.D., director of the breast cancer program at the Mayo Clinic in Jacksonville, Fla., found a 25 percent reduction in the risk of breast cancer recurrence when trastuzumab was administered concurrently, rather than following chemotherapy.

Perez said these findings are very important and estimated that they will inform treatment decisions for about 50,000 women in the United States and 200,000 women around the world every year.

“Often the research community conducts studies that conclude with ‘that was interesting, but let’s do more research.’ This is an important finding on how we can help prevent breast cancer recurrence and improve survival,” said Perez.

All patients enrolled in this phase III trial were receiving standard chemotherapy of doxorubicin and cyclophosphamide followed by paclitaxel.

The researchers conducted two separate comparisons.

The first included 2,448 patients randomly assigned to chemotherapy alone or chemotherapy followed by trastuzumab. After 5.5 years, the researchers observed 386 events. After adjustment for possible confounding variables, they found that event-free survival increased from 72 percent with chemotherapy alone to 80 percent with chemotherapy followed by trastuzumab.

The second comparison included 1,903 women. The researchers compared those who received trastuzumab after chemotherapy with those who received it concurrently with paclitaxel. At five years, disease-free survival increased from 80 percent to 84 percent.

“This study has global implications. In the United States, Herceptin is approved for use either following or concurrently with chemotherapy,” said Perez. “However, currently in some countries trastuzumab is only approved for use following chemotherapy as adjuvant therapy for HER2-positive breast cancer. We hope our findings will change those policies. In the United States, this will clearly inform physician decision making.”

### **3011. Circulating Tumor Cells (CTCs) and Epithelial Mesenchymal Transition (EMT) in Breast Cancer: Describing the Heterogeneity of Microscopic Disease**

*Embargoed until 5:30 p.m. CT, Dec. 11, 2009*

Circulating tumor cells (CTCs) are an important predictor of survival in metastatic breast cancer patients. When CTCs undergo epithelial-mesenchymal transition (EMT), resulting in a loss of epithelial markers, they may escape conventional detection, according to data presented at the CTRC-AACR San Antonio Breast Cancer Symposium.

“Our data suggest that current CTC detection methods may underestimate the most important subpopulation of CTCs, which are involved in tumor dissemination,” said Michal Mego, M.D., Ph.D., a scientist at the National Cancer Institute in the Slovak

Republic. The research was conducted while Mego was an International Union Against Cancer Scholar in the Morgan Welch Inflammatory Breast Cancer Research Program and Clinic at The University of Texas M. D. Anderson Cancer Center.

The presence of an increased number of CTCs is associated with poor prognosis in breast cancer patients, Mego explained. Cells with this EMT phenotype are probably involved in tumor dissemination and represent tumor initiating cells. Identification of therapeutic targets on these cells could lead to eradication of micrometastatic disease in breast cancer, as well as in other epithelial tumors.

“When we retrospectively evaluated the outcome of breast cancer patients, we observed that there were subgroups of patients, such as those with brain metastasis, triple negative or inflammatory breast cancer, who had poor prognosis and low or undetectable CTCs by conventional methods,” Mego said. “We found that the low or undetectable CTCs were due to the existence of a subpopulation of cancer cells that undergoes a process of EMT.”

When epithelial cells undergo EMT, they lose their epithelial receptors. As a result, they are no longer detected by current detection assays.. In addition, these cancer cells become resistant to chemotherapy or radiation therapy, according to Mego.

“This observation led us to hypothesize that EMT CTCs are responsible for tumor dissemination,” Mego said. “Hence, we developed a novel detection method that would be capable of identifying EMT CTCs in peripheral blood from breast cancer patients.”

In this prospective study, Mego and colleagues used approximately 5 mL of peripheral blood from patients with varying stages of breast cancer and isolated the CTCs using magnetic beads coated with monoclonal antibodies. Using a polymerase chain reaction, they then isolated RNA to detect genes that are involved in EMT.

Patients who had triple-negative breast cancer more commonly overexpressed EMT genes compared to non-triple-negative patients.

“Our data indicate that a subpopulation of CTCs with EMT really exists, and that these cells are more commonly detected in patients with poor prognosis such as those with triple-negative breast cancer or in patients pretreated by neoadjuvant chemotherapy who have developed resistance to therapy,” Mego said. “A novel detection method such as ours that is capable of detecting CTCs after EMT could add new important prognostic information, and could be useful for monitoring treatment efficacy.”

Mego and colleagues also initiated a confirmatory study in metastatic breast cancer patients as well as in prostate and colorectal cancer patients to confirm their findings. These studies were aimed to identify therapeutic targets on these cells.

Ongoing research at The University of Texas M. D. Anderson Cancer Center and the National Cancer Institute in the Slovak Republic will continue to focus on the detection of CTCs with tumor-initiating properties, as well as the identification of potential

therapeutic targets for CTCs. Trastuzumab treatment based on detection of HER-2/neu amplification on CTCs represents proof of this new concept of targeted therapy, according to Mego.

**4117. Mucinous Breast Carcinoma: Occult Multifocality/Multicentricity in a Favorable Disease**

*Embargoed until 7:00 a.m. CT, Dec. 12, 2009*

A large sample of patients with pure mucinous breast cancer demonstrated a favorable prognosis. However, researchers also found an association with significant occult multicentricity/multifocality.

“Our findings indicate another potentially unfavorable aspect associated with a widely accepted as favorable breast cancer subtype,” said George H. Perkins, M.D., associate professor in the Division of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center.

“In an era of concern regarding overtreatment, we caution in our findings that undertreatment could also become a significant hazard for patients and thus should be a significant area of concern,” he said.

Perkins presented results of this study at the CTRC-AACR Annual San Antonio Breast Cancer Symposium, held Dec. 9-13, 2009.

Mucinous carcinoma is a rare form of cancer, diagnosed in about 2 percent of patients with breast cancer. Cancer cells within the breast produce mucous, forming a jelly-like tumor. Previous research has shown that the disease has a favorable prognosis; therefore, investigators have recommended treating patients with the minimal effective therapy vs. the maximum tolerated treatment.

“Our results are from one of the largest single institution experiences with a relatively uncommon subtype and has significant, long-term follow-up of patients,” Perkins said. “We emphasize multidisciplinary, comprehensive care to avoid the non-recognition of additional occult disease, which could affect patient outcomes.”

Perkins and colleagues reviewed charts for 264 patients diagnosed with a pure mucinous carcinoma from 1965 to 2005.

At five years, overall survival was 95 percent; the 10- and 15-year rate was 97 percent. Rates for distant metastases-free survival were similar: 88 percent at five years; 95 percent at 10 years; and 94 percent at 15 years. The five-year local regional control rate was 83 percent; at 10 years it was 92 percent; and at 15 years it was 85 percent.

Initially, 10 percent of the patients had a multicentric/multifocal presentation; however, a detailed pathology review revealed a 38 percent rate of multicentric/multifocal disease after resection. This finding surprised the researchers.

“We have been previously surprised by the decreasing age at presentation in this population, and by the regression of favorable outcomes towards the lower outcomes of other common breast cancer subtypes over time,” Perkins said. “This reinforces our commitment to interdisciplinary care and true personalized patient treatment in this variant. Patients should receive the care indicated, rather than receive the assumption that it may not matter which treatment approach is taken because this is a favorable disease.”

The researchers hope that these data, coupled with other data, will help practitioners understand the various presentations of favorable breast cancer subtypes. They also plan to “identify patients who may need additional multidisciplinary evaluation prior to disposition to a minimalist approach inclusive of observation and limited use of radiation therapy,” Perkins said.

### **78. Tumor Ki67 Proliferation Index within 4 Weeks of initiating Neoadjuvant Endocrine Therapy for Early Identification of Non-Responders**

As a prognostic tool, the preoperative endocrine prognostic index (PEPI) has been developed as a way to identify estrogen-receptor positive (ER+) breast cancers that have a poor long-term outcome because of a failure to respond to tamoxifen or an aromatase inhibitor after three to four months of pre-surgical treatment.

The PEPI is based on pathological tumor size, nodal stage, ER status and a protein marker for proliferation — Ki67. A team at Washington University School of Medicine has now developed a faster way to identify patients with poor outcome disease by measuring tumor Ki67 early, just two to four weeks after starting neoadjuvant endocrine therapy. By assessing tumor response to endocrine therapy sooner, non-responding tumors can be triaged to neoadjuvant chemotherapy. This approach is currently undergoing prospective evaluation in the American College of Surgeons Z1031 trial.

“We’d like to identify poor prognosis ER+ disease earlier than three to four months,” said Matthew Ellis, Ph.D., professor of medicine at Washington University School of Medicine and program leader for the Breast Cancer Research Program at Siteman Comprehensive Cancer Center. “That way, we don’t continue ineffective neoadjuvant endocrine treatment and can switch to a more intensive treatment approach.”

Researchers measured Ki67 levels in tumors of 158 postmenopausal women in two independent trials with confirmed ER+ stage II and III breast cancers two to four weeks into endocrine therapy.

Tumor Ki67 measuring more than 10 percent accurately predicted higher rates of relapse, and the absence of a group of patients with such a low score suggested adjuvant chemotherapy is not likely to be of benefit.

“Through these trials, we are also obtaining high-quality tumor samples from patients for sophisticated molecular profiling, including whole genome sequencing,” said Ellis. “The

investigations will determine the molecular basis for endocrine therapy resistance so we can intervene with new regimens that might be more effective than standard chemotherapy.”

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The mission of the CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for breast cancer patients. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR), and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor, and the AACR’s scientific prestige in basic, translational and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. The 32nd annual symposium is expected to draw more than 8,500 participants from more than 90 countries.

**Presenter Name:** Edith Perez, M.D.

**Institution:** Mayo Clinic in Jacksonville Florida

**Abstract Number:** 80

**Abstract Title:** Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial

**Abstract Body:**

**Background:** N9831 is the only randomized phase III trial comparing safety and efficacy of the addition of trastuzumab (H) to doxorubicin and cyclophosphamide then paclitaxel (Arm A: AC→T) either following (Arm B: AC→T→H) or starting concurrently with paclitaxel (Arm C: AC→T+H→H) for women with resected Stage I-III invasive HER2+ breast cancer. The 3 yr cumulative incidence of NYHA class III or IV congestive heart failure or sudden cardiac death was previously reported: 3.3% in Arm C, 2.8% in Arm B (Perez EA, et al. JCO 2008). The comparison of AC→T to AC→T+H→H was reported in a joint analysis of N9831 and NSABP B-31 in 2005 and updated in 2007, demonstrating a 52% reduction in risk of a disease event (Romond E et al., NEJM 2005; Perez EA, et al. ASCO 2007).

**Materials and Methods:** Primary endpoint is disease-free survival (DFS). At the second planned interim analysis of Arm A vs. Arm B, the O'Brien-Fleming boundary (OFB) was crossed. NCCTG Independent Data Safety Monitoring Committee approved the release of these data as well as the data pertaining to Arm B vs. Arm C due to slow pace of events [expected 647 events in 4 yr follow-up period (f/u) vs. actual 334 events in 4.5 yr f/u]. Shortly thereafter, there were sufficient events to perform the first planned interim analysis of B vs. C. We present the results of each of these pairwise comparisons taking into account the potential for crossover to Arm C after the release of the joint analysis findings in 2005.

**Results:** From 5/2000 to 4/2005, 2448 eligible women were enrolled for the Arm A (n=1087) vs. Arm B (n=1097) comparison. Median f/u is 5.5 yrs. with 386 events. The addition of trastuzumab sequentially to AC→T significantly improved DFS, univariately [HR(Arm B/Arm A)=0.70, 95% CI: 57-86%, logrank p=0.0005] and after adjusting for age, tumor size, number of positive nodes, and ER [PPH: HR<sub>adj</sub>=0.67 (95% CI: 0.55-0.82)]. 5 yr DFS was increased from 72% with AC→T to 80% with AC→T→H.

From 5/2000 to 4/2005, 1903 eligible women were enrolled for the Arm B (n=954) vs. Arm C (n=949) comparison. Median f/u is 5.3 yrs. with 312 events. The log-rank p-value testing whether DFS differs with respect to starting time of trastuzumab was 0.019. [Not crossing pre-specified OFB for statistical significance]. After adjusting for tumor size, number of positive nodes, and ER, HR<sub>adj</sub>(Arm C/Arm B)=0.75 (95% CI: 0.60-0.94)]. 5 yr DFS was increased from 80% with AC→T→H to 84% for AC→T+H→H.

**Conclusions:** DFS is significantly improved with the addition of 52 weeks of H (sequentially or concurrently) to AC→T. There is a statistically significant 33% reduction in the risk of an event

with the sequential addition of H following AC→T. There is a strong trend for a 25% reduction in the risk of an event with starting H concurrently with T relative to sequentially after T. Therefore, based on a positive risk/benefit ratio, we recommend that trastuzumab be incorporated in a concurrent fashion with T chemotherapy.

Acknowledgements: NIH CA25224, Breast Cancer Research Foundation, Genentech

**Presenter Name:** Michal Mego, M.D., Ph.D.

**Institution:** University of Texas, MD Anderson Cancer Center

**Abstract Number:** 3011

**Abstract Title:** Circulating tumor cells (CTCs) and Epithelial Mesenchymal Transition (EMT) in breast cancer: Describing the heterogeneity of microscopic disease.

**Abstract Body:**

**Background:** Circulating tumor cells (CTCs) are an independent predictor of survival in metastatic breast cancer (BC) patients. CTC are readily detected by CellSearch System based on their expression of EpCAM. Epithelial-mesenchymal transition (EMT) gives rise to cells with stem cell-like properties with increased chemotherapy resistance. Human mammary epithelial cells (HMEC) transformed by the EMT transcription factor TWIST1 and spiked into normal peripheral blood (PB) are not detected by EpCAM enrichment based conventional detection methods compared to non-transformed HMECs. We hypothesize that CTCs undergoing EMT and resultant loss of epithelial markers may escape detection by conventional detection methods. The aim of this study was to detect CTCs based on expression of EMT genes in breast cancer patient's peripheral blood.

**Methods:** This prospective ongoing study of breast cancer patients consisted of 16 (57.1%) patients with metastatic disease, 19 (67.9%) patients with inflammatory breast cancer (IBC) and 12 (42.9%) patients with primary, non-IBC breast cancer, respectively. Isolated peripheral blood mononuclear cells (PBMC) were depleted of cells of hematopoietic origin (CD45<sup>+</sup>) using anti-CD45 coated magnetic beads. RNA extracted from CD45-depleted (CD45<sup>-</sup>) PBMC were interrogated for expression of TWIST1, SNAIL1, SLUG, ZEB1, FOXC2 and EpCAM gene transcripts by quantitative reverse transcription-PCR. Expressions of gene transcripts in CD45<sup>-</sup> PBMC from patients were compared to those of CD45<sup>-</sup> PBMC of healthy donors (HD). Expression of one or more gene transcripts was considered a positive result. Concurrently, a 7.5 mL PB sample was collected for determination of CTC by CellSearch.

**Results:** Median age was 54 year (range: 34-72 years). Overall, the median CTC count by CellSearch was 2 (range; 0-750) per 7.5 mL of PB. TWIST1, SNAIL1, SLUG, ZEB1 and FOXC2 were overexpressed in CD45<sup>-</sup> PBMC in 7%, 4 %, 4%, 0% and 14 % of patients, respectively. At least one of the EMT genes was overexpressed in 6 (21%) of patients. TWIST1 and SLUG were overexpressed only in IBC patients (10.5% and 5.3% of patients, respectively). Patients with triple negative breast cancer more commonly overexpressed EMT genes compared to non-triple negative patients (30.8% vs. 13.3%). There was no correlation between expression of EMT genes, EpCAM expression or CTC count measured by CellSearch, respectively.

**Conclusions:** These data suggest that EMT genes may be involved in the dissemination of CTCs. Loss of epithelial antigen on CTC due to EMT, triggered by high expression of these genes, may be responsible for their undetection by conventional methods in a fraction of patients with early or advanced breast cancer.

**Presenter Name:** George H. Perkins M.D.

**Institution:** The University of Texas M D Anderson Cancer Center

**Abstract Number:** 4117

**Abstract Title:** Mucinous Breast Carcinoma: Occult Multifocality/Multicentricity in a Favorable Disease

**Abstract Body:**

**Purpose:** Mucinous carcinoma is a distinctive tumor that reportedly has a very favorable prognosis. Accordingly, investigators have recommended that patients be treated with minimal effective therapy rather than maximum tolerated treatment. However, previous reports have been limited by small sample sizes and very short follow-up intervals. We have previously reported outcomes for a mature data set with long term follow-up and now perform the current analysis to emphasize comprehensive multidisciplinary management in an era of minimal effective therapy for so-called favorable disease.

**Methods and Materials:** We retrospectively reviewed charts for 264 patients with a pure mucinous carcinoma diagnosis at our institution from 1965-2005. Multidisciplinary management is emphasized for all patients at our institution including this patient cohort. All pathology was centrally reviewed. Overall survival, DM-free survival, and local-regional control were compared using Kaplan Meier method and log rank statistics.

**Results:** Median age was 57 years (range 25-89). Median follow-up was 168 months. 86% of patients were stage T2 or less. Patients who were lymph node negative compared with 1-3 LN+, or 4 or more LN+ were 80%, 15%, and 5% respectively. 44% received BCT while the remainder underwent mastectomy. 51% of all patients received XRT. No patient in this cohort received partial breast irradiation. 10% of patients had an initial multicentric/multifocal presentation. However, a detailed pathology review revealed a 38% multifocal/multicentric disease rate after surgical resection. The occult tumors were not initially detected by mammography or ultrasonography.

5, 10, and 15 year OS, DMFS, and LRC rates for all patients were: 95%/88%/83%; 97%/95%/92%; and 97%/94%/85% respectively. There was no statistically significant difference in OS, DMFS, or LRC based upon surgical management by mastectomy in comparison with BCT. Likewise, there was no statistically significant improvement in OS or DMFS with utilization of whole breast XRT. There was, however, a trend for improved LRC in patients who received XRT ( $p=0.06$ ) in comparison with patients who underwent mastectomy or BCT without XRT.

**Conclusions:** This large series of patients diagnosed with pure mucinous breast carcinoma demonstrates potentially favorable prognosis. However, this is the first known report of an association with significant occult multicentricity/multifocality. In an era of minimal effective cancer therapy which includes no additional treatment post resection in favorable histology, and

partial breast XRT in favorable histology, multidisciplinary management inclusive of pathology and diagnostic imaging is recommended. Current treatment guidelines should reflect that before omitting whole breast XRT, patients should have pathologic and radiologic intraoperative correlation and MRI should be a consideration in efforts to identify potential occult disease.

**Presenter Name:** Matthew Ellis, Ph.D.

**Institution:** Washington University School of Medicine

**Title:** Tumor Ki67 Proliferation Index within 4 Weeks of initiating Neoadjuvant Endocrine Therapy for Early Identification of Non-Responders

**Abstract Number:** 78

**Abstract Body:**

**Background:** The Preoperative Endocrine Prognostic Index (PEPI) scores the independent prognostic effects of tumor pathologic staging and expression levels of ER and the “proliferation” marker Ki67 in the surgical sample to predict long term outcomes after completion of neoadjuvant endocrine treatment (Ellis et al JNCI 100:1380, 2008). A limitation of the PEPI is that the prognostic information becomes available only after 4 months of treatment. We therefore evaluated the value of an early assessment of the Ki67 level in a tumor biopsy sample taken two to four weeks after initiating treatment in two neoadjuvant endocrine therapy trials for the purposes of the early identification of non-responders

**Methods:** A Ki67 cut point of greater than 10% for poor outcome in ER+ breast cancer was derived by comparing the PAM50 intrinsic subtype profile using a qRT-PCR assay with Ki67 data in a 700+ sample data set. A baseline level of 10% or less correlated most closely with a PAM50-based definition of LumA breast cancer and above 10% LumB breast cancer. We subsequently applied the 10% cut point to the baseline and early on-treatment Ki67 data in two trials, POL (Olson et al JACS 208:906, 2009) and IMPACT (Smith et al JCO: 23, 5108, 2005).

**Results:** At baseline the dichotomized Ki67 definition was not significantly predictive for surgical Ki67 level, PEPI score or RFS in this modest size sample set. In contrast, in a result that emphasizes the enhanced prognostic properties of the on-treatment Ki67 approach, the one month POL sample Ki67 values (62 patients) predicted a higher level of Ki67 in the surgical samples at four months after treatment initiation (P=.01), a poorer PEPI score (P=0.01), a smaller number of patients in the PEPI risk point zero group (P=0.08) and worse relapse free survival (P=0.003). The IMPACT data (153 patients) confirmed that a two week Ki67 >10% predicted higher Ki67 in the surgical specimen (P=0.001), a poorer PEPI score (P=0.001), smaller numbers of patients in the PEPI 0 risk point group (P= 0.004) and worse relapse free survival (P=0.008).

Ki67 and Outcome		
POL 4W Ki67	% PEPI 0	RFS (events)
10%>	1/19 (5%)	5/21 (23%)
10%≤	10/36 (28%)	1/41 (2.4%)
P Value	P=0.08 (Fisher)	P=0.003 (log rank)
IMPACT 2W Ki67	% PEPI 0	RFS (events)
10%>	0/32 (0%)	9/35 (26%)
10%≤	21/101 (21%)	13/118 (11%)
P Value	P=0.004 (Fisher)	P=0.008 (log rank)

**Conclusions:** A tumor Ki67 assessment taken a short time (2 to 4 week window) after the initiation of neoadjuvant AI identifies patients with poor outcome ER+ disease. Amendment 6 of the neoadjuvant endocrine therapy protocol ACOSOG Z1031 will triage patients with an “on treatment” Ki67 value above 10% to chemotherapy in order to assess the pathological response rate to cytotoxic therapy in this important tumor subset.

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