NSABP B-38: Definitive analysis of a randomized adjuvant trial comparing dose-dense (DD) AC followed by paclitaxel (P) plus gemcitabine (G) with DD AC followed by P and with docetaxel, doxorubicin, and cyclophosphamide (TAC) in women with operable, node-positive breast cancer.

Sandra M. Swain, Gong Tang, Charles E. Geyer, Priya Rastogi, James Norman Atkins, Paul P. Donnellan, Louis Fehrenbacher, Catherine A. Azar, Andre Robidoux, Jonathan Polikoff, Adam Brufsky, David D. Biggs, Edward A. Levine, John L. Zapas, Louise Provencher, Edith A. Perez, Soonmyung Paik, Joseph P. Costantino, Eleftherios P. Mamounas, Norman Wolmark; National Surgical Adjuvant Breast and Bowel Project and Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC; NSABP Biostatistical Center and University of Pittsburgh Graduate School of Public Health, Department of Biostatistics, Pittsburgh, PA; National Surgical Adjuvant Breast and Bowl Project and University of Texas, Southwestern Medical Center, Dallas, TX; National Surgical Adjuvant Breast and Bowl Project and University of Pittsburgh Cancer Institute, Pittsburgh, PA; National Surgical Adjuvant Breast and Bowl Project and SCCC-CCOP, Goldboro, NC; All Ireland Cooperative Oncology Research Group and University Hospital Galway, Galway, Ireland; National Surgical Adjuvant Breast and Bowl Project and Kaiser Permanente Northern California, Vallejo, CA; National Surgical Adjuvant Breast and Bowl Project and Kaiser Permanente, Denver, CO; National Surgical Adjuvant Breast and Bowl Project and Centre Hospitalier de l’Universite de Montreal, Montreal, QC, Canada; National Surgical Breast and Bowl Project and Kaiser Permanente Southern California, San Diego, CA; National Surgical Adjuvant Breast and Bowl Project and University of Pittsburgh, Magee-Womens Hospital, Pittsburgh, PA; National Surgical Adjuvant Breast and Bowl Project and Helen F. Graham Cancer Center, Christiana Care Health System, Newark, DE; National Surgical Adjuvant Breast and Bowl Project and Surgical Oncology Service, Wake Forest University, Winston-Salem, NC; National Surgical Adjuvant Breast and Bowl Project and Medstar Franklin Square Medical Center, Baltimore, MD; National Surgical Adjuvant Breast and Bowl Project and Centre Hospitalier Affilie Universitaire de Quebec, Hopital du St-Sacrement, Quebec City, QC, Canada; National Surgical Adjuvant Breast and Bowl Project and Mayo Clinic, Jacksonville, FL; National Surgical Adjuvant Breast and Bowl Project, Pittsburgh, PA; National Surgical Adjuvant Breast and Bowl Project Biostatistical Center and University of Pittsburgh Graduate School of Public Health, Department of Biostatistics, Pittsburgh, PA; National Surgical Adjuvant Breast and Bowl Project and Aultman Hospital, Canton, OH; National Surgical Adjuvant Breast and Bowl Project and Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA

The full, final text of this abstract will be available at abstract.asco.org at 12:01 AM (EDT) on Monday, June 4, 2012, and in the Annual Meeting Proceedings online supplement to the June 20, 2012, issue of Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Monday edition of ASCO Daily News.
Randomized phase III study of adjuvant chemotherapy for high-risk, node-negative breast cancer (BC) comparing FAC with FAC followed by weekly paclitaxel: First efficacy analysis of the GEICAM/2003-02 trial.

Miguel Martin, Ana Lluch, Amparo Ruiz, Manuel Ruiz Borrego, Agust Barnadas, Sonia Gonzalez, Lourdes Calvo, Mireia Margeli Vila, Antonio Anton, Alvaro Rodriguez-Lescure, Miguel Angel Seguí-Palmer, Montserrat Munoz-Mateu, Joan Dorca Ribugent, Jose Manuel Lopez-Vega, Cesar Mendiola Fernandez, Raquel Andres, Arrate Plazaola, Cesar Rodriguez, Maria Isabel Casas, Eva Maria Carrasco, Spanish Breast Cancer Research Group GEICAM; Hospital General Universitario Gregorio Marañón, Madrid, Spain; H C U de Valencia, Valencia, Spain; Instituto Valenciano de Oncologia, Valencia, Spain; Hospital Universitario Virgen del Rocio, Seville, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Hosp Mutua Terrassa, Barcelona, Spain; CHU de A Coruña, A Coruña, Spain; Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; Hospital Universitario Miguel Servet, Zaragoza, Spain; Hospital General de Elche, Alicante, Spain; Corporació Sanitaria Parc Taulí, Sabadell, Spain; Hospital Clinico de Barcelona, Barcelona, Spain; Institut Català d’Oncologia, Gerona, Spain; Hospital Universitario Marques de Valdecilla, Cantabria, Spain; Hospital Universitario Doce de Octubre, Madrid, Spain; H Lozano Blasa, Zaragoza, Spain; Onkologikoa, San Sebastián, Spain; Spanish Breast Cancer Research Group GEICAM, Madrid, Spain; Spanish Breast Cancer Research Group-GEICAM, Madrid, Spain; GEICAM, Madrid, Spain

Background: Adjuvant weekly paclitaxel (wP) sequential to anthracyclines improves the outcome of operable node-positive BC patients (pts) [Sparano NEJM 2008, Martin BCRT 2009]; however, most BC pts are currently node-negative at diagnosis. The role of wP in these pts is not well established yet. Methods: Pts aged 18-70, with T1-T3/N0 operable BC and at least one high-risk St Gallen 1998 criteria (size >2 cm, hormone-receptor [HR] negative, grade 2/3, age <35 years,) were eligible. HER2+ pts were allowed, after 792 entered the trial, the study was amended to exclude them. Pts were stratified by site, menopausal status, nodal status diagnostic method (sentinel-node biopsy versus lymphadenectomy) and HR status and randomized to receive FAC x6 (500/50/500 mg/m² every 3w) or FAC x4 wP x8 (paclitaxel 100 mg/m² weekly). The primary endpoint was DFS. The trial was designed to detect an absolute 5-y DFS increase of 5% (80% FAC, 85% FAC→wP); a sample size of 1812 evaluable patients (906 per arm) was required to detect this difference (α=0.05, β= 80%). Assuming a drop-out rate of 6%, 1929 pts were required. The first analysis of DFS was planned when a median follow-up of 5 years was reached. Results: Between September 2003 and October 2008, 1925 pts (FAC 974, FAC→wP 951) were randomized. Patient characteristics were well balanced between arms, median age was 50, 73% of pts were HR positive and 9% HER2 positive. 97% of pts with FAC and 85% of pts with FAC→wP completed all treatment as planned. The median dose intensity was 98% with FACx6, 99% with FACx4 and 98% with wP. The most frequent grade 3-4 toxicities (>3% in either arm) with FAC vs FAC→wP were neutropenia (25% vs 22%) with 4% vs 3% of febrile neutropenia, fatigue (3% vs 8%), sensory neuropathy (0 vs 5%), and vomiting (4% in each arm). After a median follow-up of 5.3 years, the proportion of patients disease free is 93% and 90% with FAC→wP and FAC (HR for relapse 0.732, 95% CI: 0.542 to 0.990; log-rank p-value=0.0423). Conclusions: For pts with high-risk node-negative BC, adjuvant FAC→wP was associated with a small but significant improvement in DFS compared with FAC, with manageable toxicity.
CALGB 40502/NCCTG N063H: Randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC).

Hope S. Rugo, William Thomas Barry, Alvaro Moreno-Aspitia, Alan P. Lyss, Constance Cirrincione, Erica L. Mayer, Michael Naughton, Rachel M. Layman, Lisa A. Carey, Robert A. Somer, Edith A. Perez, Clifford Hudis, Eric P. Winer; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Alliance Statistical Center, Duke University, Durham, NC; Mayo Clinic, Jacksonville, FL; Missouri Baptist Cancer Center, Heartland Cancer Research CCOP, St. Louis, MO; Dana-Farber Cancer Institute, Boston, MA; Washington University School of Medicine, St. Louis, MO; The Ohio State University, Columbus, OH; University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Cooper Cancer Institute, Voorhees, NJ; Memorial Sloan-Kettering Cancer Center, New York, NY

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A phase III, multicenter, randomized trial of maintenance versus observation after achieving clinical response in patients with metastatic breast cancer who received six cycles of gemcitabine plus paclitaxel as first-line chemotherapy (KCSG-BR 0702, NCT00561119).

Young-Hyuck Im, Yeon Hee Park, Kyung Hae Jung, Seock-Ah Im, Joo Hyuk Sohn, Jungsiil Ro, Sung-Bae Kim, Jin-Hee Ahn, Do Youn Oh, Sae-Won Han, Soohyeon Lee, In Hae Park, Keun-Seok Lee, Jee Hyun Kim, Seok Yun Kang, Moon Hee Lee, Jin-Hee Ahn; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Samsung Medical Center, Seoul, South Korea; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Division of Hematology/Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Center for Breast Cancer, National Cancer Center, Goyang, South Korea; Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University, College of Medicine, Seoul, South Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; National Cancer Center, Gyeonggi-do, South Korea; Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Gyeonggi-do, South Korea; Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, South Korea; Inha University School of Medicine, Incheon, South Korea; Soonchunhyang University Hospital, Seoul, South Korea; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Chemotherapy provides a survival benefit in patients with metastatic breast cancer (MBC), but the optimal duration of chemotherapy remains controversial. Primary purpose of the study was to evaluate whether the maintenance chemotherapy with gemcitabine/paclitaxel (GP), which is one of the two regimens which showed a survival gain from a randomized trial, is superior to observation in terms of progression free survival (PFS) in responding patients with MBC after 6 cycles of GP as first-line treatment.

Methods: This study is a prospective, randomized, multi-center, phase III study. Patients who achieved response (CR/PR/SD) following 6 cycles of GP chemotherapy (gemcitabine 1250 mg/m² on day 1 and 8 plus paclitaxel 175 mg/m² on day 1 every 3 weeks) randomized to maintenance till progression or observation arm. The trial was conducted by the Korean Cancer Study Group (KCSG).

Results: Among total 324 patients enrolled between 2007 and 2010 from 10 centers, 231 responding patients to were randomly assigned to maintenance chemotherapy (n=116) or observation (n=115). Median age was 49 (range 28-76). The numbers of hormone receptor (HR)+ve and HR-ve patients were 172 (74.5%) and 59 (25.5%), respectively. The median No. of chemotherapy cycles in maintenance group was 12 (range 6-32). During median 33 months of follow-up, median PFS was superior in maintenance than in observation (12.0 vs. 8.3 months, p=0.030). Patients < age 50 years (hazard ratio 0.50, p=0.001) and HR-ve patients (hazard ratio 0.52, p=0.019) received more benefit from maintenance chemotherapy in terms of PFS. Median OS was superior in maintenance than in observation (36.8 vs 28.0 months, p=0.047). Neurotoxicity (≥ grade 2) was more common in maintenance than in observation without statistical significance (41.7% vs 33.3%, p=0.210). Serial assessment of Quality of Life (QoL) did not show any significant difference between two groups.

Conclusions: Maintenance GP chemotherapy for responding patients with MBC showed clinical benefit in terms of PFS and OS without impairment of QoL.
RTOG 9804: A prospective randomized trial for “good risk” ductal carcinoma in situ (DCIS), comparing radiation (RT) to observation (OBS)

Beryl McCormick; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Whole breast RT following conservation surgery (BCS) for low risk DCIS has remained controversial despite several large trials comparing RT to OBS, all showing significant benefit in local control with RT. RTOG 9804 compares RT to OBS for mammographically detected disease, of low or intermediate nuclear grade, <2.5 cm size, and surgical margins ≥ 3 mm. Tamoxifen (TAM) use for 5 years was allowed but not required. Methods: The primary endpoint was ipsilateral breast local failure (LF). LF and contralateral breast failures (CBF) were estimated by the cumulative incidence method and treatment arms compared by log-rank test. Disease-free (DFS) and overall survival (OS) were estimated by the Kaplan-Meier method and treatment arms compared by log-rank test. Patients were stratified by age, margin width, grade, TAM use, and primary size. With 1790 patients, 80% power and using a 2-sided log rank test at 0.05, the study was designed to detect a reduction in 5-year local recurrence from 6% to 3.5% with RT. Results: Accrual goals for the planned 1790 patients were not met; the study was closed early. From December 1999 to July 2006, 636 women were randomized to receive 50 Gy in 5 weeks vs. OBS. 43 women were ineligible on review and 8 withdrew consent. Median follow-up (F/U) time was 6.46 years. Mean age was 59; TAM was used in 62% of women. There were 2 LF in the RT arm vs. 15 in the OBS arm: at 5 years 0.4% RT vs. 3.2% OBS (p=0.0023, HR [95%CI] = 0.14 [0.03, 0.61]). With limited events, LF is not correlated with size, grade, margin status, or age. The rate of CBF at 5 years was 3.0% for the RT arm vs. 1.9% for the OBS arm (p=0.42, HR [95%CI] = 1.46 [0.59, 3.62]) and does not appear to be influenced by TAM use (3.6 versus 2.7% TAM). The DFS and OS results were excellent. Rate of grade 1-2 toxicity was 76% in the RT arm vs. 30% in the OBS arm, and the rate of ≥ 3 grade toxicities was 4% on both arms. Conclusions: In this “good risk” subset of DCIS, the LF rate was decreased significantly with the addition of RT. Longer follow-up is planned.
Correlation between the DCIS score and traditional clinicopathologic features in the prospectively designed E5194 clinical validation study.

Sunil S. Badve, Robert James Gray, Frederick L. Baehner, Lawrence J. Solin, Steven M Butler, Carl Yoshizawa, Steven Shak, Lorie L. Hughes, David L Page, George W. Sledge, Nancy E. Davidson, Edith A. Perez, James N. Ingle, William C. Wood, Joseph A. Sparano; Indiana University School of Medicine, Indianapolis, IN; Dana-Farber Cancer Institute, Boston, MA; Genomic Health, Redwood City, CA; Albert Einstein Medical Center, Philadelphia, PA; The Hope Center, Cartersville, GA; Vanderbilt University, Nashville, TN; Indiana University Simon Cancer Center, Indianapolis, IN; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Mayo Clinic, Jacksonville, FL; Mayo Clinic, Rochester, MN; Department of Surgery, Emory University, Atlanta, GA; Albert Einstein College of Medicine, Bronx, NY

Background: We previously reported that in the E5194 clinical trial patients with ductal carcinoma in situ (DCIS) treated with wide local excision (WLE) without radiation (RT), the DCIS Score was significantly associated with 10 year risk of an ipsilateral breast event (IBE - recurrence of in situ or invasive carcinoma), whether evaluated as a continuous or categorical variable (P<0.02 for both). Here we evaluate correlation between DCIS Score and clinicopathologic (CP) features and if DCIS Score provides independent recurrence risk information. Methods: The study population included 327 women with DCIS prospectively selected for treatment with WLE without RT, including low-intermediate grade tumors ≤2.5 cm or high-grade ≤1 cm. CP variables included age, menopausal status, tamoxifen treatment (used in 29%) and expert centrally determined tumor size, grade, comedo necrosis, tumor type, and margin status. The association between DCIS Score and CP variables was examined by spearman rank correlation, and proportional hazards regression models were used to determine variables significantly associated with IBE. Results: Lesion size (p=0.009) and menopausal status (p=0.03) were significantly associated with IBE, while grade (p=0.69) and comedo necrosis (p=0.47) were not. DCIS Score was significantly associated with IBE after adjustment for CP features and tamoxifen use (p=0.02). DCIS Score was moderately correlated with grade (r_s=0.46; 95% CI 0.37,0.54), percentage comedo necrosis (r_s=0.49; CI 0.41,0.57), and lesion size (r_s=0.18; CI 0.08,0.29) but not other features. Exploratory analyses in all CP subgroups, including the multicomponent Van Nuys Prognostic Index, showed a wide range of DCIS Scores in each subgroup. Concordance of the grades among readers was low: local vs parent central, 68%; local vs central nuclear grade, 45%; parent central vs central nuclear grade, 37%. Conclusions: DCIS Score is moderately correlated with grade, comedo necrosis, and tumor size. DCIS Score provides recurrence risk information independent of these features and identifies subjects with DCIS who are at high risk for local invasive and in-situ local recurrence after WLE alone.
Targeting the androgen receptor (AR) in women with AR+ ER-/PR- metastatic breast cancer (MBC).

Ayca Gucalp, Sara M. Tolaney, Steven J. Isakoff, James N. Ingle, Minetta C. Liu, Lisa A. Carey, Kimberly L. Blackwell, Hope S. Rugo, Lisle Nabell, Andres Forero-Torres, Vered Stearns, Lamia Momen, Joseph Gonzalez, Dilip D. Giri, Sujata Patil, Kimberly Feigin, Clifford Hudis, Tiffany A. Traina, Translational Breast Cancer Research Consortium (TBCRC); Memorial Sloan-Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; Mayo Clinic, Rochester, MN; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; University of North Carolina at Chapel Hill, Chapel Hill, NC; Duke University Medical Center, Durham, NC; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of Alabama at Birmingham, Birmingham, AL; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: Patients (pts) with ER-/PR- MBC do not benefit from endocrine treatment (tx). Doane et al (Oncogene 2006;25:3994) described a subset of ER-/PR- BC with a gene expression profile similar to ER+/H11001 BC but characterized by AR expression and AR-dependent growth in vitro. Hence, we conducted a multicenter phase II trial (NCT00468715) of the AR antagonist, bicalutamide (B) for pts with AR+ ER-/PR-MBC.

Methods: Pts with ER-/PR- (IHC 10%) MBC were consented to AR testing, confirmed centrally at MSKCC. If AR+ (DAKO IHC ≥10%), pts were eligible for tx if ECOG performance status (PS) <2 and normal organ function. No limit on prior tx except prior trastuzumab required if HER2+. Eligible AR+ pts who consented to tx received B 150mg orally daily in 28-day cycles (C). Toxicity assessed q4wks, response q12wks. Primary endpoint = clinical benefit rate (CBR): CR + PR + stable disease (ds) >6mo (SD). B would be considered worthy of further study if ≥4/28 pts have clinical benefit. Results: As of 12/21/11, 436 pts consented for AR testing. 24 were ineligible, 12 await testing. 47/400 tested were AR+ (12%). 26 received tx with B (6 ineligible for tx, 15 are eligible for tx with B at progression (POD) if clinically appropriate and study slots remains). Two AR+ pts treated with B were ER+ and removed from study. Three have received tx <12wks. Treated pt characteristics (n=24): median (med) age 64 (41-83), PS 0 (0-1), HER2+ 1, visceral metastases 17. Prior chemotherapy: neo/adjuvant 16; med # regimens for MBC 1 (0-8). Med C# 3 (2-49+). Best response: (21 evaluable pts): CBR 19% (95% CI 5-42%), SD>6mo 4, CR/PR 0, SD<6mo 3, POD 14. Conclusions: ~12% of ER-/PR- MBC pts are AR+. For these pts, AR-inhibition with B is feasible, well tolerated, and has activity based on pre-specified criteria. This study has closed to accrual for AR testing as of 1/2012. These results of the primary endpoint are not expected to change by accrual of the 2 remaining pts. Supported by TBCRC/Breast Cancer Alliance/AstraZeneca.

Tx-related toxicity (n=26).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT/bilirubin</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bone pain</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>1</td>
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</tr>
<tr>
<td>Vaginal dryness</td>
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<tr>
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</tr>
<tr>
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<td>2</td>
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</tr>
<tr>
<td>Dysesthesia</td>
<td>2</td>
<td>0</td>
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</tr>
<tr>
<td>No grade 4/5 events</td>
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</table>

Use of microRNA (miR) expression profiling to identify distinct subclasses of triple-negative breast cancers (TNBC).

Charles L. Shapiro, Luciano Cascione, Pierluigi Gasparini, Francesca Lovat, Stefania Carasi, Alfredo Pulvirenti, Alfredo Ferro, Kay Huebner, Ohio State University Medical Center and Comprehensive Cancer Center; Division of Medical Oncology and the Breast Program, Columbus, OH; Department of Molecular Virology, Immunology and Medical Genetics, Columbus, OH; Department of Clinical and Molecular Biomedicine, University of Catania, Catania, Italy

Background: TNBC is divided into basal and non-basal subclasses. To further subclassify TNBC we performed microRNA (miR) expression profiles and linked them to patient overall survival. Methods: During 1996-2005, 365 consecutive TNBC (phenotypically estrogen, progesterone and HER2 negative by immunohistochemistry [IHC]) were identified from the NCCN Breast Cancer Data Base/Tumor Registry at OSU Medical Center. One hundred fifty-eight (43%) formalin-fixed paraffin embedded (FFPE) breast cancer and 40 normal breast tissue blocks were available and tissue cores were obtained for RNA. RNA was isolated using the Ambion recoverall total nucleic acid isolation kit and the expression of ~700 miRs was assessed for each sample using the nanoString nCounter method. A consensus-clustering algorithm (ConsensusClusterPlus, Bioconductor www.bioconductor.org) was used to identify subclasses of TNBC and Kaplan-Meier overall survival curves were compared using the log-rank test. Censoring occurred at the date of death from causes other than breast cancer or at time of the last known follow-up, whichever occurred first. The median follow-up was 67 mo. (range 4-171 mo.). Results: The median age was 52 yrs. (range 20-84 yrs.); 81% white and 9% African-American; stages I, II, and III were 31%, 54% and 15%, respectively; and most patients received adjuvant anthracycline-based regimens with (25%) or without taxanes (75%). The algorithm identified 5 distinct subclasses; 1 clustering with normal breast miR expression whereas the other 4 each had a unique pattern of deregulated miRs. The median overall survivals were significantly different across the 5 cancer subclasses (log-rank p=0.028) (Table). Conclusions: miR expression profiling identifies and discriminates 5 TNBC subclasses, which do not coincide with those identified as basal and non-basal by IHC. Molecular analyses are ongoing to associate the miR-based subclasses with specific clinical features or the expression of specific pathways.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Median overall survival (mo.)</th>
<th>Log-rank p</th>
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<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>46</td>
<td>0.028</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>50</td>
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<td>3</td>
<td>51</td>
<td>66</td>
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<tr>
<td>4</td>
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<td>67</td>
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</tr>
<tr>
<td>5</td>
<td>37</td>
<td>82</td>
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</table>
Quantitative hormone receptors, triple-negative breast cancer (TNBC), and molecular subtypes: A collaborative effort of the BIG-NCI NABCG.

Maggie Chon U. Cheang, Miguel Martin, Torsten O. Nielsen, Aleix Prat, Alvaro Rodriguez-Lescure, Amparo Ruiz, Stephen K. L. Chia, Lois E. Shepherd, David Voduc, Philip Seth Bernard, Matthew James Ellis, Charles M. Perou, Angelo Di Leo, Lisa A. Carey, on behalf of Breast International Group-North American Breast Cancer Group; British Columbia Cancer Agency, Vancouver, BC, Canada; Hospital General Universitario Gregorio Marañón, Madrid, Spain; University of North Carolina at Chapel Hill, Chapel Hill, NC; Hospital General de Elche, Alicante, Spain; Instituto Valenciano de Oncologia, Valencia, Spain; NCIC Clinical Trials Group, Queen’s University, Kingston, ON, Canada; BC Cancer Agency, Vancouver, BC, Canada; University of Utah Health Sciences Center, Salt Lake City, UT; Department of Internal Medicine, Division of Oncology and Siteman Cancer Center, Washington University Medical Center, St. Louis, MO; Sandro Pitigliani Medical Oncology Unit, Prato, Italy

Background: Most TNBC trials focusing on biology of the basal-like subtype (BLBC) allow borderline (1-10% staining) estrogen receptor (ER) and progesterone receptor (PgR) expression by immunohistochemistry (IHC); however the optimal ER and PgR cut points to enrich for non-luminal subtypes has not been studied. In this study, we compared quantitative ER/PgR status with gene expression-based intrinsic subtype in order to determine if borderline cases should be included in TNBC trials. Methods: ER, PgR, and HER2 status was determined by central review of tumors collected from three phase III randomized trials: GEICAM 9906 (n=820), NCIC CTG MA.5 (n=476) and MA.12 (n=398). PAM50 intrinsic subtyping (BLBC, HER2-enriched, Luminal A, Luminal B and Normal-like) was performed using the qRT-PCR-based assay. Quantitative ER/PgR expression by IHC and subtype was tested using ANOVA and Fisher’s exact test. Results: Of 1,694 tumors, 15% were BLBC, 21% HER2-Enriched, 33% Luminal A, 25% Luminal B and 4% Normal-like. BLBC subtypes were significantly associated with low expression of ER and PgR (median = 0.05%) compared to other subtypes (p < 0.001). The vast majority of BLBC (96%) did not express any ER or PgR protein by IHC. BLBC represented 73% of TNBC (borderline cases not included) and significantly more than the additional TNBC with borderline ER/PgR (p < 0.001). Within borderline ER/PgR and HER2-negative cases only, 17% were BLBC and 46% were luminal subtypes (Table). Conclusions: BLBC rarely express ER or PgR by IHC. The majority of borderline TNBC (1-10% ER/PgR) are not BLBC; half of them are categorized as luminal categories that may be endocrine sensitive. TNBC trials seeking to target BLBC tumor biology should use the ASCO/CAP guidelines of 0% as the cutoffs for ER and PgR negativity.

<table>
<thead>
<tr>
<th>Clinical subtypes</th>
<th>Basal-like</th>
<th>HER2-enriched</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>Normal-like</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PgR (0%)/HER2-</td>
<td>207 (73%)</td>
<td>48 (17%)</td>
<td>6 (2%)</td>
<td>15 (5%)</td>
<td>7 (3%)</td>
<td>283</td>
</tr>
<tr>
<td>ER/PgR (1-10%)/HER2-</td>
<td>8 (17%)</td>
<td>14 (29%)</td>
<td>10 (21%)</td>
<td>12 (25%)</td>
<td>4 (8%)</td>
<td>48</td>
</tr>
<tr>
<td>ER/PgR 11-100%/HER2-</td>
<td>8 (17%)</td>
<td>10(12%)</td>
<td>490 (49%)</td>
<td>301 (30%)</td>
<td>47 (55%)</td>
<td>999</td>
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Phase I, open-label study of olaparib plus cisplatin in patients with advanced solid tumors.

Judith Balmaña, Nadine M. Tung, Steven J. Isakoff, Beğöña Graña, Paula D. Ryan, Rezvan Rafi, Michael Tracy, Eric Winer, José Baselga, Judy Ellen Garber; Vall d’Hebron University Hospital, Barcelona, Spain; Beth Israel Deaconess Medical Center, Boston, MA; Massachusetts General Hospital, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; AstraZeneca, Wilmington, DE; AstraZeneca, Macclesfield, United Kingdom; Dana-Farber Cancer Institute, Boston, MA

Background: Olaparib (AZD2281) is an oral PARP inhibitor active in advanced ovarian and breast cancers. We conducted a multicenter, dose-finding study assessing safety/tolerability of olaparib capsules plus cisplatin in patients (pts) with advanced solid tumors (NCT00782574), for potential use in the neoadjuvant setting. Methods: Pts received 21-day(d) cycles of olaparib, continuously (Cont) or intermittently (Int), plus cisplatin on d1 of each cycle. Each cohort recruited ≥3 evaluable pts with expansion to ≥6 pts if ≥1 had a dose-limiting toxicity. The last cohort was expanded to ensure ≥6 pts completed 4 treatment cycles. Pts who completed 6 combined therapy cycles or who stopped cisplatin due to cisplatin-related toxicity could enter the monotherapy phase (up to 400 mg BID olaparib). Primary objective: safety/tolerability of ≥4 combined cycles; secondary objectives: pharmacokinetics, antitumor activity. Results: 54 pts received treatment; pts had breast (n=42), ovarian (n=10), pancreatic (n=1) or peritoneal (n=1) cancer. Median number of prior regimens = 4 (1–13). C2, C4 and C6 enrolled ≥6 pts. Most common grade (G) 3/4 AEs: neutropenia (n=9; 16.7%), leukopenia (n=4; 7.4%), anemia (n=3; 5.6%), vomiting (n=3; 5.6%). In C1–C5, 3 pts had AEs leading to discontinuation: 1 in C2 (thrombocytopenia); 2 in C3 (fatigue; complex migraine, dyspnea). In C6, all pts have ended combination phase and no G3/4 hematologic AEs were seen. Overall, 46% of pts had a dose reduction; 32% due to hematologic AEs. There were no drug-related deaths. 35 pts (65%) completed ≥4 combined cycles (C6, n=8). 18/54 evaluable pts (33%) had an objective response (complete, n=1; partial, n=17); 23 (43%) achieved stable disease. 7 pts (13%) had durable responses on monotherapy for ≥1 year. PK and BRCA1/2 data will be presented. Conclusions: Hematologic AEs led to dose reductions + schedule changes of olaparib with cisplatin 75 mg/m². Tolerability improved with cisplatin 60 mg/m². Antitumor activity was seen during combination and olaparib monotherapy phases, with some long responders.

<table>
<thead>
<tr>
<th>Cohort (C)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>Cisplatin, d1/21</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>60</td>
</tr>
<tr>
<td>Olaparib, mg BID</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>100</td>
<td>50</td>
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<td>13</td>
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<td>14</td>
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<td>12</td>
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George Somlo, Joseph A. Sparano, Tessa Cigler, Gini F. Fleming, Thehang H. Luu, Arti Hurria, Joanne E. Mortimer, Paul Henry Frankel, Helen K. Chew, Rita Nanda, Cynthia X. Ma, Alice P. Chen, Agustin Garcia, Linda T. Vahdat, David R. Gandara, Jeffrey N. Weitzel; City of Hope, Duarte, CA; Albert Einstein College of Medicine, Bronx, NY; Weill Cornell Medical College, New York, NY; The University of Chicago Medical Center, Chicago, IL; City of Hope Cancer Center/Beckman Research Institute, Duarte, CA; University of California, Davis Cancer Center, Sacramento, CA; The University of Chicago, Chicago, IL; Washington University School of Medicine, St. Louis, MO; National Cancer Institute, Bethesda, MD; USC Norris Comprehensive Cancer Center, Los Angeles, CA; University of California Davis Cancer Center, Sacramento, CA

Background: Platinum and PARP inhibitors have both shown activity in BRCA-associated breast cancer (BC) patients (pts). We have conducted a phase I trial of carboplatin (Carb) and veliparib [V], a PARP inhibitor, to define dose limiting toxicities [(DLT) during cycle (C) 1] and the maximum tolerated dose (MTD). Methods: BRCA 1 or 2 carriers with stage IV BC were eligible. Carb starting at an AUC of 6 was given IV every 21 days (length of planned C) and V was administered orally, BID at dose levels (L) L1 through L5 (highest L planned). Results: 22 pts (21 eligible/evaluable, 20 with measurable BC) carrying BRCA1 (10) or BRCA2 (11), or both (1) mutations were accrued. Median age: 45 years, (32-65); 68% of BCs were ER+/HER2-, and 10% were HER2+. In the table below are the schema, incidence of DLTs, and # of Cs on study. Toxicities: At L1, grade ¾ DLTs with C 1 were seen in 2/6 evaluable pts (1 pt w/grade 3 hyponatremia, pleural effusion, and dehydration, and 1pt w/grade 4 thrombocytopenia [PLT]), leading to deescalation of carb (AUC 5) for pts treated at Ls 2-5. At L2, 1 of 6 pts had grade 4 PLT. There were no DLTs at Ls 3 and L4. L5 is currently being expanded to 6 pts (3 currently enrolled, 1 pt w/grade 4 granulocytopenia (Gr) and grade PLT reached DLT). Non-DLT dose delays mostly due to grade 2 Gr or PLT were needed at 60%, 53%, 53%, and 43% of Cs in pts treated on Ls 1-4. Response: In 12 eligible pts treated at Ls 1 and 2, 2 complete and 6 partial responders (67%) and a clinical benefit (CB) of 75% were seen. All pts at Ls 3-5 are still being treated, and in pts treated at Ls 3 and 4, 2 unconfirmed PRs, and 4 cases of stable disease were seen, with L5 too early to assess. Conclusions: The combination of Carb at an AUC of 5 and daily V at doses 150 to 200 mg BID is feasible and the MTD is being defined. In preliminary analysis, response and CB rates are better than expected with the individual agents alone, providing justification to proceed with a planned phase II randomized single agent versus combination trial.

<table>
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<tr>
<th>Dose levels</th>
<th>L1</th>
<th>L2</th>
<th>L3</th>
<th>L4</th>
<th>L5 (highest planned L)</th>
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<tbody>
<tr>
<td>Carb AUC</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>V in mg</td>
<td>50 BID</td>
<td>50 BID</td>
<td>100 BID</td>
<td>150 BID</td>
<td>200 BID</td>
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<tr>
<td># of pts</td>
<td>7 (1 ineligible)</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Evaluable pts</td>
<td>6</td>
<td>6</td>
<td>3</td>
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<td>3</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td># of Cs given</td>
<td>9 (1-15)</td>
<td>8.5+ (1-11)</td>
<td>6+ (6+)</td>
<td>3+ (3+ to 4+)</td>
<td>1+ (1+ to 2+)</td>
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</table>

BREAST CANCER—TRIPLE-NEGATIVE/CYTOTOXICS/LOCAL THERAPY

SOLTI NeoPARP: A phase II, randomized study of two schedules of iniparib plus paclitaxel and paclitaxel alone as neoadjuvant therapy in patients with triple-negative breast cancer (TNBC).

Antonio Llombart, Ana Lluch, Cristian Villanueva, Suzette Delalorge, Serafin Morales, Judith Balmaña, Kepa Amillano, Herve R. Bonnefoi, Ana Maria Casas, Luis Manso, Henri Hubert Roche, Santiago Gonzalez-Santiago, Joaquin Gavila, Pedro Sánchez-Rovira, Serena Di Cosimo, Eric Charpentier, Ignacio Garcia-Ribas, Frederique Madeleine Penault-Llorca, Claudia Aura, José Baselga, SOLTI Group; Solti Group, Valencia, Spain; Hospital Clinic Universitario de Valencia, Valencia, Spain; CHU Besançon, Besançon, France; Institut Gustave Roussy, Villejuif, France; Hospital Arnau de Vilanova, Lleida, Spain; Breast Cancer Department, Vall d’Hebron University Hospital, Barcelona, Spain; Hospital Sant Joan de Reus, Reus, Spain; Institut Bergonie Cancer Center, Bordeaux, France; Hospital Virgen Del Rocio, Sevilla, Spain; Hospital Universitario 12 de Octubre (ONCOSUR), Madrid, Spain; Institut Claudius Regaud, Toulouse, France; Complejo Hospitalario Cáceres, Cáceres, Spain; Instituto Valenciano de Oncología, Valencia, Spain; Complejo Hospitalario de Jaén, Jaén, Spain; Breast Cancer Center, Vall d’Hebron University Hospital, Barcelona, Spain; Sanofi-aventis, Malvern, PA; Sanofi-Aventis, Madrid, Spain; Centre Jean Perrin, Clermont-Ferrand, France; Hospital Vall d’Hebron, Barcelona, Spain; Massachusetts General Hospital, Boston, MA

**Background:** Iniparib is an anticancer agent with a mechanism of action still under investigation. A phase 2 randomized neoadjuvant study in patients (pts) with TNBC was designed to explore the activity and tolerability of two schedules of iniparib with weekly paclitaxel (PTX). Here we report the efficacy and safety results from a planned interim analysis (IA). **Methods:** The trial accrued a total of 141 pts in October 2011, of whom, 74 are included in this IA. All were chemo-naive, histologicallyconfirmed Stage II-IIIA TNBC (IIA 47%; IIB 35%; IIIA 16%) with a median age of 50 yr. Triple negative status was centrally confirmed [ER/PR <10%, HER2 IHC (0+, 1+) or FISH negative]. Pts were randomized (1:1:1) to receive weekly PTX (80 mg/m₂, IV, d 1; N=25) alone or in combination with iniparib, either on a once weekly (QW) (11.2 mg/kg, IV, d 1; N=25) or twice weekly (BIW) (5.6 mg/kg, IV, d 1, 4; N=24) schedule. The total planned treatment duration was 12 wks. The IA endpoint is pathological complete response in the breast (pCR) as assessed by independent pathologists. **Results:** Two/2/3 pts in the PTX/QW/BIW arms, respectively, discontinued due to progressive disease per RECIST. Another 3/2/2 pts, respectively, discontinued due to investigator decision or an adverse event (AE). Thirteen pts presented with Grade 3/4 Treatment Emergent AE: 3 pts in PTX arm (1 neutropenia, 1 presyncope, 1 ALT elevation), 3 in QW arm (1 lymphopenia, 1 hyperkalemia, 1 pulmonary embolism), and 8 in the BIW arm (1 febrile neutropenia, 3 neutropenia, 1 aphonya, 1 syncope, 1 radius fracture and 1 vertigo). Laboratory Grade 3/4 neutropenia occurred in 4% of pts in PTX, 0% in QW and 21% of BIW arms, with 1/2/3 pts, respectively, requiring G-CSF usage. There were 4/7/6 pts in the PTX/QW/BIW arms with PTX dose modifications. Four pts (16%) in PTX arm, 4 pts (16%) in the QW arm and 6 pts (25%) in the BIW arm had confirmed pCR in the breast. **Conclusions:** In this IA population, the addition of iniparib regardless of the schedule to weekly PTX did not seem to add clinically significant toxicity. pCR rate in the breast is similar across treatment arms at this IA. NCT01204125.
DNA repair metagene signature as a prognostic and predictive factor in molecular breast cancer subtypes.

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**Background:** We aimed to assess the prognostic and predictive role of DNA repair genes in breast cancer (bc) molecular subtypes. **Methods:** We evaluated Affymetrix gene expression profiling from untreated N-patients (N = 684), neoadjuvant treated tumors with taxanes- (N = 320), anthracyclines- (N = 211), and cisplatin- (N = 22) containing regimens. We assessed within 3 BC molecular subgroups (ER+/HER2-, HER2+, and ER-/HER2-) bimodality distribution, prognosis by association with distant relapse (N = 454, N = 105, and N = 125) and predictive value for likelihood of pathological complete response (pCR) (N = 208, N = 105, and N = 240). Moreover, we explored the function of relevant genes in BC cell lines. **Results:** Three genes (ERCC2, XRCC3, and RECQL4) showed bimodality in each bc subtype. Eight genes were associated with poor prognosis (including RECQL4) and 1 gene with good prognosis (ATM) [P < .0001] only in ER+/HER2- tumors. Our results suggest a subtype and treatment specific association with pCR although they did not satisfy stringent criteria for false discovery correction. In ER-/HER2- mismatch repair (MR) (MSH2 and MSH6) and MTMR15 genes were associated with response and resistance to taxane-containing regimens, respectively. TOP2A was the only gene associated with response to anthracycline but not taxanes in HER2+ tumors. RECQL4 had a positive trend with higher pCR in both ER+ and ER-/HER2- tumors. In in vitro studies we found that RECQL4 interacts with PARP1 and that the expression of these genes was correlated with sensitivity to chemotherapy and PARP inhibitors. **Conclusions:** We identified MR genes as potential predictive markers of response to taxanes-based regimens in ER-/HER2-. A novel gene RECQL4 showed bimodal distribution, prognostic value, and a trend for predictive association with response to taxanes-based chemotherapy, which was also confirmed by in vitro analysis. ATM deserves further evaluation as prognostic marker in ER+/HER2-.
HAGE (DDX43) protein expression as an independent biomarker of poor clinical outcome of breast cancer (BC) and potential as a therapeutic target for ER-negative BC.

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Background: Recently, we have confirmed that HAGE is involved in promoting proliferation as assessed by increased thymidine incorporation and our preliminary results using shRNA to permanently knockdown HAGE expression also suggests the involvement of HAGE in tumor motility and metastasis. In this study we aimed to analyze the expression of HAGE in large well-characterized BC cohorts to determine its relationship with other clinico-pathological parameters and to investigate its prognostic value. Methods: HAGE protein expression was assessed in: a) 40 normal breast tissue (NBT), b) 60 invasive BCs and their matching NBT, c) BC cell lines, d) A series of 1650 consecutive cases of primary BC who treated with adjuvant CMF and/or endocrine therapies. Further validation was performed in 2 independent series of high risk ER- BC: a) 300 ER-BC who did not received any CT and b) 396 ER- BC treated with adjuvant anthracycline (ATC) based CT. Results: The NBT showed negative HAGE expression (HAGE-) throughout. HAGE overexpression (HAGE+) was observed in 10% of BC and was significantly associated with aggressive clinico-pathological features including: ER-, high grade and triple negative phenotypes. Moreover, HAGE+ expression showed an adverse outcome with a 2-4 fold increase in the risk of death, recurrence and metastases (ps<0.00001) compared to HAGE-; ps<0.0001. Using a multivariate Cox regression model including ER status, grade, size and tumour stage, HAGE expression was confirmed as a powerful independent prognostic factor (p<0.0001). The poor clinical outcome of HAGE+ was further confirmed in high risk (NPI>3.4) ER- patients who did not received any CT (p<0.0001). While, adjuvant CT either CMF or ATC had a positive impact on HAGE+/high risk ER- BC as HAGE+ had a similar risk of death, recurrence and distant metastases to HAGE- expression. Conclusions: This is the first report which shows HAGE to be a potential predictor for poor prognosis in BC patients, and may be an attractive novel target for molecular and vaccine therapy for those patients. A prospective trial of adjuvant chemotherapy/vaccine to confirm this finding is warranted.
Targeting XRCC1 (X-ray repair cross-complementing gene 1) deficiency in tumors for personalized cancer therapy.

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Background: XRCC1 is essential for DNA base excision repair, single strand break repair and nucleotide excision repair. XRCC1 deficiency promotes genomic instability and may increase cancer risk. Methods: We evaluated XRCC1 immunohistochemically in early stage breast (n=2046), ovarian (n=157), gastric (n=140), colorectal (n=250) and pancreaticobiliary cancers (n=240). Pre-clinically, we evaluated a panel of XRCC1 deficient and proficient Chinese hamster ovary and human cancer cell lines. Double strand break repair (DSB) inhibitors targeting ATM (KU55933), DNA-PKcs (NU7441) and ATR (NU6027) were evaluated for synthetic lethality and cisplatin alone or in combination with DSB inhibitors for chemopotentiation. Results: In breast cancer, XRCC1 loss (16%) was associated with higher grade (p<0.0001), loss of hormone receptors (p<0.0001) and basal like phenotypes (p=0.001). Loss of XRCC1 was associated with a 2-fold increase in risk of death and metastasis (p<0.0001) and independently with poor outcome (p<0.0001). In ovarian cancer, XRCC1 was positive in 44% of tumour and was significantly associated with higher stage (p=0.001), clear/endometroid type (p=0.015) and sub-optimal debulking (p=0.004). XRCC1 positive tumours were more resistant to platinum chemotherapy (p=0.0001). XRCC1 positivity conferred a 2 fold increase of risk of death (p=0.002) and independently associated with poor survival (p=0.002). In gastric cancers, XRCC1 was positive in 37% of tumours. This was significantly associated with high stage disease (p=0.001) and poor survival (p=0.001). Pre-clinically, KU55933, NU7441 and NU6027 were synthetically lethal in XRCC1 deficient compared to proficient cells as evidenced by DSB accumulation, G2/M cell cycle arrest and apoptosis. XRCC1 deficient cells were hypersensitive to cisplatin which was enhanced by DSB repair inhibitors compared to proficient cells. Conclusions: This is the largest study to confirm the clinical significance of XRCC1 expression in solid tumours. XRCC1 deficiency in human tumours may be suitable for synthetic lethality application and exploited for cisplatin chemotherapy potentionation.
Cancer gene profile of metastatic breast cancer.

Funda Meric-Bernstam, Garrett Frampton, Jaime Ferrer-Lozano, Roman Yelensky, Gary A. Palmer, Maureen T. Cronin, Philip J Stephens, Katherine Stemke Hale, Juan Barrera, Octavio Burgues, Ana Lluch, Gordon B. Mills, Ana M. Gonzalez-Angulo; University of Texas M. D. Anderson Cancer Center, Houston, TX; Foundation Medicine, Cambridge, MA; Hospital Clinico Universitario de Valencia, Valencia, Spain; Hospital C.U. de Valencia, Valencia, Spain

Background: There is great interest in using genomic information to guide therapy selection in cancer patients. The aim of this study was to determine the spectrum of genomic alterations identified in MBC patients, and evaluate the concordance of alterations between primary and recurrent tumors. Methods: We performed comprehensive profiling on formalin-fixed paraffin embedded samples from 42 patients with MBC using a targeted next generation sequencing (NGS) assay in a CLIA laboratory (Foundation Medicine). Genomic libraries were captured for 3,230 exons in 182 cancer related genes plus 37 introns from 14 genes often rearranged in cancer and sequenced to an average depth of 390X with 99% of bases covered >100X. In total 30 primary and 37 recurrent tumors were profiled, including 3 separate recurrences in 1 patient and matched primary-recurrences in 22 patients. Point mutations, indels, copy number alterations and rearrangements were assessed. Alterations that are targetable with established or investigational therapeutics were considered “actionable”. Results: At least 1 genomic alteration was identified in all but 2 breast samples (both primary tumors). Point mutations were identified in several cancer-related genes including PIK3CA, TP53, PTEN, CDH1, ARID1A, AKT1, NF1, FBXW7 and FGFR3. Amplification was observed in HER2; 11 of 12 HER2 IHC positive samples were found to have HER2 gains by NGS; in addition, a HER2 gain was identified by NGS in a HER2- (1+ IHC) sample. Amplification of PIK3CA, IGF1R, FGFR2, AKT2, MDM2, and MCL1 plus a CDKN2A homozygous deletion were also identified. While the majority of known driver alterations (85%) were concordant in the matched pairs of primary and recurrent tumors, in 11 of 22 sets there was at least 1 discordant driver alteration, and these included both gains and losses of potential therapeutic targets. Overall 32 of 42 patients (76%) had an actionable genomic alteration. Conclusions: Genomic profiling of breast cancer samples reveals genomic alterations in most metastatic breast cancer patients. Over three quarters of patients have actionable findings, suggesting that genomic profiling may assist in individualized pathway-directed therapy.
Tesetaxel: Activity of an oral taxane as first-line treatment in metastatic breast cancer.

Andrew David Seidman, Lee Steven Schwartzberg, Joyce O’Shaughnessy, Gabriella D’Andrea, Peter Rubin, Seth Katz, Hassan Danesi, Loretta Itri, Clifford Hudis; Memorial Sloan-Kettering Cancer Center, New York, NY; The West Clinic, Memphis, TN; Baylor Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, TX; Moses Cone Regional Cancer Center, Greensboro, NC; Genta Incorporated, Berkeley Heights, NJ

**Background:** Tesetaxel, unlike standard taxanes (docetaxel, paclitaxel), is not a substrate for Pgp, a major cause of taxane resistance in tumor models. In a DU4475 breast cancer xenograft that overexpresses Pgp, tesetaxel induced a 94% reduction in tumor size, markedly exceeding the activity of docetaxel (46%) and paclitaxel (26%). Tesetaxel is associated with substantially less neuropathy preclinically than equi-myelotoxic doses of docetaxel. In clinical studies to date, tesetaxel is not associated with hypersensitivity reactions (0% incidence in > 450 patients [pts]), thus eliminating the need for premedication and extended observation. In a prior study, tesetaxel (27-35 mg/m^2 Q3 wks) achieved a 38% partial response (PR) rate as 2nd-line therapy in pts with metastatic breast cancer (MBC) who had progressed after multidrug anthracycline-containing regimens. To extend these data, we initiated a phase 2 study of tesetaxel as 1st-line therapy in women with MBC. **Methods:** Eligibility included MBC; HER2-; ECOG PS 0-1; and adequate organ function. Adjuvant chemotherapy (including taxanes) was allowed. Tesetaxel was administered orally without anti-allergic premedication at a starting dose of 27 mg/m^2 once every 3 wks. Overall response rate (ORR; RECIST) was the primary endpoint. **Results:** All 45 pts have been accrued. Median age is 58 y (range 36-80); median time from diagnosis, 4.0 y (range 0-21); triple negative status, 8 pts at diagnosis, 14 at time of metastasis. Metastatic sites are lung (22 pts), lymph nodes (22), liver (24), and bone (21). Prior treatment includes anti-estrogen therapy (32 pts), adjuvant chemotherapy (31), prior taxane (25), and radiotherapy (28). ORR in 24 pts evaluable for response is 50% (1 CR [4%], 11 PR [46%]); 5 responding pts had prior taxane therapy. Neutropenia is the most common Grade 3 adverse event with 50% of cases observed after dose escalation to 35 mg/m^2; febrile neutropenia and Grade 3 peripheral neuropathy occurred in 2 pts each. There were no hypersensitivity reactions. **Conclusions:** Tesetaxel is highly active in 1st-line MBC and overcomes multiple limitations of standard taxanes. Updated ORR and PFS for all pts will be presented. Weekly dosing will be evaluated in a new cohort of pts.
Final analysis of phase II study of EZN-2208 (PEG-SN38) in metastatic breast cancer (MBC).

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Background: EZN-2208 is a water-soluble PEGylated conjugate of SN38. EZN-2208 results in prolonged exposure of tumors to SN38 via preferential accumulation of EZN-2208 in the tumor and prolonged release of SN38. These data represent the final analysis of our study evaluating EZN-2208 in MBC. Methods: EZN-2208 9 mg/m² (SN38 equivalents) was delivered as a 60-minute IV infusion, weekly for 3 wks in 4-wk cycles. The primary objective was to determine the overall response rate (RR) in female patients with metastatic breast cancer (MBC) who had received prior adjuvant or metastatic therapy with either 1) anthracycline and taxane (AT) or 2) anthracycline, taxane, and capecitabine (ATX). Secondary objectives included evaluation of RR based on tumor receptor status, duration of response, progression-free survival (PFS), overall survival (OS), and safety. Results: Patients with MBC (n=164) were treated with a median (range) of 3.3 (0.3-22) cycles of EZN-2208. The objective response rate (RR) was 20% for AT and 9% for ATX. The clinical benefit rate (CBR=CR + PR + SD ≥6 months) was 41% and 27% in patients in the AT and ATX cohorts, respectively. The RR and CBR among ER+ patients were 11% (10/91 pts) and 41.8% (38/91 pts). In patients who progressed during or within 30 days of prior platinum-containing regimens (Platinum Progressors), the CBR was 20% (8/40 pts). Among triple negative breast cancer (TNBC) patients, the RR and CBR were 22.5% (11/49 pts) and 36.7% (18/49 pts). For TNBC, Platinum Progressors, the CBR was 26.1% (6/23 pts). Overall, most common reported drug-related adverse events were diarrhea, nausea and neutropenia. Conclusions: EZN-2208 has notable activity in patients with previously treated MBC and appears to be an active agent for treatment of TNBC. Patients with TNBC, who had been previously treated with a platinum-based regimen, also derive clinical benefit from EZN-2208. The safety profile of EZN-2208 is acceptable with good tolerability in most patients. Further evaluation of EZN-2208 in MBC in general and TNBC in particular is warranted.
Everolimus with paclitaxel plus bevacizumab as first-line therapy for HER2-negative metastatic breast cancer (MBC): A randomized, double-blind, placebo-controlled phase II trial of the Sarah Cannon Research Institute (SCRI).

Denise Aysel Yardley, Linda D. Bosserman, Nancy Walker Peacock, Anne Favret, Susan Kay Morgan, Victor M. Priego, J. David Bass, Paula L. Griner, Howard A. Burris, John D. Hainsworth, Joyce O’Shaughnessy; SCRI/Tennessee Oncology, PLLC, Nashville, TN; Wilshire Oncology, Pomona, CA; Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; US Oncology, Fairfax, VA; Florida Cancer Specialists/Sarah Cannon Research Institute, Naples, FL; Center for Cancer and Blood Disorders, Bethesda, MD; SCRI, Nashville, TN; Baylor Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, TX

Background: Constitutive activation of mTOR and amplified PI3K/Akt/mTOR signaling are common in MBC, and increase as treatment-resistance is acquired. Everolimus (E), an mTOR inhibitor, has single agent activity, combines well with paclitaxel (P) and bevacizumab (B), and prolonged PFS when added to AI therapy in BOLERO-2. In this randomized phase II trial, E was added to P/B as first-line treatment of HER2-negative MBC. Methods: Women with untreated HER2-negative MBC were randomized (1:1) to P 90mg/m² IV (days 1, 8, and 15) and B 10mg/kg IV (days 1 and 15) q28 days with E 10mg PO (Arm 1) or placebo PO (Arm 2) daily. Response assessment was performed q8 weeks until progression or intolerable toxicity. Primary endpoint was PFS. Secondary endpoints: safety, overall response rate, response duration, overall survival. 110 pts allowed detection of improvement in median PFS from 11 to 16 months with 70% power. Results: Between 8/2009 and 6/2011, 112 pts were randomized (Arm 1/H11005 55; Arm 2/H11005 57). Median age: 58 years (range: 25-79). 88% were ER+ or PR+. Pts received a median 5 treatment cycles (range: <1-26+); 18 (16%) pts remain on treatment (Arm1, 9; Arm 2, 9). Median PFS were 8.8 months (Arm 1) and 7.1 months (Arm 2) (95% CIs 7.4-9.6; 5.5-9.1 months, p=0.79, HR 0.94). Complete responses were observed in 5% [Arm1, 4 (7%); Arm 2, 2 (4%)] with partial responses in 49% [Arm1, 29 (53%); Arm 2, 26 (46%)]. Responses rates in taxane pretreated pts Arm 1 22%, Arm 2 12%. Hematologic toxicity was similar in both arms: grade 3 mucositis occurred in 13% of E pts. Dose reductions (47% vs 25%) and interruptions (42% vs 26%) were more frequent with E due to mucositis and rash. Treatment discontinuation rates were similar. Conclusions: The addition of E did not result in a significant improvement in the efficacy of weekly paclitaxel/bevacizumab in the first-line treatment of HER2-negative MBC although response rates and median PFS were better with E. Possible explanation for these results may include lower dose intensity in the E arm, treatment of less resistant pts, or intrinsic differences in E activity when added to antiestrogen vs chemotherapy.
Metformin in early breast cancer (BC): A prospective, open-label, neoadjuvant “window of opportunity” study.

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Background: There is growing evidence that metformin may exert anti-cancer effects through indirect (insulin-mediated) or direct (insulin-independent) mechanisms. Here, we report final results of a neoadjuvant “window-of-opportunity” study of metformin in women with operable BC. Methods: Newly diagnosed, untreated, non-diabetic BC patients received metformin 500 mg tid after diagnostic core-biopsy until definitive surgery (no other treatment). Clinical [weight, symptoms, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C-30)] and biologic characteristics [insulin, glucose, homeostatic model assessment (HOMA), C-reactive protein (CRP), leptin] were compared pre- and post-metformin as were Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL, an apoptotic marker) and Ki67 (primary end-point) scored blinded by manual count of positive nuclear-staining. The planned sample-size of 40 patients gave 90% power to detect a 5.5 percentage point change in Ki67. Results: Thirty-nine patients were enrolled and mean age was 51 years; metformin was given for 18 days (median), range 13-40 days. Twenty patients had T1 and 19 T2/T3 tumors; 16 tumors were grade III; 24 were N0; 32 ER/PR positive, 5 HER-2 positive. Grade 1-2 self-limiting diarrhea, anorexia and abdominal distention occurred in 50%, 41% and 32%. EORTC QLQ scores were stable in all function domains and overall scores. Main study outcomes are tabulated here. Conclusions: Short-term preoperative metformin was well-tolerated and resulted in clinical and cellular effects in keeping with beneficial anti-cancer effects as demonstrated by improved insulin resistance (HOMA), decreased proliferation (ki67) and increased apoptosis (TUNEL).

<table>
<thead>
<tr>
<th>Variable (units)</th>
<th>Pre-metformin mean (SD)</th>
<th>Mean change (SD)</th>
<th>p change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>70.3 (12.3)</td>
<td>-1.2 (1.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 (4.6)</td>
<td>-0.5 (0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>2.0 (2.7)</td>
<td>-0.2 (2.6)</td>
<td>0.35</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.30 (0.56)</td>
<td>-0.14 (0.43)</td>
<td>0.045</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>43.4 (23.9)</td>
<td>-4.7 (18.1)</td>
<td>0.069</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.47 (0.95)</td>
<td>-0.21 (0.75)</td>
<td>0.047</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>16.5 (13.0)</td>
<td>-1.3 (7.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>TUNEL</td>
<td>0.56 (0.58)</td>
<td>-0.49 (1.00)</td>
<td>0.0037</td>
</tr>
<tr>
<td>Ki67</td>
<td>36.5 (24.8)</td>
<td>-3.0 (9.8)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

The impact of genetic variability on severe toxicity of (neo-)adjuvant chemotherapy in breast cancer patients receiving 5-fluorouracil, epirubicin, and cyclofosfamide (FEC).

Background: We assessed the impact of single nucleotide polymorphisms (SNP) of potential genes of interest in germline DNA on severe adverse events in breast cancer (bc) patients receiving (neo-) adjuvant FEC chemotherapy. Methods: Cases were retrospectively evaluated through electronic chart review for febrile neutropenia (primary endpoint), febrile neutropenia first cycle, prolonged grade 4 or deep (<100/µl) neutropenia, anemia grade 3-4, thrombocytopenia grade 3-4 and non-hematological grade 3-4 events. The panel of genes, genotyped using iPLEX technology on a MALDI-TOF based MassARRAY Compact Analyser (Sequenom Inc., CA, USA), included ABCB1, ABCC1, ABCC2, ABCG2, ALDH3A1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, DPYD, FGFR4, GPX4, GSTA1, GSTP1, MTHFR, NQO1, TYMS, XPD/ERCC2, XRCC1, UGT1A1, UGT1A6 and UGT2B7. These genes are involved in the metabolism of the studied chemotherapeutics. Because of multiple testing the false discovery rate (FDR) was calculated. Results: We identified 1089 patients treated between 2000-2010 with 3-6 cycles of FEC, for whom germline DNA was available. Homozygous (TT, 0.5%) and heterozygous (GT, 11%) genotypes for rs4148350 in the Multi Drug Resistance Protein I (ABCC1/MRP1), compared to wild-type (GG, 88.5%), were associated with febrile neutropenia, febrile neutropenia in first cycle, prolonged grade 4 or deep neutropenia and thrombocytopenia (80 vs 25 vs 15.7%, 40 vs 17.6 vs 9.5%, 100 vs 41.7 vs 33.8% and 20 vs 2.8 vs 0.34% respectively; p 0.0006, 0.01, 0.002 and 0.008 FDR 0.03, 0.65, 0.06 and 0.2). Variant genotypes for rs45511401 (GT/TT, 12%) in ABCC1, compared to wild-type (GG, 88%), were associated with febrile neutropenia, febrile neutropenia in first cycle and thrombocytopenia (26.5 vs 15.8%, 17.1 vs 9.7% and 3.4 vs 0.3%, respectively; p 0.007, 0.03 and 0.005, FDR 0.2, 0.75 and 0.2). Conclusions: Genetic variation in the ABCC1 gene was strongly associated with severe hematological toxicity of FEC. Other previously described SNP were not validated. This is the largest bc study in which the impact of genetic variability on the adverse events of FEC chemotherapy was investigated.
10-year update of E2197: Phase III doxorubicin/docetaxel (AT) versus doxorubicin/cyclophosphamide (AC) adjuvant treatment of LN+ and high-risk LN- breast cancer and the comparison of the prognostic utility of the 21-gene recurrence score (RS) with clinicopathologic features.

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Background: At 5 years, AT did not improve disease free survival or overall survival and RS was a more accurate predictor of relapse than standard clinicopathologic characteristics for patients with hormone receptor (HR) positive tumors. Methods: A Phase III Intergroup trial tested adjuvant AT vs. AC. Women with 1-3 N+ or N- and T-size > 1cm were randomized to 4 cycles of AT (60 mg/m²/60 mg/ m²) or AC (60 mg/m²/600 mg/m²) q 3 wk x 4. Patients(pts) with ER + and/ or PR + tumors received tam for 5 yrs. Pts were stratified by nodal, HR (ER+/PR+, ER+PR-, ER-PR+, ER-PR-, ER/PR unk) and menopausal status. The primary endpoint was DFS. A sample of 465 pts with HR + breast cancer with 0 to 3 positive axillary nodes who did (N =116) or did not have a recurrence had tumor tissue evaluated using the 21- gene assay. Grade and HR expression were evaluated locally and centrally. Results: 2952 pts were randomized between 7/30/98 and 1/21/00. 2883 were eligible and analyzable. Arms were balanced for age, HR, menopause, nodes, surgery, grade and T-size: median age 51; 64% ER+/PR+; 65% LN-; grade: 10% low, 38% int., 46% high; and median T-size - 2.0 cm. At a median follow-up of 11.5 years the DFS/OS results are shown in the table below. RS was a highly significant predictor of recurrence including node negative and node positive disease (P < .0001) and predicted recurrence more accurately than clinical variables. Conclusions: At 11.5 yrs. median follow-up, there remains no difference in DFS or OS, although there continue to be fewer events in the AT arm in the prespecified ER/PR negative subgroup. At 10 years, the RS continues to be a more accurate predictor of relapse than standard clinical features.

<table>
<thead>
<tr>
<th>Hazard ratio (HR)*, 5-yr DFS</th>
<th>5-yr DFS Hazard ratio (HR)*, 10-yr DFS</th>
<th>Hazard ratio (HR)*, 5-yr OS</th>
<th>5-yr OS Hazard ratio (HR)*, 10-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall DFS</td>
<td>AT AC</td>
<td>AT AC</td>
<td>AT AC</td>
</tr>
<tr>
<td>Overall DFS</td>
<td>1.02 (0.86-1.22), 0.78</td>
<td>1.02 (0.86-1.22), 0.78</td>
<td>1.02 (0.88-1.18), 0.83</td>
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<td>ER +</td>
<td>0.89 (0.71-1.21), 0.32</td>
<td>0.89 (0.71-1.21), 0.32</td>
<td>0.89 (0.76-1.01), 0.34</td>
</tr>
<tr>
<td>ER -</td>
<td>1.28 (1.05-1.62), 0.12</td>
<td>1.28 (1.05-1.62), 0.12</td>
<td>1.28 (1.28-1.65), 0.11</td>
</tr>
<tr>
<td>OS</td>
<td>1.06 (0.85-1.31), 0.22</td>
<td>1.06 (0.85-1.31), 0.22</td>
<td>1.06 (0.85-1.31), 0.22</td>
</tr>
</tbody>
</table>

*HR>1 favors AT; **based on log-rank test.
Comparison of molecular (BluePrint + MammaPrint) and pathological subtypes for breast cancer among the first 800 patients from the EORTC 10041/BIG 3-04 (MINDACT) trial.

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Background: Biology has become the main driver of breast cancer therapy. Intrinsic biological subtypes by gene expression profiling have been identified. Pathology can be used to define surrogates of these subtypes but these are not always concordant, which may lead to different treatment plans. We investigated the concordance between BluePrint (BP) + MammaPrint (MP) (micro array based) breast cancer subtypes and pathological surrogates (based on ER, PR, HER2, and Ki67). Contrary to the Perou gene set (evolved into PAM50), BluePrint was trained using pathological data. Methods: Using available data (centrally assessed pathology and genomic) from the MINDACT pilot phase (Rutgers et al 2011) 621 tumors were analyzed. Two pathology classifications were used: one with 4 categories and one with 5 categories (Goldhirsch et al 2011). Based on BP 3 subtypes are formed: Luminal, HER2 and Basal. The Luminal subtype is further split into Luminal A (MP low risk) and Luminal B (MP high risk). Results: See table. Conclusions: All pathological Basal cases are BP Basal, apart from 1 BP HER2 case. Of the BP Basal cases, 15 are not pathological Basal: 1 is Luminal A, 11 are Luminal B (of which 8 are IHC ER/PR borderline (≥1% and <10%)) and 3 are HER2. All pathological Luminal (A & B) that are BP HER2 are HER2- by TargetPrint. 25 of the 26 pathological HER2+ that are BP Luminal A are ER+. Most discordant cases are seen within the Luminal subtype, indicating that Ki67 discriminates Luminal A vs. B differently than MammaPrint does.

The observed subtype discrepancies reveal potential important impact for treatment-decision making. MINDACT will provide important information.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>4 category</th>
<th>5 category</th>
<th>Luminal A BP Luminal MP low risk</th>
<th>Luminal B BP Luminal MP high risk</th>
<th>HER2 BP HER2</th>
<th>Basal BP Basal</th>
<th>Total</th>
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<tr>
<td>Luminal A</td>
<td></td>
<td></td>
<td>263</td>
<td>19</td>
<td>4</td>
<td>1</td>
<td>287</td>
</tr>
<tr>
<td></td>
<td>ER- and PR-</td>
<td>HER2-</td>
<td>(all TP*) HER2-</td>
<td></td>
<td></td>
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<tr>
<td>Luminal B</td>
<td>ER- and PR-</td>
<td>HER2+</td>
<td>111</td>
<td>70</td>
<td>(all TP*) HER2-</td>
<td>11</td>
<td>196</td>
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<tr>
<td></td>
<td></td>
<td>HER2-</td>
<td></td>
<td></td>
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<td>HER2+</td>
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<td>3</td>
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<td>(all ER+)</td>
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<tr>
<td></td>
<td></td>
<td>HER2+</td>
<td></td>
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<tr>
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<td>ER-, PR-,</td>
<td>HER2-</td>
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<td>0</td>
<td>(all TP*) HER2-</td>
<td>61</td>
<td>62</td>
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<tr>
<td></td>
<td>HER2-</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>400</td>
<td>92</td>
<td>55</td>
<td>76</td>
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*TP = TargetPrint.
Prognostic and predictive impact of Ki-67 before and after neoadjuvant chemotherapy on PCR and survival: Results of the GeparTrio trial.

Gunter Von Minckwitz, Berit Mueller, Jens U. Blohmer, Manfred Kaufmann, Holger Eidtmann, WOLFGANG Eiermann, Bernd Gerber, Hans Tesch, Joern Hilfrich, Jens Bodo Huober, Tanja N. Fehm, Jana Barinoff, Christian Jackisch, Judith Prinzler, Thomas Ruediger, Erhard Erbstoesser, Sibylle Loibl, Carsten Denkert; German Breast Group, Neu-Isenburg, Germany; Charité Universitätsmedizin, Berlin, Germany; University Hospital, Frankfurt, Germany; Universitätsklinikum Schleswig-Holstein - Klinik für Gynäkologie und Geburtshilfe, Kiel, Germany; Klinikum zum Roten Kreuz, Muenchen, Germany; Klinikum Süd, Department of Obstetrics and Gynecology, Rostock, Germany; Fachpraxis, Frankfurt, Germany; EilenriedeKlinik, Hannover, Germany; University of Tuebingen and Kantonsspital St. Gallen, St. Gallen, Switzerland; University Hospital Tuebingen, Department of Obstetrics and Gynecology, Tuebingen, Germany; Department of Gynecology and Gynecologic Oncology, Klinik-Even-Mitte, Essen, Germany; Klinikum Offenbach, Offenbach, Germany; Charité-Universitätsmedizin Berlin, Berlin, Germany; Staedisches Klinikum Karlsruhe, Karlsruhe, Germany; Harz Klinikum, Wernigerode, Germany; Charité Universitätsmedizin Berlin, Berlin, Germany

Background: We previously reported as a result of the GeparTrio phase III trial that response-guided neoadjuvant chemotherapy (CT) with TACx8 or TAC/NX, compared to TACx6, can improve survival especially in hormone-receptor (HR)-positive tumors. As this benefit could not be predicted by pathological complete response (pCR), better surrogate response markers are warranted. Methods: 2072 patients with operable or locally advanced breast cancer were treated with 2 cycles TAC before interim response assessment. Responders were randomized to additional TACx4 or TACx6 and non-responders to TACx4 or NXx4. We centrally measured Ki-67 in 1165 pre-CT core biopsies and in 676 post-CT surgical samples. Counting patients with a pCR as having 0% Ki-67, 757 pre-/ post-CT pairs were available. Ki-67 percentage levels were grouped to low (0-15%), moderate (15.01-35%), and high (35.01-100%) according to cut-point finding analysis in a training and validation cohort. Results: pCR rates were 4.2%, 12.9%, and 29.0% in tumors with low, moderate, and high pre-CT Ki-67 levels (p<0.0001). Pre-CT Ki-67 levels significantly predicted disease-free survival (DFS) (log rank p<0.0001) overall, in the HR+ (p<0.0001), but not in the HR- (p=0.5) subgroup. Post-CT Ki-67 levels correlated with DFS (p<0.0001). Patients with low post-CT Ki-67 levels showed comparable outcome to patients with pCR. Patients with increased Ki-67 levels from before to after CT showed an impaired outcome compared to patients with stable or decreased Ki-67 levels (p<0.0001). However, post-CT Ki-67 levels appeared to have more prognostic relevance than Ki-67 changes. Low post-CT Ki-67 levels were not more frequent after response-guided treatments (response-guided vs conventional: p=0.153; TACx6 vs TACx8: p=0.335; TACx6 vs TAC/NX: p=0.420). Similar negative results were found for HR+ and HR- subgroups. Conclusions: Pre-CT Ki-67 levels are predictive for pCR and prognostic for DFS. Post-CT Ki-67 levels and changes between pre- and post-CT Ki-67 levels are prognostic for DFS. As neither could predict different treatment effects on DFS, Ki67 cannot replace pCR as a surrogate marker for outcome after neo-adjuvant CT.
A gene expression signature of MEK pathway activation to predict survival in triple-negative breast cancer.

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Background: Tumor cell proliferation measured by Ki67 in the surgically removed tumor after neoadjuvant chemotherapy (NAC) has been shown to predict patient outcome in breast cancer. It is unclear from these studies if breast cancer subtype may account in part for the predictive ability of Ki67. Thus, we tested whether Ki67 score in the surgically-resected residual tumor (RT) after NAC predicted outcome in a cohort of triple negative breast cancer (TNBC). Gene expression profiling was performed to identify molecular subtype and test the association with gene modules indicative of signaling pathway activation. Methods: Ki67 was scored in the RT of 89 patients with stage II-III TNBC (ER/PR/HER2 negative by IHC at diagnosis) that had been treated with NAC. Expression levels for 450 genes were quantified by Nanostring.Ki67, node and menopause status, age, therapy type (± taxanes), molecular subtype, and gene expression scores were tested for association to RFS and OS using univariate and multivariate CoxPH models. Results: Ki67 score in the post-NAC RT demonstrated a wide range (1.5-77.7%; median: 36.2%). Twenty seven % of RTs were 3+ HER2 by IHC. Molecular subtype in the RT was as follows: 64% Basal-like; 20% HER2-enriched; 6% LumA; 6% LumB; 4% Normal-like. In univariate analyses to respectively predict RFS and OS, node status (p=0.005 and p=0.02), number of nodes (p=0.003 and p<0.001), and the score of a gene expression module of MEK pathway activation (p=0.04 and p=0.01,) were significant. Basal-like subtype approached significance for RFS (p=0.1) and OS (p=0.05). In multivariate analyses, node status (p=0.002 for RFS and p<0.001 for OS) and MEK pathway activation score (p=0.04 and p=0.01) were significant predictors. Conclusions: Ki67 in the RT after NAC was not predictive of outcome in a cohort of TNBC. However, a gene expression signature of activated MEK was negatively associated with outcome. These data are consistent with the reported preclinical activity of MEK inhibitors against basal-like breast cancer cells and a possible role of this signaling pathway in chemotherapy resistance. They also support deep sequencing studies to identify genetic alterations in the RAS/MEK/MAPK pathway in TNBC.
NSABP FB-6: Phase II trial of weekly paclitaxel (WP) and pazopanib following doxorubicin and cyclophosphamide (AC) as neoadjuvant therapy for HER2-negative locally advanced breast cancer (LABC).

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Background: Pazopanib is an oral, small molecule inhibitor of VEGFR-1, -2, and-3, PDGFR-α, and -β, and c-kit tyrosine kinases. The purpose of this trial was to determine the activity and safety profile of pazopanib when added to neoadjuvant WP following AC in LABC. The primary endpoint was pathologic complete response in the breast and nodes (pCR-BN). Methods: Women with HER2-negative stage IIIA-IIIC breast cancer were treated with AC (60 mg/m²/600 mg/m²) for 4 cycles every 3 weeks followed by WP 80 mg/m² on days 1, 8, and 15 every 28 days for 4 cycles concurrently with pazopanib 800 mg orally daily prior to surgery. Postoperatively, pazopanib was given for 6 months. The regimen would be considered active if ≥14 responses (16% pCR rate in breast and nodes) were observed in 87 evaluable patients. Patients were considered evaluable if they received at least 1 dose of pazopanib.

Results: Between July 2009 and March 2011, 101 pts (median age 51 yrs, range 30-71) were enrolled; 56% had stage IIIA, 34% stage IIIB, and 10% stage IIIC disease. 74 pts (73%) had ER-and/or PR-positive tumors and 27 pts (27%) were triple negative. 8 patients did not begin pazopanib. The pCR-BN rate in evaluable patients for whom surgical information was known was 18% (16/89). The pCR-BN rate in ER positive disease was 9% (6/65) and was 42% (10/24) in TNBC. Toxicities observed with WP and pazopanib included diarrhea (gr 2/3, 10%/5%), hand-foot syndrome (gr 2/3, 11%/1%), hypertension (gr 2/3, 12%/3%), neuropathy (gr 2/3, 14%/1%), and neutropenia (gr 3/4, 25%/1%). Liver toxicity during WP and pazopanib included ALT (gr 2/3/4, 13%/7%/1%), AST (gr 2/3, 7%/7%), and total bilirubin (gr 2, 2%). Conclusions: A regimen of WP and pazopanib following AC was active as neoadjuvant therapy in women with LABC and met the pre-specified criteria of interest. The activity in TNBC was notable. The toxicity profile of WP and pazopanib was consistent with previous experience. Support: GlaxoSmithKline.
A phase II study of preoperative (preop) bevacizumab (bev) followed by dose-dense (dd) doxorubicin (A)/cyclophosphamide (C)/paclitaxel (T) in combination with bev in HER2-negative operable breast cancer (BC).

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Background: Two recent preop studies evaluating bev showed conflicting results, particularly in hormone receptor (HR)+ BC. Identification of predictive markers and their relationship to the pharmacodynamic effects of bev would facilitate the identification of BCs most likely to benefit from bev. To accomplish these goals, we conducted a unique preop trial with a run-in of single agent bev followed by ddACT with bev in two cohorts, one with HR+HER2– BC, and a smaller triple negative (TN) cohort. Methods: Pts with HR+, HER2– or TN BC were eligible if their tumor (T) was ≥1.5 cm and high grade, or had axillary LN involvement; or if T≥2.5cm and was low/intermediate grade. Treatment consisted of a single dose of bev 10 mg/kg, followed two wks later by A 60 mg/m² and C 600 mg/m² with bev 10 mg/kg q2 wks x 4, followed by T 175 mg/m² with bev 10 mg/kg q2 wks x 3, followed by T 175 mg/m² x1. Research core biopsies and interstitial fluid pressure (IFP) were assessed pre- and post- bev alone. Pathologic response was confirmed centrally and Miller-Payne (MP) was assessed. Results: 84 pts with HR+ and 20 pts with TN breast cancer were enrolled. Amongst HR+ pts, 74 had surgical tissue centrally reviewed, and 6 (8%) had a pCR. Amongst TN pts, 18 pts had tissue centrally reviewed and 8 (44%) had a pCR. Grade was found to predict MP response in both HR+ and TN pts (p=0.001). Several biomarkers were evaluated as predictors of response to bev. Baseline sVEGFR1 correlated with MP response to treatment among TN pts (p=0.015). Single-agent bev reduced the mean vascular density by 18.5% (p=0.049) in HR+ patients and the mean IFP in the overall cohort and HR+ patients by 20 (p=0.020) and 24.5% (p=0.001), respectively. The reductions in IFP correlated with higher levels of sVEGFR2 (p=0.003). The IFP decreased > 50% in 24/65 pts and did not change in others. Gene expression profiling by PAM50 is underway. Conclusions: The addition of bev to preop chemotherapy is well tolerated. Tumor grade appears to predict MP response in HR+ and TN tumors, and sVEGFR1 may be a predictor of MP response to bev in TN tumors. Further work for biomarker predictors of response to bev is ongoing.
Association of a compact 13-gene VEGF signature with OS in E2100.

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Background: E2100, an open-label, randomized, phase III trial, demonstrated a significant improvement in progression free survival and overall response rate with paclitaxel plus bevacizumab compared with paclitaxel alone as initial chemotherapy for patients with HER2-negative metastatic breast cancer. Genentech completed additional clinical trials and submitted these data to the FDA. On 18 Nov, 2011, the FDA Commissioner revoked the agency’s approval of bevacizumab for the breast cancer indication because of the lack of evidence of an improvement in overall survival or a clinical benefit to patients sufficient to outweigh the risks. However, the Commissioner “encouraged Genentech to consider additional studies to identify if there are select subgroups of women who might benefit from this drug”. Hu et al. (BMC Medicine 2009) published a compact 13 gene VEGF-signature associated with distant metastases and poor outcomes. Supervised analyses comparing patients with distant metastases versus primary tumors or regional metastases showed that the distant metastases were distinct and distinguished by the lack of expression of fibroblast/mesenchymal genes, and by the high expression of a 13 gene profile that included VEGF, ANGPTL4, ADM and the monocarboxylic acid transporter SLC16A3. Methods: We have investigated the VEGF signature in silico on Illumina DASL analysis of 122 FFPE samples remaining from E2100. Results: PFS benefit is seen for pacli + bev vs pacli in both treatment arms with the low VEGF signature (HR 0.45 95% CI .27-.77 p .009 n 67) and with the high VEGF signature (HR 0.57 95% CI .32-1.0 p .015 n 55). However, OS benefit is only seen for pacli + bev vs pacli in the high VEGF group (HR 0.56 95% CI .30-1.05 p .02 n 52) and not in patients with the low VEGF signature (HR 1.12 95% CI .66-1.90 p .81 n 67). Conclusions: Hence, this signature, which suggests that the response to hypoxia includes the ability to promote new blood and lymphatic vessel formation, shows great potential as a predictive biomarker of those patients to whom bevacizumab would convey an OS advantage benefit. We note with great caution that this exploratory analysis of trial subset is underpowered, hence, this compact VEGF signature is being pursued in other bevacizumab trial sets.
Are mastectomy rates really increasing? Experiences from a single institution and a population-based database.

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**Background:** Recent studies have reported increased mastectomy rates for the treatment of early stage breast cancer during the last decade. The aims of this study were to examine trends in mastectomy rates at a single institution and in a population-based database and to compare differences between the two cohorts.

**Methods:** Patients with stage 0-II breast cancer diagnosed from 2000 to 2008 were identified from our cancer center institutional database (CC cohort, n=8,915) and the Surveillance, Epidemiology and End Results database (SEER cohort, n=359,572). Patients without primary surgery or unknown surgery type were excluded. Mastectomy rates by the year of diagnosis were evaluated and multivariable logistic regression models were built to identify clinicopathologic factors that predicted mastectomy as the treatment choice.

**Results:** The proportion of patients treated with mastectomy decreased from 44.5% to 37.8% between 2000 and 2005 in the CC cohort (P<0.003) and from 42.8% to 36.6% in the SEER cohort (P<0.0001). Subsequently, the mastectomy rate increased to 48.6% in the CC cohort (P<0.0001) and to 40.1% in the SEER cohort by 2008 (P<0.0001). Multivariable analysis found that patients with younger age (<50), stage 0 or II cancer vs. stage I, high grade tumor, low median household income, and lobular histology were more likely to choose mastectomy in both the SEER and CC cohorts. In the CC cohort, patients with preoperative breast MRI were also more likely to undergo mastectomy. The percentages of patients receiving preoperative MRI and choosing prophylactic contralateral mastectomy increased each year in the CC cohort. The rate of preoperative breast MRI increased from 4.7% in 2005 to 9.6% in 2008 (P<0.0001). Patients choosing prophylactic contralateral mastectomy increased from 8.4% in 2005 to 11.8% in 2008 (P=0.06).

**Conclusions:** Our study shows that there was a decrease in mastectomy rates from 2000 to 2005 and a subsequent increase in mastectomy rates from 2005-2008 in both the CC and SEER cohorts. Increased use of preoperative breast MRI and the decision to undergo contralateral prophylactic mastectomy likely contributed to the increased mastectomy rates in the CC cohort.
Breast cancer multifocality-multicentricity and locoregional recurrence.

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**Background:** The impact of multifocality (MF) and multicentricity (MC) on locoregional (LR) control for invasive breast cancer, and the optimal local treatment strategy for these tumors, is unknown. In particular, there is disagreement in the literature regarding the use of Breast Conservation Therapy (BCT). We evaluated a large single institution cohort of MF and MC breast cancers to determine if they had inferior LR control rate when compared to their unifocal counterparts. **Methods:** MF and MC were defined pathologically as more than one lesion in the same quadrant and more than one lesion in separate quadrants, respectively. Patients were categorized by presence or absence of MF or MC disease and by the LR treatment modality received – BCT (n=256), mastectomy alone (n=466), or mastectomy plus post-mastectomy radiation therapy (n=184). 10 patients who underwent BCT for MC disease against physician advice were excluded. MF and MC tumors were analyzed both as a group and as separate entities. Kaplan-Meier product limit method was used to calculate 5-year LR control rate. Cox proportional hazards models were fit to determine independent associations of MF/MC disease with LR control. **Results:** Median follow up was 52 months. Out of 3722 patients with stage I-III disease who did not receive neoadjuvant chemotherapy, 906 (24%) had MF (n=673) or MC (n=233) disease. 5-year rate of LR control rate was 99% in the MF group, 96% in the MC group, and 98% in the unifocal group, (p = 0.44). Subset analysis revealed no statistical difference in LR control regardless of the type of LR treatment, (p = 0.67 in the BCT group, p = 0.37 in the mastectomy alone group, and p = 0.29 in the mastectomy plus post-mastectomy radiation therapy group). There were 21 in-breast recurrences after BCT (8.2%). After controlling for other risk factors, MF and MC did not have an independent impact on LR control rate. **Conclusions:** MF and MC disease are not independent risk factors for LR recurrence. Patients with MF and MC breast cancer had similar rates of LR control to their unifocal counterparts, regardless of LR treatment modality. Our data suggest that BCT is a safe option for patients with MF tumors and that MF or MC disease alone is not an indication for post-mastectomy radiation therapy.

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Background: Brachytherapy as an alternative to whole-breast irradiation (WBI) for early-stage breast cancer has disseminated into clinical practice; however, current national treatment patterns and associated complications remain unknown. Methods: We constructed a national sample of Medicare beneficiaries aged 66 to 94 who underwent breast conserving surgery in 2008-2009 and who were treated with brachytherapy or WBI. We used hospital referral regions to assess national treatment variation and an instrumental variable analysis to compare complication rates between treatment groups, adjusting for patient and clinical characteristics such as age, number of comorbidities, receipt of chemotherapy or screening mammogram, and type of radiation facility. We compared one-year overall, wound and skin, and deep tissue and bone complications between brachytherapy and WBI using specific procedure and diagnosis codes identified in Medicare claims. Results: Of the 29,648 women in our sample, 4,671 (15.8%) received brachytherapy. The median percent of patients receiving brachytherapy varied substantially across hospital referral regions (interquartile range: 7.5%-23.3%). In the bivariate analysis, 34.3% of women treated with brachytherapy had a complication compared to 27.3% of those who received WBI (P<0.001). After adjusting for patient and clinical characteristics, 35.3% (95% CI: 34.7, 35.8) of women treated with brachytherapy had a complication compared to 18.7% (95% CI: 18.2,19.2) treated with WBI (average predicted difference: 16.5%, 95% CI: 15.8, 17.3, P<0.001). While brachytherapy was associated with a 16.9% (95% CI: 10.0, 23.8, P<0.001) higher absolute percentage of wound and skin complications compared to WBI, there was no difference in deep tissue and bone complications. Conclusions: Brachytherapy is commonly used among Medicare beneficiaries; in some regions nearly one in four women who underwent adjuvant radiation received brachytherapy. After one year, wound and skin complications were significantly more common among women who received brachytherapy compared to those receiving WBI, but there was no difference in deep tissue and bone complications.

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Background: The treatment for patients with DCIS remains controversial. Current guidelines based upon best available evidence suggest that breast-conserving surgery (BCS) followed by adjuvant radiation therapy (RT) result in acceptable local control and breast cancer-specific survival. The purpose of this study was to analyze trends in patterns of care as well as identify factors associated with surgery type and use of adjuvant radiation therapy in a select cohort of patients enrolled into the SEER database.

Methods: The study included females 18 years and older with focal DCIS and known tumor size of 5 cm or less diagnosed between 1996 and 2007. The Cochran-Armitage trend test was applied to identify trends in the use of BCS and RT over time. Multivariate logistic regression analyses were used to determine factors associated with receiving BCS vs. mastectomy and BCS plus RT vs. BCS alone. Cox proportional hazard model was used to determine associations with breast cancer-specific mortality.

Results: Of the 34,233 women with DCIS, 76.59% were treated with BCS. 66.36% of BCS patients received adjuvant RT over the study period. The proportion of women receiving BCS increased from 71.5% in 1996 to 76.9% in 2007 (p<0.0001). Additionally, the proportion of women who underwent BCS and received adjuvant radiation therapy over the same time period increased from 55.3% to 69.7% (p<0.0001). Multivariate analysis demonstrated that year of diagnosis, race, marital status, geographic region, tumor size, tumor grade and comedo necrosis all were significantly associated with the use of adjuvant radiation therapy, but age was not. Cox proportional hazards models did not associate either surgery type or use of adjuvant radiation in patients undergoing BCS with breast cancer-specific mortality.

Conclusions: Based upon reporting within the SEER database, the proportion of DCIS patients undergoing BCS and the BCS patients receiving adjuvant radiation increased over the study time period. Surgery type and use of adjuvant radiation therapy in patients with BCS was not associated with decreased risk of breast-cancer specific death in this cohort.
Impact of surgery and radiation of the primary among women with de novo stage IV breast cancer.

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Background: The aim of this retrospective study was to determine the impact of surgery(S) and radiation(R) therapy to the primary tumor among patients (pts) with stage IV denovo breast cancer. Methods: The SEER registry was used to identify pts with denovo stageIV breast cancer diagnosed between 1988 and 2008. Pts were divided into 4 groups based on type of treatment to primary tumor: both S+R, S alone, R alone, or no treatment of primary (no S/R). Breast cancer specific survival (BCS) was calculated from the date of diagnosis of breast cancer to the date of death from breast cancer or last follow up. Survival outcomes were estimated by the Kaplan-Meier method, and Cox models were fit to determine the association between treatment of primary and survival after adjusting for potential confounders (e.g age, grade, hormone receptor and race). Results: 25903 pts were identified; 4640 (17.9%) S+R, 6556 (25.3%) S, 4467 (17.2%) R, and 10240 (39.5%) no S/R. 1183 (4.6%) had surgery to sites other than the primary. Median age was 63 years. Median follow-up was 14 months. Median BCS was 23 months. Median BCS among pts who underwent S+R, S, R and no S/R was 36 months, 31 months, 18 months and 15 months respectively (p<0.0001). Among pts who underwent S+R, median BCS among pts who did and did not have surgery to sites other than primary was 50 months and 41 months respectively (p=0.029). Of the pts treated with S+R 10-year BCS was 18%. In the multivariable model compared to women who were in the no S/R group those who underwent S (HR= 0.59, 95%CI 0.55- 0.62,p<0.0001) and S+R (HR=0.51, 95%CI 0.47-0.55,p<0.0001) had decreased risk of death from breast cancer and those who underwent R (HR=1.13, 95% CI 1.04-1.21, p=0.002) had an increased risk of death from breast cancer. Pts who had surgery to sites other than the primary tumor had decreased risk of death from breast cancer compared to those who did not (HR=0.80, 95%CI 0.72-0.89,p<0.0001). Conclusions: Our results indicate that S+R of the primary breast tumor among pts with denovo stage IV breast cancer maybe associated with a decreased risk of death from breast cancer. A select subgroup of pts who undergo S+R may also benefit from surgery to sites other than the primary which may afford them maximum survival advantage.
Utilization of post-lumpectomy radiation therapy in women 70 years of age or older: A report from the National Cancer Data Base.

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**Background:** The Cancer and Leukemia Group B (CALGB) 9343 trial published in 2004 showed no overall survival benefit from radiation in patients >70 years old with estrogen receptor (ER) positive, pT1 tumors with the use of tamoxifen. We tested the hypothesis that the use of radiotherapy decreased in this group of patients following publication of the trial, utilizing the National Cancer Data Base. **Methods:** 34,853 breast cancer patients 70 years or older with pT1N0/NX, ER positive tumors who underwent a lumpectomy between 2004 and 2007 were studied. Chi-square tests and logistic regression models were used to determine trends and factors related to the use of radiation. **Results:** The use of radiation decreased from 70.6% in 2004 to 66.4% in 2005, 66.6% in 2006, and 67.2% in 2007 (p<0.001). The use of standard external beam radiation decreased from 58.8% in 2004 to 45.8% in 2007 while the use of accelerated partial breast radiation using brachytherapy (APBI) increased from 4.5% to 10.0%, IMRT radiation from 3.1% to 5.3%, and 3D conformal radiation from 3.7% to 5.7% (p<0.001). Patients between the ages of 86+ years old were less likely to undergo radiation than patients 70-75 years old (OR=0.12, 95% CI: 0.11-0.13). Asian Pacific Islanders were more likely to undergo radiation than whites (OR=1.39, 95% CI: 1.13-1.70). In community cancer programs, 67% patients received radiation, compared to 69.1% in comprehensive community programs and 65.5% in academic programs (p<0.001). The use of radiation varied by facility location; 73.5% of facilities located in the Midwest radiated these patients as opposed to 62.6% in the South. In patients who had no nodes examined, 37% underwent radiation as opposed to 74% who did have nodes examined (p<0.001). Likewise, 79.4% of patients who received hormone therapy underwent radiation as opposed to 54.6% of patients who did not receive hormonal therapy (p<0.001). **Conclusions:** The use of radiation therapy decreased only slightly and remained high in women with ER+ stage I breast cancer over the age of 70, despite findings from the CALGB 9343 study. However, there was a large shift in radiation modality over the study period in the older patients.
Impact of adjuvant chemotherapy on recurrence-free survival in patients with pT1a/b hormone-negative and HER2-positive breast cancer.

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Background: T1ab triple-negative (TN) or Her-2-positive (H2+) breast cancers are reported to pose relatively high risk of relapse, but benefits of adjuvant chemotherapy are uncertain. We studied the impact of chemotherapy on recurrence-free survival in this group. Methods: Records of all consecutive cases diagnosed in Brown-affiliated centers in 2000 - 2010 were reviewed. Factors influencing chemotherapy decision were studied with logistic regression, and recurrence-free interval (RFI) with a Cox proportional hazard model and Kaplan-Meier estimator. Results: Among 1415 screened T1a/b N0 cases, 161 were eligible (57 TN; 104 HER2+), with a median age of 57 years; 66% tumors were T1b. 20% of patients underwent mastectomy, 76% received radiation and 30% hormonal therapy. Adjuvant chemotherapy was recommended in 53% of cases. Younger age (p<10^-6), stage T1b (p<10^-5), high grade (p=0.001), HER2+/ERPR- status (p=0.017) and diagnosis after 2006 (p=0.007) were significantly predictive of the medical oncology recommendation. There was a significant trend with decrease in anthracycline (p<0.001) and increase in taxane use (p<0.001). With a median follow up of 46 months, the 5-year rate of relapse was 6.1% (95%CI 2.7-13.9%), somewhat higher in T1b tumors (8.1%) and without detectable difference in TN/HER2+ subgroups. In a univariate analysis chemotherapy did not significantly impact the recurrence-free interval (HR=0.45; 95%CI 0.09-2.34; p=0.32), however there was a detectable benefit (p=0.02) for T1b tumors in a multivariable Cox model including age (p=0.02) and LVI (p=0.01). The histology, type of surgery and year of diagnosis were not significant. There were no relapses among ER/PR+ patients who received hormonal therapy or HER2+ patients who received trastuzumab. Conclusions: The risk of relapse in biologically aggressive T1ab breast cancers is very low with judicious use of adjuvant therapy. The benefit of chemotherapy is likely restricted to the highest-risk patients with T1b tumors, lymphovascular invasion and younger age.
Pathologic complete response rates observed in women with locally advanced and inflammatory breast cancer receiving neoadjuvant carboplatin and paclitaxel.

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Background: Pathologic complete response (pCR) following neoadjuvant chemotherapy (NCT) is predictive of outcome in patients with locally advanced breast cancer (LABC). A non-anthracycline containing NCT regimen (Sikov et al. JCO 10/09) may reduce the risk of associated secondary hematologic malignancies and cardiac toxicity while yielding comparable pCR rates. Methods: A retrospective review of all LABC and inflammatory breast cancer (IBC) cases treated from 4/09 to 12/11 with a NCT regimen of carboplatin (AUC of 6, administered on day 1) and paclitaxel 80 mg/m² (given weekly on a 21-28 day cycle) was conducted at the City of Hope Cancer Center (COHCC). Pts with HER2+ (HER+) tumors received trastuzumab during the NCT treatment. All pCRs (pCR of primary only – "pCR1°"; pCR of primary and lymph nodes – "pCR-All") were determined by a COHCC pathologist based on final surgical specimens.

Results: 38 pts were identified, with 39 breast primaries; 18% had IBC, 62% of LABCs/IBCs were hormone receptor positive (HR+), 46% of tumors were HER2+, and 26% were triple negative. Median age was 51 [27-63]. All pts completed the planned number of cycles. Four pts required carboplatin dose reductions, 4 pts required dose reductions in paclitaxel, 3 pts had paclitaxel changed to nab-paclitaxel, and 17 pts required G-CSF to complete their planned treatment. One pt receiving trastuzumab experienced asymptomatic LVEF decline below normal limits.

Conclusions: A non-anthracycline-containing NCT regimen of carboplatin/paclitaxel was well tolerated and resulted in high pCRs when given to triple negative (HER2-/HR-) pts, and HER2+ pts, especially with HER2+HR- subtypes. The findings warrant further studies of this regimen in a prospective randomized setting.

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A phase II study of foretinib in triple-negative, recurrent/metastatic breast cancer: NCIC CTG trial IND.197 (NCT01147484).

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Background: Met, a receptor tyrosine kinase, is preferentially expressed in basal-like compared to luminal breast cancer. In murine models, overexpression of the oncogenic Met receptor transgene induces tumors with human basal gene expression characteristics supporting Met inhibition as a treatment strategy for triple negative (TN) breast cancer. Foretinib is an oral multi-kinase inhibitor of Met, RON, AXL, TIE-2 and VEGF receptors with anti-tumor activity in advanced HCC and papillary renal cell cancer. Methods: Patients (pts) with TN breast cancer and 0-1 prior regimens for metastatic disease received daily foretinib 60 mg po in a 2-stage single arm trial. Primary endpoints were objective response and early progression rates per RECIST 1.1. Tumor samples were centrally reviewed to confirm ER/PR/HER2 status and for correlative studies including Met, PTEN and EGFR expression. Stage 1 accrual required 23 response-evaluable Met unselected patients with accrual continuing if ≥1 response or ≥17 early progressions (PD ≥17 weeks on study) were observed. Results: Accrual is 29 pts to date; 24 are eligible, 22 evaluable for toxicity and 15 for response. Median age is 56 y (43-81), ECOG PS 0-1 in 23/24. Grade 3 laboratory adverse events were: lymphopenia (9%), elevations in ALT (5%), GGT (5%) and INR (5%). Treatment-related non-hematologic toxicities included (all/grade 3-4) fatigue (64%/5%), nausea (55%/5%), diarrhea (41%/5%), hypertension (32%/14%), vomiting (27%/0%), anorexia (23%/5%) and rash (14%/0%). Three SAEs possibly related to foretinib included; asymptomatic pulmonary embolism, reversible CHF and pleural effusion with QTc prolongation. One PR (7%), 8 early PD (53%) and 6 SD (40%) have been observed to date with median SD duration of 5.4 months (range 2.7-5.5). Preliminary correlative results (IHC): 5/8 (62.5%) evaluable Met positive cases had SD and 4/5 (80%) Met negative cases had PD as best response. Met IHC was negative in the pt with PR. Conclusions: Foretinib shows preliminary evidence of activity and tolerability in metastatic, TN breast cancer. Stage 2 of accrual will include 15 pts with pre-treatment biopsies of metastases and circulating tumor cell collection.

Comprehensive investigation of adverse event (AE)-related costs in patients with metastatic breast cancer (MBC) treated with first- and second-line chemotherapies.


Background: MBC is incurable and managed with ongoing therapy. This study examined the incremental costs of chemotherapy-associated AEs in MBC. Methods: The PharMetrics Integrated Database (2000-2010) was used to identify MBC pts treated either 1st or 2nd line with a taxane (T) (paclitaxel or docetaxel) or capecitabine (C)-based regimen for ≥30 days (defined as a treatment episode (TE)). Incremental costs attributable to AEs were assessed by comparing costs incurred during TEs with and without AEs. AEs were identified using medical claims with a diagnosis for ≥1 event of interest (e.g., infections, fatigue, anemia, neutropenia). Pt characteristics were balanced between comparison groups (with and w/o AEs) using inverse probability weighting method. Incremental monthly costs due to AEs were estimated during the TEs and included the following cost components: inpt (IP), outpt (OP), emergency room (ER), other medical service, pharmacy costs (chemotherapy and other drugs), and total healthcare costs. Statistical comparisons were conducted using Wilcoxon tests. Results: 3,222 women (mean age=57) received a T or C as 1st or 2nd-line therapy for MBC. Of the 2,678 1st-line pts, 69.7% received T and 30.3% with C; average monthly total costs ranged from $9,159 to $10,298. AEs were commonly seen in pts treated with 1st-line T and C (94.6% and 83.7%). On average, the total monthly incremental cost associated with AEs was 38% higher ($3,547) for T and 9% higher ($854) for C. IP and other drug costs accounted for a majority of these costs. Of 1,084 2nd-line pts, 66% received T and 34% C, with average monthly total costs ranging from $5,950 to $12,979. 94.4% of T pts and 84% of C pts in the 2nd-line had an AE. The average total monthly incremental cost associated with AEs for T was $5,320 and $4,933 for C (69.5% and 82.9% higher vs pts w/o AEs). Pharmacy costs accounted for a majority of increased costs seen in pts with AEs treated with T; IP and OP accounted for a majority of these costs in pts treated with C. Conclusions: This is the 1st study assessing costs associated with AEs for tx of mBC. AEs are associated with a substantial economic burden that is mainly explained by increased IP, OP, and pharmacy costs.
Single institution experience with neoadjuvant chemotherapy for metaplastic breast cancer (MBC).

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**Background:** Metaplastic breast carcinoma (MBC) is a rare subtype that accounts for <1% of all breast carcinomas. MBC is frequently triple negative and neoadjuvant chemotherapy (NAC) is often used in triple negative breast cancer (TNBC). The objective of this analysis is to ascertain response rates of MBC to NAC as compared to non-metaplastic TNBC. **Methods:** We searched the Magee Women’s Cancer Center of UPMC IRB-approved neo-adjuvant treatment database which contains outcome data on 594 patients treated from 2004-2010. 116 patients with triple negative breast cancer (ER/PR negative or ER/PR weakly positive (H score of 10 or less) and HER2 negative or indeterminate (HER2 1+ or 2+ without amplification by FISH)), were identified. Nine of these TNBCs had metaplastic subtype and 2 groups were analyzed: metaplastic breast carcinoma (MBC) (N = 9) and non-metaplastic breast carcinoma (NMBC) (N = 107). Tumor volume reduction (TVR), pathologic complete response (pCR), recurrence and mortality were compared in both groups. **Results:** Mean follow up in MBC group was 43 months and no patients were lost to follow up. Mean tumor size on presentation in MBC group was 4.47 cm while in NMBC group it was 3.33 cm. pCR was noted in 0/9 MBC and 43/107 NMBC cases (p = 0.0253). 6/9 patients had mastectomy, 2/9 had breast conserving surgery (BCS) and 1/9 patients did not have a surgery yet. Average TVR was 28% in MBC cases compared to 74% in NMBCs when cases with pCR were included (p = 0.0001) and 56% when cases with pCR were excluded (p = 0.0202). Follow up on 9 MBC cases revealed 1 recurrence and subsequent death (11%). Follow up on 64 NMBC patients who failed to achieve pCR revealed 22 recurrences (34%) and 18 of them subsequently died (28%). Follow up on 43 NMBC cases that achieved pCR revealed 3 recurrences (7%) and 1 death (2%). **Conclusions:** MBC was characterized by larger size at baseline as compared to NMBC. There were no pCR’s seen in MBC, but some MBC did achieve response that allowed for breast conservation. Although the average tumor volume reduction was significantly less in MBC compared to NMBC, the NMBC that failed to achieve pCR fared much worse than MBC who did not achieve pCR. Therefore, the triple negative paradox is likely not applicable to MBC.
Association between vitamin D deficiency and breast cancer histology: A retrospective database review.

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Background: Vitamin D (Vit D) deficiency has been shown to be associated with a higher risk of developing breast cancer. Inverse association has also been shown between vit D level and tumor size. However, the association between vit D deficiency and breast cancer histology remains unclear. Preclinical data has suggested that vit D plays an essential role in the terminal differentiation of breast cells. Thus, we hypothesize that vit D deficiency would be associated with estrogen receptor-negative tumors, particularly triple-negative breast cancers (TNBC) which are associated with aggressive clinical course. 

Methods: We conducted a retrospective database review to obtain information including age, race, tumor histology, size, stage, and vit D levels in newly diagnosed breast cancer patients at University of Maryland Greenebaum Cancer Center. 

Results: 150 patients presented between July 2008 and August 2011 were included in this analysis. Average age at diagnosis was 57 (range 30-87), and 56% of patients were African American. Overall, 80% of the patients were vit D deficient at diagnosis, with levels < 30 ng/ml. African-American patients were more likely to be severely vit D deficient with levels < 10 ng/ml compared to Caucasians (33% vs. 7.5%, p = 0.0002). Patients with TNBC were more likely to be vit D deficient at diagnosis compared to hormone receptor-positive patients (93% vs. 76%, p =0.015). These patients also had the lowest mean (18) and median (16) of vit D levels compared to all other patients. This difference is also statistically significant in multivariate analysis when adjusted for age, race, and stage (OR 3.96; p =0.04). Regardless of the ER/PR status, Her 2 negative patients were more vit D deficient compared to Her 2 positive patients (86% vs. 61%, p=0.001). Unlike previous studies, no correlation was seen between tumor size and vit D levels. Furthermore, there is also no association between stage, nodal involvement, or Ki67 and vit D level. 

Conclusions: Vit D deficiency is common among patients with newly-diagnosed breast cancer, particularly African American patients. Patients with TNBC have a significantly higher likelihood of being vit D deficient than patients with other histological subtypes.
Frequency of TLE3 overexpression in breast carcinoma subtypes including a large cohort of triple-negative patients.

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Background: The taxanes are an important class of agents for the treatment of a broad range of malignancies including breast cancer. They improve survival in patients with early stage and metastatic breast cancer. Transducin-like enhancer of split 3 (TLE3) is a transcriptional repressor which influences growth and microtubule stability and its expression has been implicated in response to taxane therapy in breast cancer. We investigated the tumor expression of TLE3 in breast cancer patients, including a large cohort of the triple negative subtype. Methods: We analyzed TLE3 (M-201), ER(1D5), PR(PgR636) and HER2/neu(Polyclonal) expression by immunohistochemistry in 978 breast cancer patients. Immunoreactivity was assessed by scoring the percentage of cells stained in each field and by the intensity of staining. Results: To sub-classify the 978 breast cancer patients, we utilized hormone receptors (ER and PR) and HER2 expression/amplification. Overall, 36% of the total breast cancer patients were hormone receptor positive, 15% were HER2 positive and 49% were triple negative. The percentage of triple negative patients was higher in our cohort, given the fact that molecular profiling services are used more frequently for this subtype. A total of 477 patients were triple negative of which 61% stained positive for TLE3 expression. Of the 150 HER2 positive patients, 73% stained positive for TLE3 expression as compared with 82% TLE3 positivity in the 351 hormone receptor positive patients. By pairwise comparison, the hormone receptor positive vs triple-negative subtype showed the highest statistical significance in ratios of TLE3 positives (p =2.5e-10). Conclusions: Our results show that TLE3 is over-expressed in the majority of HER2 positive and hormone receptor positive breast cancer patients. Interestingly, the frequency of over-expression of TLE3 was lowest in the triple negative subtype thereby making it more important to identify those patients in this group who are most likely to respond to taxanes prior to therapy. To our knowledge, this is the first study providing a comprehensive review of TLE expression in breast cancer subtypes.
Epigenetic aspects of triple-negative in patients with breast cancer.

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Background: Identification of gene expression-based breast cancer subtypes is considered a critical means of prognostication. Genetic mutations along with epigenetic alterations contribute to gene-expression changes occurring in breast cancer. However, the reproducibility of differential DNA methylation discoveries for cancer and the relationship between DNA methylation and aberrant gene expression have not been systematically analysed. The present study was undertaken to dissect the breast cancer methylome and to deliver specific epigenotypes associated with particular breast cancer subtypes. Methods: By using Real Time QMSPCR SYBR green we analyzed DNA methylation in regulatory regions of 107 pts with breast cancer and analyzed association with prognostics factor in triple negative breast cancer and methylation promoter ESR1, APC, E-Cadherin, Rar B and 14-3-3 sigma. Results: We identified novel subtype-specific epigenotypes that clearly demonstrate the differences in the methylation profiles of basal-like and human epidermal growth factor 2 (HER2)-overexpressing tumors. Of the cases, 37pts (40%) were Luminal A (LA), 32pts (33%) Luminal B (LB), 14pts (15%) Triple-negative (TN), and 9pts (10%) HER2+. DNA hypermethylation was highly inversely correlated with the down-regulation of gene expression. Methylation of this panel of promoter was found more frequently in triple negative and HER2 phenotype. ESR1 was preferably associated with TN(80%) and HER2+(60%) subtype. With a median follow up of 6 years, we found worse overall survival (OS) with more frequent ESR1 methylation gene(p>0.05), Luminal A;ESR1 Methylation OS at 5 years 81% vs 93% when was ESR1 Unmethylation. Luminal B;ESR1 Methylation 86% SG at 5 years vs 92% in Unmethylation ESR1. Triple negative;ESR1 Methylation SG at 5 years 75% vs 80% in unmethylation ESR1. HER2;ESR1 Methylation SG at 5 years was 66.7% vs 75% in unmethylation ESR1. Conclusions: Our results provide evidence that well-defined DNA methylation profiles enable breast cancer subtype prediction and support the utilization of this biomarker for prognostication and therapeutic stratification of patients with breast cancer.
Preclinical evaluation of PARP inhibition in breast cancer: Comparative effectiveness of olaparib and iniparib.

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**Background:** The main function of PARP1 is repair of single-strand DNA. Phase I/II clinical trials have shown that the PARP inhibitor, olaparib has efficacy in BRCA1/2-related breast cancer. Due to the similarities between BRCA1/2-associated and triple negative breast cancer (TNBC), we hypothesise that TNBC may also be sensitive to PARP inhibition. In order to assess this we addressed the effects of 2 PARP/PARP-like inhibitors, on a panel of breast cancer cell lines. **Methods:** PARP1 was measured by immunohistochemistry in 101 TNBC and 116 non-TN cancers. Comparative growth inhibitory capacity of olaparib and iniparib was evaluated using cell viability (MTT) and colony formation assays in 12 breast cancer cell lines (TN/H110057, non-TN/H1105). **Results:** Using immunohistochemistry, PARP1 staining was predominantly nuclear with some cytoplasmic staining. High staining intensity for PARP1 was found more frequently in ER-negative (p = 0.001), in high grade (p = 0.013) and in Ki67-positive (p = 0.003) samples. Potentially important was the finding that high PARP1 staining intensity was detected more frequently in TN than non-TN samples (p = 0.0001). IC_{50} concentrations across 12 cell lines ranged from 3.7-31 μM for olaparib and 13-70 μM for iniparib. No difference in sensitivity was observed between the TN and non-TN cell lines (by MTT). Olaparib also reduced the ability of cells to form colonies with IC_{50} values ranging from <0.01-2.5 μM. Addition of the CDK1 inhibitor CDK1i (Calbiochem) to olaparib resulted in formation of significantly fewer colonies compared with either inhibitor alone, in a cell line dependent manner. **Conclusions:** Our results suggest that although PARP1 is expressed in the majority of breast cancer, significantly higher staining intensity was found in TN than non-TN samples. Furthermore, our work suggests that olaparib is a more potent inhibitor of the in vitro growth of breast cancer cells than iniparib. Combined inhibition of PARP1 with olaparib and CDK1 with CDK1i may be a way forward for the treatment of TNBC. Acknowledgement: The authors thank SFI (SRC award, 08/SRC/B1410 MTCI) for funding this work.
Molecular characteristics and metastasis predictor genes of triple-negative breast cancer.

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Background: Triple-negative breast cancer (TNBC) is a subtype of breast cancer with aggressive tumor behavior and distinct disease etiology. Due to the lack of an effective targeted medicine, treatment options for triple-negative breast cancer are few and recurrence rates are high. Although various multi-gene prognostic markers have been proposed for the prediction of breast cancer outcome, most of them were proven clinically useful only for estrogen receptor-positive breast cancers. Reliable identification of triple-negative patients with a favorable prognosis is not yet possible. Methods: Clinicopathological information and microarray data from 157 invasive breast carcinomas were collected at National Taiwan University Hospital from 1995 to 2008. Gene expression data of 51 triple-negative and 106 luminal breast cancers were generated with oligonucleotide microarrays. A prognostic 45-gene signature for triple-negative breast cancer was identified using Student’s t test and receiver operating characteristic analysis. Results: Hierarchical clustering analysis revealed that the majority (94%) of triple-negative breast cancers were tightly clustered together carrying strong basal-like characteristics. A novel 45-gene signature giving 98% predictive accuracy in distant metastasis recurrence was identified in our triple-negative patient cohort. External validation of the prognostic signature in an independent microarray dataset of 59 early-stage triple-negative patients also obtained statistical significance (hazard ratio 2.29, 95% CI 1.04-5.06, Cox $P = 0.04$), outperforming five other published breast cancer prognostic signatures. The prognostic signature was statistically predictive with the node-negative triple-negative patients in the validation cohort. Conclusions: The 45-gene prognostic signature identified in this study revealed that TGF-β signaling in immune/inflammatory regulation may be critically involved in distant metastatic invasion of TNBC. The 45-gene signature, if further validated, may be a clinically useful tool in risk assessment of metastasis recurrence for early-stage triple-negative patients.
Background: Obesity represents a well-known risk factor for the development of breast cancer and an adverse prognostic factor in early disease. Overweight is associated with reduced efficacy of aromatase inhibitors in adjuvant setting. Few data have been reported about the potential relationship of overweight and outcome in advanced breast cancer (ABC).

Methods: We retrospectively evaluated body mass index (BMI) in a consecutive series of 400 ABC patients treated at our institution. BMI was calculated at baseline of diagnosis of ABC. We evaluated association of BMI and other prognostic and predictive markers with Progression Free Survival (PFS) and Overall Survival (OS). We evaluated PFS at first and subsequent lines of chemotherapy (CT) and endocrine therapy (ET). Overweight patients were defined as having BMI $\geq 25$.

Results: Overweight patients were 52%. Median age of the population was 58 years. Median OS was 33.7 months. Overall, 76% of patients presented with ER+ and 17.7% with HER2+ ABC. Overweight was associated with increased age at diagnosis, menopausal status and luminal B or triple negative immuno-phenotype. At multivariate analysis, BMI $\geq 25$ was associated with better PFS at first-line ET (HR = 0.68, 95% CI 0.46-0.99). BMI was not associated with OS.

Conclusions: BMI at baseline does not seem to be an adverse prognostic factor for ABC patients. Overweight may be associated with better PFS in endocrine responsive ABC treated with ET, especially in first-line setting. The role of BMI in ABC deserves to be further investigated.
Neoadjuvant weekly nab-paclitaxel (wA), carboplatin (Cb) plus bevacizumab (B) with or without dose-dense doxorubicin-cyclophosphamide (ddAC) plus B in ER+/HER2-negative (HR+) and triple-negative (TN) breast cancer (BrCa): A BrUOG study.

**Background:** High risk BrCa patients (pts) often receive weekly paclitaxel (wP) as well as ddAC. Switching to wA(Abraxane) or adding B or Cb may enhance its efficacy, especially in TN pts. **Methods:** Pts with clinical stage IIA-IIIC BrCa received wA 100 mg/m², Cb AUC 6 + B 15 mg/kg q3wks x 12 wks only (cohort 1/Yale) or followed by ddAC + B x 4 (cohort 2/Brown). Endpoints: pathologic complete response (pCR) - absence of invasive BrCa in breast + axillary nodes, residual cancer burden (RCB), clinical CR/partial response (cCR/cPR), and toxicity. Correlative studies are being performed on biopsies obtained at baseline and after run-in doses of wA or B only. Post-op pts resume B for 34 wks; other systemic therapy, including ddAC in cohort 1, is at MD discretion. **Results:** 55 of 60 pts (median age 47, range 25-68; 31 HR/29 TN) are evaluable for response (see table below). Median # doses wA 11,Cb 4, ddAC 4. Dose reductions: wA 25% for neutropenia (ANC), Cb 15% for thrombocytopenia (tcp). B 7% held for hypertension. Grade 3-4 toxicities (>5%): ANC 85%, tcp 35%, anemia 25%. Serious adverse events during wA: 3 nausea/dehydration (N/D), 3 infection w/o neutropenic fever (FN), 2 GI bleed; during ddAC: 6 (21%) FN despite G-CSF, 3 N/D. **Conclusions:** The combination of wA, q3wk Cb + B was well tolerated, with cCR/cPR 84%. However, overall pCR was only 11% (27% in TN) after 12 wks of this regimen (cohort 1). Subsequent preop ddAC raised overall pCR to 54%, and 81% in TN, demonstrating that longer treatment duration or inclusion of anthracycline-based therapy improves responses. Results for cohort 2 compare favorably with those from I-SPY, GeparQuinto and NSABP B-40; the addition of Cb and/or B in TN is being evaluated in CALGB 40603.

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<th>cCR/cPR after ddAC</th>
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*2 pts not restaged after ddAC excluded.
Patterns in circulating microRNA in black (B) versus white (W) patients with triple-negative (TN) breast cancer (BC).

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Background: Breast cancer is by far more common in W than in B women. Black women have more aggressive disease that occurs almost a decade earlier, it is usually triple negative and has a lower survival. Objectives to determine 1) if plasma miRNA expression differs between B and W women, and 2) if variation in miRs may explain the observed survival difference in TNBC in W compared to B women. Methods: We determined miRNA profiles in plasma collected before removal of breast tumors in three groups of W and B women: 1) normal controls (N), 2) TN and 2) ER/PR positive BC. Expression miRNA profiling of 754 miRNAs on the ABI Open Array detected 101 miRNAs in plasma. We compared miRNA expression in cancer patients and race-matched controls. A moderated t-statistic through the R/Bioconductor 'limma' was used to compare the mean response between subject factors of interest. Results with a p<0.05 were considered statistically significant. Characteristics: 32 patients were included in this analysis (mean age 50 years; range 31-68), 10 had stage III TNBC (5 B & 5 W); 10 had stage III ER/PR + BC (5 B, 5 W); and 12 were controls (6 B, 6 W) Results: W TNBC patients overexpressed (15 fold higher than normal) 20 miRs in plasma (let-7d, let7g, miR-103, -10a, 15a, -9, -99b, -181a, -18a, -502, -187, -365 and others), these miRs were not found in any of the B patients. Six microRNAs (such as miR-34a, -127 and others) were 15 fold higher than normal controls in B cancer patients, these miRs were not detected in W patients with TNBC. Four miRs in B and 8 miRs in W were not previously reported in association with breast cancer suggesting that they may be connected to the host response. Conclusions: The striking difference in the patterns of plasma miRNA expression between B and W patients may provide the key to the large difference in outcome between these groups when receiving similar treatments, the worse prognosis group may carry the miRs that promote metastasis. The seed-soil hypothesis may explain the better prognosis in W patients. W women may carry those miRNAs that support an “exaggerated” response to systemic treatment, while the B may have the miRs that favour metastasis.

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Background: IBC has a poor prognosis because of its high rate of recurrence. There is an urgent need to define the biology of IBC to develop molecular-based targeted therapies for this disease. TNBC has a similar poor prognosis. Recently, Lehmann et al. (JCI, 2011) identified 7 subtypes of TNBC: basal-like (BL) 1 and 2, immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), and “unknown.” In light of these findings, we hypothesized that the distribution of TNBC subtypes differs between TN-IBC and TN-non-IBC.

Methods: We qualitatively reproduced the Lehmann et al. experiments using Affymetrix CEL files from the same datasets to ensure the reproducibility of their findings. We quantified all arrays using frozen robust multiarray analysis with a linear model adjustment to account for batches. Then validated the results in a TNBC cohort from the World IBC Consortium for which IBC status was known (41 cases of TN-IBC; 53 cases of TN-non-IBC). We used the Fisher exact test to determine associations between TNBC subtypes and IBC status. We used Kaplan-Meier curves and log-rank tests to compare clinical outcomes between TNBC subtypes. Results: We found the 7 subtypes for both TN-IBC and TN-non-IBC. While the correspondence between our findings and those of Lehmann et al. was not perfect, there was a very significant correlation. We found no association between TNBC subtype and IBC status. As expected, we found that patients with IBC had significantly worse recurrence-free survival (RFS) than a comparison cohort of patients with advanced non-IBC that included not only patients with TNBC but also patients with ER-positive and HER2-amplified tumors. TNBC subtype did not predict RFS. IBC status was not a significant predictor of RFS or overall survival in the TNBC cohort.

Conclusions: Both TN-IBC and TN-non-IBC are heterogeneous. TNBC subtypes are unrelated to IBC status. TN-IBC and TN-non-IBC have the same subtypes and clinical outcome.

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Racial differences in outcomes of triple-negative breast cancer.

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Background: The incidence and mortality of breast cancer can differ significantly among racial and ethnic groups. African American (AA) women have a lower incidence of breast cancer, but higher mortality compared to other racial groups. Triple negative breast cancer (TNBC: negative for the expression of estrogen receptor, progesterone receptor and HER2), which is an aggressive type of breast cancer, occurs more frequently in AA women. The few studies addressing whether racial differences exist in the outcomes of patients with TNBC have yielded inconsistent results. Methods: The Washington University Medical Oncology Database captures the clinical information for all new patients (pts) seen at the Breast Oncology Clinic. Most of these pts reside in the St. Louis metropolitan area. Using this database, we performed a retrospective analysis to examine the association of race with the clinical presentation and outcome of TNBC in this geographically defined patient population. Results: Between May 2006 and March 2011, 506 pts with TNBC were entered in the database. Analysis was done on 499 patients for whom follow up data is available. The median follow up (F/U) time was 24.5 months and the median age at diagnosis was 53 (24 to 98) years. Thirty percent of pts were AA. Only 5% presented with stage IV at diagnosis and the majority of tumors (86%) were high grade. Neoadjuvant chemotherapy was administered in 151 pts, 22% of whom achieved a pathologic complete response (pCR). There was no significant difference between races in the age of diagnosis, F/U time, tumor stage, grade, frequency of receiving neo/adjuvant chemotherapy and pCR rate to neoadjuvant chemotherapy. There was no difference in disease free survival (DFS) and overall survival (OS) between AA and other racial groups by either univariate or multivariate analysis that took into account tumor stage, grade, patient age and menopausal status. The HR for OS was 1.154 (CI 0.772 – 1.725, p value 0.4860) and for DFS it was 0.947 (CI 0.650 – 1.380, p value 0.7764) in AA compared to other races. In the 92 pts who recurred, there was no racial difference in time from recurrence to death. Conclusions: Race does not significantly affect the clinical presentation or outcome of TNBC in the St. Louis metropolitan area.
A prognostic model for predicting breast cancer (BC)-related survival in operable triple-negative (TN) patients (pts).

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Background: TNBC represent a heterogeneous disease in terms of biology, prognosis, and treatment response. We propose a prognostic model to identify homogeneous subgroups of patients and tailor risk-adapted adjuvant therapies indications. Methods: We analyzed 1,049 pts operated in our institute from 1997 to 2007 for early TNBC. Pts who received neoadjuvant chemotherapy (CT), with T4 tumors or previous history of cancer were excluded. Death from BC was the primary endpoint of the study. We calculated an individual predicted risk using a multivariable Cox regression model, with age, tumor size, number of positive lymph nodes and Ki-67 analyzed as continuous covariates, and tumor grade and perivascular invasion as categorical covariates. Results: Median age was 52 years, 562 (53.4%) and 670 (65.1%) pts had a pT1 and pN0 TNBC, respectively. Median Ki-67 was 48%. Adjuvant CT regimens were distributed as follows: classical CMF 388 (37.0%), anthracycline containing regimens 455 (43.4%), taxanes 12 (1.1%), other regimens 66 (6.3%) and no CT 128 (12.2%). After a median follow-up of 6 years, 131 deaths from BC were observed (5-year cumulative incidence 11.9%). At multivariable analysis, age, tumor size, number of positive lymph nodes, Ki-67, tumor grade and perivascular invasion were associated with the risk of death and were included in the prognostic model. Its predictive accuracy was good (C-index 0.73). We subsequently identified three homogeneous prognostic subgroups - low, medium and high-risk - according to the tertiles values of the predicted risk. The outcomes are shown in the table. Conclusions: We could identify homogeneous prognostic subgroups of TNBC pts according to clinical-pathological features. This prognostic model suggests that the use of CT in TN low-risk pts might be questionable. We are currently externally validating this model on a different series of pts.

<table>
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<th>Risk subgroup</th>
<th>Treatment</th>
<th>No. (%)</th>
<th>Deaths from BC</th>
<th>5-year survival %</th>
<th>P value</th>
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<td>95.5</td>
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<td>No CT</td>
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<td>Medium-risk</td>
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Evaluation of a multiparametric system able to predict nonsentinel lymph node status in breast cancer patients with a micrometastatic sentinel node assessed by the one step nucleic acid amplification (OSNA) assay.

Simonetta Buglioni, Marcella Mottolese, Beatrice Casini, Enzo Gallo, Irene Terrenato, Edoardo Pescarmona, Simona Di Filippo, Ferdinando Marandino, Gianluigi Ferretti, Franco Di Filippo; Regina Elena National Cancer Institute, Rome, Italy

**Background:** Axillary lymph node dissection (ALND) may not be necessary in women with breast cancer (BC) who have micrometastasis in a sentinel lymph node (SLN), owing to the low risk of non-SLN (NSLN) involvement. In our Institute we validated and adopted the molecular diagnostic tool OSNA based on the quantitative measurement of Cytokeratin 19 (CK19) mRNA. The aims of our work in a subgroup of women with micrometastatic SLN, were: 1) to correlate the copy numbers of CK19 mRNA with the risk of additional positive NSLNs; 2) to assess the relationships between the molecular subtype classification and the probability of a positive ALND; 3) to verify whether a combination of the new above mentioned parameters is able to identify a subgroup of patients with a micrometastatic SLN and a negligible risk of positive NSLNs in whom ALND may be avoided. **Methods:** The SLN lysates from 709 patients were analyzed by OSNA assay. We considered only patients with a micrometastatic SLN (copy numbers between 250 and 5000/µL) and the probability of having a positive ALND was calculated by the logistic regression model. This series of BC patients were divided into four main subtypes taking in account the BC classification as defined by a combination of estrogen, progesteron receptors and HER2 status. **Results:** OSNA positivity for micrometastasis was reported in 91/709 cases (12.8%). The number of patients with positive ALND was 20 (22%). The statistical analyses showed that the metastatic involvement of NSLNs is associated with SLNs with a high copy numbers (>2000) of CK19 mRNA together with HER2 subtype. Otherwise none of the luminal A patients with a positive SLN but presenting a copy number <1000, had a positive NSLNs. **Conclusions:** We showed that biologically-driven analyses may be able to build new models with higher performance in terms of breast cancer axillary status prediction after positive SLN biopsy for micrometastasis. The copy numbers of CK19 mRNA and the molecular subtypes are more advantageous than traditional parameters because they are not pathologist-dependent and therefore they are more reliable and reproducible.
Impact of biomarkers in predictivity of the efficacy and toxicity of a combination of panitumumab plus FEC 100 followed by docetaxel in a phase II neoadjuvant trial for triple-negative breast cancer (TNBC) patients.

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**Background:** We evaluated the combination of a standard chemotherapy with panitumumab as neoadjuvant therapy of operable TNBC. Complete pathologic response (pCR) was the primary endpoint, with toxicity and biologic ancillary studies as secondary endpoints. **Methods:** Sixty patients with stage II-IIIA disease were prospectively included in this multicentre pilot study. Systemic therapy (ST) consisted of 4 cycles of FEC 100 (500/100/500 mg/m²) q.3 weeks followed by 4 cycles of T (100 mg/m²) q.3 weeks, in combination with panitumumab (9 mg/kg) for 8 cycles q.3 weeks. All patients underwent surgery at completion of ST. Paraffin-embedded samples and frozen samples have been systematically realised before and after neoadjuvant treatment in order to evaluate the biological profile of the tumor. Patients characteristics are: median age 50; median tumor size: 40 mm; invasive ductal carcinoma: 96%; Scarff-Bloom-Richardson Grade III: 70%; grade II: 30%; ki-67-positive: 100%; EGFR-positive: 78%; cytokeratine5-6-positive: 48% and p53-positive: 59%. Pathological response showed a pCR according to Sataloff’s classification of 52.38% and according to Chevallier’s classification of 46.52%. Skin toxicity was the main side-effect: Cutaneous toxicity grade IV: 5%, grade III: 30%, grade II: 20%. Neutropenia grade IV: 5%. Infection: 0%. Hand-foot syndrome grade III: 3.3%. Ungueal toxicity grade III: 1.6%, grade II: 20%. **Results:** We have tested the predictive value of ki-67, EGFR, cytokeratine 5-6 and p53. Only ki-67 is predictive of a pCR according to Chevallier’s classification (p=0.026), with a cut-off of 40% of positive cells (ROC curve): 62% of pCR if ki-67 > 40% versus 23% if not (relative risk: 2.7). Low EGFR, high p53, and high cytokeratine 5-6 tended to be associated with poor response. No correlations were found between cutaneous toxicities and these biomarkers. The cutaneous toxicities were not predictive. **Conclusions:** High Ki-67 is predictive of more pCR. High EGFR, low p53 and low cytokeratine 5-6 tended to be associated with better response, but the data are not significant.
Effect of therapeutic targeting of the oncogene EMP2 in triple-negative breast cancer on tumor load.

Madhuri Wadehra, Meagan Kiyohara, Maoyong Fu, Lynn K Gordon, Jonathan Braun; DGSOM at UCLA, Los Angeles, CA

Background: Understanding tumor induced angiogenesis is a challenging problem with important consequences for the diagnosis and treatment of cancer. In this study we define a novel function for the tetraspan epithelial membrane protein-2 (EMP2) in the control of neoangiogenesis. EMP2 is an oncogene whose expression has been shown to correlate with tumor progression and survival in a number of human cancers including triple negative breast, ovarian, and endometrial tumors. In breast cancer, EMP2 is highly expressed on the majority of invasive tumors examined, and in particular 70% of triple negative breast tumors showed surface expression of this marker. In this study, we examine the control of EMP2 on the tumor microenvironment and further characterize its therapeutic efficacy in breast cancer. Methods: A number of cancer cell lines were utilized both in vitro and in vivo to determine if EMP2 expression levels altered the tumor microenvironment. Cells were tested for their expression of pro-angiogenic proteins HIF-1α and VEGF-A as well as for their ability to induce endothelial cell migration and capillary-like tube formation. Cells with modulated EMP2 levels were also tested in vivo for tumor formation and examined for histological changes in the tumor microenvironment. In addition, we recently constructed a fully human EMP2 IgG1 and determined its therapeutic efficacy in a number of triple negative breast cancer cells. Results: In vitro, upregulation of EMP2 promoted VEGF expression through a HIF-1α dependent pathway and resulted in successful capillary-like tube formation. In contrast, reduction of EMP2 correlated with reduced HIF-1α and VEGF expression with the net consequence of poorly vascularized tumors in vivo. Treatment of breast cancer cells with EMP2 IgG1 reduced tumor load with a significant improvement in survival. Conclusions: Clinically, EMP2 has been shown to correlate with poor survival, and these results suggest that this occurs in part through its control on tumor vasculature. In addition, we provide additional evidence on the potent cytotoxic effects of EMP2 treatment in vivo.
Clinical characteristics and chemotherapy options of triple-negative breast cancer: Role of classical CMF regimen.

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**Background:** Triple-negative breast cancer is a high risk breast cancer that lacks the benefit of specific targeted therapy. We investigated the clinicopathologic characteristics between triple-negative breast cancers (TNBC) and non-TNBC. And we also analyzed the effect of chemotherapy options such as classical CMF regimen, anthracycline-based, or taxane-based chemotherapy. **Methods:** A total of 826 invasive breast cancer patients were evaluated from March 2003 to December 2008. We investigated them retrospectively, who had the median follow-up for 88 months. We examined the differences between TNBC compared with non-TNBC in relation to the clinicopathologic parameters, chemotherapy regimen, overall survival (OS). **Results:** 156 (18.9%) cases among 826 patients were triple negative breast cancers. There were significantly positive associations with younger age (below 35 years), large tumor (>2cm), high stage, poorly differentiated nuclear grade, poorly histologic grade in TNBC. Positive lymph node, lymphovascular invasion were not significantly different between TNBC and non- TNBC. A total of 677 patients were treated with chemotherapy. In TNBC patients, 142 (93.4%) patients were treated with chemotherapy more than in 535 (61.4%) of non- TNBC patients. The chemotherapy in TNBC patients was composed of classical CMF (47.9%), anthracycline-based regimen (25.4%), taxane-based regimen (26.8%). 19 cases (12%) of TNBC experienced locoregional or systemic metastases. 48 (7.2%) patients of non- TNBC did local or systemic metastases. Patients with TNBC had worse 5-year OS than with non-TNT (95.7% vs 98.6%, p<0.01). Interestingly, patients treated with CMF regimen were better 5-year OS than with anthracycline-based, or taxane-based regimen in TNBC (100% vs 96.9% vs 89.2%, p=0.001). There was no survival difference among chemotherapy regimens in non-TNBC patients. **Conclusions:** Patients with TNBC have poor prognosis compared with non-TNBC. Classical CMF regimen for TNBC patients may be more effective than anthracycline-based or taxane-based regimens.
Biomarkers of response to Akt inhibitor MK-2206 in breast cancer.

Takafumi Sangai, Argun Akcakanat, Huiqin Chen, Emily Tarco, Yun Wu, Kim-Anh Do, Todd W Miller, Carlos L. Arteaga, Gordon B. Mills, Ana M. Gonzalez-Angulo, Funda Meric-Bernstam; University of Texas M. D. Anderson Cancer Center, Houston, TX; Vanderbilt University, Nashville, TN

Background: Akt significantly contributes to cancer pathogenesis. PTEN, a negative regulator of PI3K/Akt signaling, is mutated or decreased, and PIK3CA is frequently mutated in multiple cancer lineages. We hypothesized that MK-2206, an allosteric Akt inhibitor, would inhibit Akt signaling thus blocking cancer cell growth, and PTEN and/or PIK3CA mutations may confer MK-2206 sensitivity in breast cancer.

Methods: After determining sensitivity to MK-2206 in 16 cell lines, the effect on Akt signaling was tested by reverse-phase protein array analysis and western blotting. The effect to cell cycle progression and cell death were analyzed by flow cytometry. Using RNA knockdown technique, the effect of PTEN, PIK3CA and Akt on MK2206 sensitivity was tested. Anti-tumor effect in vivo with or without paclitaxel was tested using PTEN-mutant ZR75-1 breast cancer xenografts. Results: MK-2206 inhibited Akt signaling and cell cycle progression, and increased apoptosis in a dose-dependent manner in breast cancer cell lines. Cell lines with PTEN or PIK3CA mutations were more sensitive to MK-2206 (P=0.0337), however, a number of lines with PTEN/PIK3CA mutations were MK-2206-resistant. Small interfering RNA (siRNA) knockdown of PTEN in breast cancer cells increased Akt phosphorylation concordant with increased MK-2206 sensitivity. Stable transfection of PIK3CA E545K or H1047R mutant plasmids into normal-like MCF10A breast cells enhanced MK-2206 sensitivity. Cell lines that were less sensitive to MK-2206 had lower ratios of Akt1/Akt2 and had less growth inhibition with Akt siRNA knockdown. In ZR75-1 xenografts, MK-2206 treatment inhibited Akt signaling, cell proliferation, and tumor growth. In vitro, MK-2206 showed a synergistic interaction with paclitaxel in MK-2206-sensitive cell lines, and this combination had significantly greater antitumor efficacy than either agent alone in vivo. Conclusions: MK-2206 has antitumor activity alone and in combination with chemotherapy. This activity may be greater in tumors with PTEN loss or PIK3CA mutation, providing a strategy for patient enrichment in clinical trials. However, not all tumors with PIK3CA/PTEN aberrations are MK-2206-sensitive, emphasizing the need for additional markers of response.
Preclinical evaluation of selective inhibitors of nuclear export (SINE) in basal-like breast cancer (BLBC).

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Background: Basal-like breast cancers (BLBC) compose up to 15% of breast cancer (BC) and are usually triple negative characterized by lack of ER, PR, and HER-2 amplification. In addition, most BRCA1-associated BCs are BLBC and TNBC, expressing basal cytokeratins and EGFR. BLBC is characterized by an aggressive phenotype, high histological grade, and poor clinical outcomes: high recurrence and metastasis rates. CRM1 (XPO1) is the exclusive nuclear exporter of multiple Tumor Suppressor Proteins (TSP) including p53, p21, BRCA1&2, pRB, FOXO. CRM1 inhibition forces nuclear accumulation of TSPs, inducing apoptosis in cancer cells. KPT-SINE are novel, small molecule, irreversible inhibitors of CRM1 with potent anti cancer activity. Methods: The Cancer Genome Atlas (TCGA) and BC cell line databases were used for mRNA analyses. MTT assay was used to determine the cytotoxic effect of KPT-SINE (KPT-185 and KPT-330) on 44 breast cell lines including luminal A, luminal B, HER2 positive, BLBC and TNBC cells. The effect of KPT-330 treatment on tumor growth was tested in vivo in the TNBC model MDA-MB-468 xenograft. Results: Analyses of nuclear pore complex (NPC)-related mRNA levels (including CRM1) showed clear separation of BCs into high and low NPC expression. BLBC subtype was enriched with high NPC transcripts while luminal BC was enriched in low NPC levels (p<1.53e-20). High NPC levels had higher mutation levels in BRCA2 (cor=0.33, p=1.83e-8) and ABL1. NPC expression was inversely correlated with ER mRNA expression (cor=-0.58, p=1.37e-7). KPT-SINE showed potent cytotoxicity on >75% of the cell lines (IC50 values <1 μM). Only three of 24 TNBC cell lines displayed IC50 values >1.5 μM upon KPT-SINE treatment. Genomic analyses on all BC lines indicated that p53, PI3K/AKT and BRCA1 or 2 status did not affect cytotoxicity. In MDA-MB-468 xenograft, KPT-330 displayed efficacy in a dose-dependent manner inhibiting nearly 100% of tumor growth compared with vehicle treated animals, and was well tolerated. Conclusions: These data show that NPC/CRM1 mRNAs are overexpressed in BLBC/TNBC and that CRM-1 mediated nuclear export inhibition by SINE represents a potentially novel and well tolerated therapy for BLBC / TNBC.
The role and significance of FoxM1 in invasive breast cancer.

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Background: The Forkhead Box protein M1 (FoxM1) is known to regulate a variety of biologic processes in mammalian cells including cell growth and survival, angiogenesis, DNA damage response, chemotherapeutic drug resistance, and cancer cell migration and invasion. We evaluate the role and significance of FoxM1 in primary breast cancer in vitro and analyzed the relation with FoxM1 expression and clinicopathologic features. Methods: Immunohistochemical staining was used for evaluation of cytoplasmic expression of FoxM1 with TMA of invasive breast cancer. In various breast cancer cell lines, we evaluated FoxM1 expression and treated docetaxel/cisplatin in combination with Siomycin A (FoxM1 inhibitor) for BT20 cell line. Results: From Nov 1995 to Jul 2007, in 84 patients with stage 1-3 invasive breast cancer, FoxM1 expression was noted in 58.7%. Median follow-up duration was 85.1 months. Lymphovascular invasion was positively correlated with FoxM1 expression (p=0.040). In multivariate analysis, FoxM1 expression (p=0.005), HR negativity (p=0.002), high histologic grade (p=0.023), high nuclear grade (p=0.045), lymphovascular invasiveness (p=0.017), and stage 3 cancer (p=0.015) matched poor disease-free survival. In vitro study, FoxM1 was expressed BT474, JIMT-1, BT20, HCC-1937, and MDA-MB-231 cell lines. The inhibition of FoxM1 had synergistic effect on cisplatin treatment, not docetaxel in BT20 cell. Conclusions: FoxM1 expression was noted in triple negative breast cancer cell lines and its inhibition had synergistically cytotoxic effect on BT20 cell line in combination with cisplatin. Although the further in vivo and clinical study should be needed to draw the solid conclusions, FoxM1 could be both a promising target of treatment for triple negative breast cancer and a independent prognostic factor.
Use of gene expression and alternative splicing signatures to discriminate breast cancer stem cells from fibroblasts.

David T. Weaver, Irina M Shapiro, Alan G Derr, Daniel Paterson, Jonathan A Pachter; Verastem Inc, Cambridge, MA

Background: Tumors frequently contain cancer stem cells (CSCs) or tumor-initiating subpopulations, with an ability to self-renew and regenerate all cell types within the tumor. Basal-like breast cancers exhibit features of CSCs, including expression of surface markers, even though these cells are rare. Given the role of CSCs in the recurrence and spread of cancer, there is an urgent need to develop new therapeutic agents that target CSCs. Development of CSC-targeted drugs will be greatly facilitated by biomarkers that can identify CSCs to aid in patient selection and determination of drug response. Defining the CSCs in tumors is complicated by the high mesenchymal nature of fibroblasts. Analysis of gene expression and alternative splicing patterns in CSCs that are not observed in fibroblasts may provide valuable new CSC-specific markers. Methods: Alternative splicing and gene expression microarray strategies were used to identify selected exons and differentially expressed genes between 10 Basal human breast cancer cell lines and a combination of 12 Luminal and 3 fibroblast cell lines. Q-PCR analysis was conducted to determine candidate CSC gene differential expression between Basal, Luminal, and Fibroblast cell lines. Results: Expression levels of 11 genes were higher and 24 genes were lower in the Basal cell lines versus Luminal or fibroblastic cell lines. Comparison of Basal cell lines to the Luminal/Fibroblast cell lines identified 36 cassette exons that were included, and 26 that were excluded in Basal cell lines. Also, 19 genes were upregulated in Basal cell lines compared to the other groups as detected by Q-PCR. Interestingly, the 19-multigene model defined the Triple Negative Breast Cancer patients that were Likely to Recur under standard chemotherapy with a $p = 1.90e-03$ and AUC 0.723. Conclusions: Gene and exon marker sets distinguish CSC versus fibroblasts and may be instructive in identifying patients that recur early in Triple Negative Breast Cancer. The CSC-associated RNA signatures identified here will be further refined to develop new CSC-specific diagnostic markers to stratify breast cancer patients and monitor response to novel CSC-targeted therapies.
Next-generation sequencing mutational analysis of triple-negative breast cancer patients from matched FFPE and fresh frozen samples.

Mark Landers, Rhonda Meredith, Jerry Lee, Yipeng Wang, Byung-In Lee, Joseph Monforte; AltheaDx, San Diego, CA

Background: TNBC is an aggressive subtype of breast cancer accounting for 10-15% of all cases. TNBC tumors (ER-/PR-/HER-) are more common in patients with BRCA mutations. BRCA mutations leading to homologous DNA repair deficient tumors enhance the efficacy of chemotherapy and PARP inhibitors. BRCA mutations have been identified in 20% of patients without family history. Identification of germline and somatic BRCA mutations in unselected patients could increase the number of patients who benefit from these therapies. Determining BRCA mutational status from FFPE and fresh frozen specimens may enable clinical studies in these patient populations. We describe the development of an NGS BRCA mutational assay compatible with FFPE and fresh frozen samples using tumor/adjacent normal matched tissues.

Methods: Matched samples were purchased from Cureline. gDNA was isolated by lysis/column purification (Qiagen) and enriched for BRCA exons/flanking regions (Halogenomics Selector). Fragment libraries were constructed (Ion Torrent frag express) and prepared for sequencing by emPCR (Ion Torrent Template Xpress). Libraries were sequenced for 65 cycles (Ion Torrent PGM) yielding 2-4M reads/sample. Variants were called from tMAP aligned reads by GATK and VarScan. Overlapped exonic variants were filtered by p-value (<0.0001) from VarScan. Results: In the first patient set normalized average depth of BRCA exon coverage was 64X and 72X per 150K reads in FFPE and fresh frozen tissues respectively covering 95-100% of target. hg19 alignment rates varied between 97-99% across all samples. Similar numbers of variants were called in both FFPE (12) vs. fresh frozen (13) with a corresponding mean duplicate removed depth of coverage of 23.3X and 42.4X at the called positions. 10/13 calls in fresh frozen overlapped with those in FFPE. A tumor specific somatic frameshift insertion in BRCA2 was detected in both FFPE and fresh frozen tissues. Conclusions: Results indicate that NGS mediated BRCA mutational analysis demonstrates equivalent utility in both FFPE and fresh frozen tumor samples although more sequencing reads are required to produce equivalent depth of coverage starting from FFPE samples.
A randomized phase II trial of doxorubicin plus pemetrexed followed by docetaxel versus doxorubicin plus cyclophosphamide followed by docetaxel as neoadjuvant chemotherapy (NACT) for early breast cancer: Three-year follow-up data.

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Background: NACT for early breast cancer allows in vivo chemosensitivity testing. Primary results of this randomized, non-comparative 2-arm study have been published (Schneeweiss et al, Ann Oncol 2011). Here we provide 3-year follow-up data for disease-free survival (DFS) and safety. Methods: 257 patients (pts) with untreated operable T2–T4a–c N0–2 M0 breast cancer were randomly assigned to receive either four cycles of doxorubicin 60 mg/m² plus pemetrexed 500 mg/m² every 3 weeks (q3w) followed by four cycles of docetaxel 100 mg/m² q3w (AP-D; 135 pts), or four cycles of doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² q3w followed by four cycles of docetaxel 100 mg/m² q3w (AC-D; 122 pts). Both arms were stratified according to hormone receptor (HR) status (estrogen and/or progesterone receptor positive vs both negative) and study center. Surgery was carried out within 2 months after last chemotherapy. Primary objective was pathological complete response (pCR) rate in the breast (ypT0/is). Secondary objectives included long-term efficacy and safety measures. DFS and adverse event data were collected from all patients for 3 years or until progression or death. The Kaplan-Meier (KM) analysis technique and Cox regression method were used as statistical measures. KM analyses were performed on HR-positive and -negative pts subgroups. Results: As reported earlier, pCR rates were 16.5% for AP-D and 20.2% for AC-D. The 3-year DFS rate was 76% and 77% for AP-D and AC-D, respectively. Cox regression analysis for the overall enrolled population (regardless of treatment) revealed significantly longer DFS in HR-positive than in HR-negative pts (hazard ratio 0.35; 95% CI 0.22–0.58; p < 0.001). In HR-positive pts, the 3-year DFS rate was 88% (95% CI: 81–95%) with AP-D and 83% (95% CI: 74–91%) with AC-D. In HR-negative pts, the 3-year DFS rate was 55% (95% CI: 40–70%) for AP-D and 68% (95% CI: 53–82%) for AC-D. The 3-year follow-up data did not reveal any changes in the safety profile compared to the previously published results. Conclusions: The 3-year DFS rates of both NACTs are in line with published studies.

Phase II study of a novel neoadjuvant chemotherapy (NAC) for breast cancer (BC).

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**Background:** The goal of this NAC study was to improve the pathologic response of pts with localized BC.

**Methods:** 51 pts with localized BC >1 cm were treated with this novel regimen consisting first of docetaxel 75 mg/m², epirubicin 80 mg/m², and cyclophosphamide 500 mg/m² (TEC) and PEG Filgrastim for 4 cycles. Pretreatment PET scan was done and repeated after course 1. Following the 4th course, ER+/HER2- patients received 4 additional TEC cycles if they achieved CR by MRI, or were switched to a non cross-resistant regimen (vinorelbine, bevacizumab, capecitabine) if they had < CR. HER2+ pts were given docetaxel + trastuzumab for 4 additional cycles, or were switched to a different regimen if < PR. MD Anderson residual cancer burden (MDARCB) score was used to measure pathologic response and correlation with several prognostic factors was studied.

**Results:** Median age = 53; 27 were postmenopausal; 42 had invasive ductal carcinoma, 5 invasive lobular; 12 triple negative, 11 HER2+, and 28 ER+ or PR+/HER2-.

MDARCB was significantly better in HER-2+ and triple negative tumors (table). ER+ or PR+/Her2- pts had the least favorable MDARCB with none achieving 0 and only 21% attaining MDARCB=1. MDARCB score 0-1 vs 13% with ≤ 5% drop. %Ki-67 correlated well with MDARCB (table). Ki-67 correlated well with receptor status: 85% of Triple Neg or Her2+ pts had Ki-67 >17 vs only 29% of ER+ or PR+/Her2-.

**Conclusions:** a) This novel NAC regimen leads to markedly favorable MDARCB scores in triple negative and Her-2+ cases. b) Several factors may be useful in predicting response to chemotherapy, including receptor status, Ki-67, and PET scan response after 1st chemotherapy course. c) Ki-67 proliferative rate is closely correlated with receptor status. d) Early PET could be used to predict MDARCB. The challenge now is to improve response in ER+ or PR+/Her2- pts.

<table>
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<tr>
<th>Factor</th>
<th>MDARCB 0</th>
<th>MDARCB 1</th>
<th>MDARCB 2</th>
<th>MDARCB 3</th>
<th>p</th>
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<tr>
<td>Triple neg or HER2+</td>
<td>18 (82%)</td>
<td>1 (5%)</td>
<td>2 (9%)</td>
<td>1 (5%)</td>
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<tr>
<td>ER+ or PR+/HER2-</td>
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<td>6 (21%)</td>
<td>17 (61%)</td>
<td>5 (18%)</td>
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<td>Ki-67 &gt;17</td>
<td>13 (54%)</td>
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<td>8 (33%)</td>
<td>1 (4%)</td>
<td></td>
<td>24</td>
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<tr>
<td>Ki-67 ≤ 17</td>
<td>2 (9%)</td>
<td>5 (22%)</td>
<td>11 (48%)</td>
<td>5 (22%)</td>
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<td>% drop SUV &gt; 5%</td>
<td>18 (44%)</td>
<td>6 (15%)</td>
<td>14 (34%)</td>
<td>3 (7%)</td>
<td>.04</td>
<td>41</td>
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<tr>
<td>% drop SUV ≤ 5%</td>
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<td>1 (13%)</td>
<td>4 (50%)</td>
<td>3 (38%)</td>
<td>.04</td>
<td>8</td>
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</tbody>
</table>

*One progressed in liver while on treatment and did not undergo surgery.*
The first two lines of chemotherapy for anthracycline-naïve metastatic breast cancer: A comparative study of efficacy between anthracyclines and nonanthracyclines.

Wei-Wu Chen, Twan Ying Chang, Shu-Min Huang, Ching-Hung Lin, Chian Hsu, Ann-Lii Cheng, Yen-Shen Lu; National Taiwan University Hospital, Taipei, Taiwan; Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

Background: For anthracycline-naïve metastatic breast cancer (AN-MBC) patients, past evidence indicated that anthracyclines are beneficial in the first-two lines of palliative chemotherapy but with considerable toxicities. However, with the provision of newer chemotherapies, comparative studies addressing the efficacy between anthracyclines and non-anthracyclines in the first-two lines of palliative chemotherapy for AN-MBC were lacking. Methods: We collected clinicopathological characteristics of AN-MBC patients who had received palliative chemotherapy in National Taiwan University Hospital between 2001 and 2006. Patients were classified as anthracycline or non-anthracycline group according to the first-two lines of chemotherapy. Kaplan-Meier method and log-rank test were used for the estimation and comparison of both overall survival (OS) and time to treatment failure of the first-two lines (TTF2). Cox proportional hazard model was used for OS and TTF2. Best composite response rate (BCRR) were compared with logistic regression test. Results: A total of 109 (43.1%) patients in the anthracycline group and 144 (56.9%) patients in non-anthracycline group were analyzed. Between these two groups, the distributions of clinicopathological variables were generally similar and their median OS (33.3 vs 34.2 months, \( p = 0.179 \)), TTF2 (13.3 vs 12.7 months, \( p = 0.104 \)), and BCRR (59.5 vs 61.1%, \( p = 0.81 \)) were not significantly different. Subgroup analysis showed that patients in the anthracycline group had a trend toward better OS in the estrogen receptor (ER) negative/ human epidermal growth factor receptor type II (HER2) positive subtype (median OS 58.0 vs 31.2 months, \( p = 0.081 \)). In multivariate analysis, patients in the anthracycline group had a trend toward better OS (HR 0.72, 95% CI 0.52 - 1.00, \( p = 0.052 \)). However, the exclusion of ER-/Her2+ subtype attenuated the impact of early anthracycline treatment on OS (HR 0.82, 95% CI 0.56 - 1.18, \( p = 0.28 \)). Conclusions: Our study demonstrated that anthracyclines may not be mandatory in the first-two lines of palliative chemotherapy for AN-MBC but may be more beneficial to ER-/Her2+ subtype patients.
Current patterns of chemotherapy and supportive care for early-stage breast cancer (ESBC).

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**Background:** ESBC is commonly treated with myelosuppressive chemotherapy, and high relative dose intensity (RDI) correlates with improved overall survival. A retrospective analysis of patients with ESBC treated from 1997–2000 showed that 56% received an RDI < 85% (Lyman et al. *JCO*. 2003;21:4524-4531). To determine current practice, we evaluated ESBC treatment patterns at 24 US community- and hospital-based oncology practices. **Methods:** Data were abstracted from medical records of 532 patients with ESBC treated from January 2007–December 2009. Inclusion criteria included surgically resected ESBC (stage I-IIIA); ≥ 18 years old; and completion of at least 1 standard chemotherapy cycle on an every 2 or 3 week schedule. The primary endpoint was RDI over planned cycles. Other endpoints were incidence of dose delays ≥ 7 days, dose reductions ≥ 15% from standard, grade 3/4 neutropenia (SN), febrile neutropenia (FN), FN-related hospitalization, granulocyte-colony stimulating factor (G-CSF) use, and antimicrobial therapy. Descriptive statistics were generated for all endpoints. **Results:** In this study, mean (range) age was 55 (29–85) years. Relative to previously published results, chemotherapy regimens have shifted from mainly doxorubicin + cyclophosphamide (AC) (previously 35%) to docetaxel + cyclophosphamide (TC; n = 221; 42%) and AC followed by paclitaxel (AC-T; n = 163; 31%). Mean RDI is now higher (93% for both TC and the most common AC-T schedule [dose dense AC-T; n = 84] vs 79% previously); the incidence of dose delays (16% vs 25% previously) and dose reductions (21% vs 37% previously) have decreased; and primary prophylactic use of G-CSF has increased (76% vs 3% previously). In this study, 40% of patients had SN, 3% had FN, 2% had an FN-related hospitalization, and 30% received antimicrobial therapy. These measures were not available in the previously published results. **Conclusions:** The observed changes between the two studies are noteworthy though inferential comparisons are limited by changes in treatments and other factors. RDI has improved over time, but 16% of patients in this study received an RDI < 85%. Further evaluation is needed to identify factors associated with lower RDI and determine outcomes for these patients.
Chemotherapy of methioninase-synchronized S/G2 phase-blocked cancer cells identified by cell cycle-specific fluorescent reporters.

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Background: Cancer cells of all types have a generally elevated requirement for methionine compared to normal cells. This phenomenon is termed methionine-dependence and may be due to excessive methylation reactions in cancer cells, since methionine is the global source of cellular methyl groups (Biochim. Biophys. Acta, Reviews on Cancer 738, 49-87, 1984). Deprivation of methionine selectively arrests cancer cells during late S-phase (Proc. Natl. Acad. Sci. USA 77, 7306-7310, 1980), where they are highly sensitive to chemotherapy drugs which damage DNA (J. Natl. Cancer Inst. 76, 629-639, 1986). Methods: Cancer cells, transformed to express different color fluorescent reporters during specific phases of the cell cycle (Cell 132, 487-498, 2008), were used to monitor the onset of the S/G2-phase block due to methionine deprivation effected by recombinant methioninase (rMETase). The S/G2-phase blocked cancer cells fluoresced yellow or green in contrast to cancer cells in G1 which fluoresced red. Cancer cells, including MKN45 stromal cancer and MCF-7 breast cancer, synchronously blocked in S/G2-phase by rMETase, were identified by their yellow-green fluorescence and allowed to accumulate to the maximum extent. At the point of maximum yellow/green cells in the culture, the cells were administered chemotherapy drugs which interact with DNA or block DNA synthesis such as doxorubicin, cisplatin or 5-fluorouracil. We termed this procedure color-coded chemotherapy (CCC). Results: CCC was highly effective against the cancer cells (90% cell kill). In contrast, treatment of cancer cells with drugs only, and without rMETase-effected S/G2-phase synchrony, led to the majority of the cancer cell population being blocked in G1 phase (red fluorescent) where they were resistant to the drugs (40% cell kill). Conclusions: CCC, which identifies, by fluorescent color, when cancer cells are blocked in S/G2-phase by a unique cell-cycle-blocking agent, rMETase, demonstrates the potential of cell-synchronization-based chemotherapy.
Low-dose, short-course sunitinib may normalize tumor vasculature and improve tumor blood flow to enhance chemotherapy efficacy in breast cancers.

Soo-Chin Lee, Andrea LA Wong, Thian C Ng, Choon Hua Thng, Ting Ting Wang, Maricel Cordero Tiemsim, Eugene Ong, Tong San Koh, Dennis Cheong, Pei-Jye Voon, I Peng Thomas Soh, Ching-Wan Chan, Philip Iau, Chee Seng Tan, Angela Pang, Boon C. Goh; National University Cancer Institute, Singapore, Singapore; National University of Singapore, Singapore, Singapore; National Cancer Centre Singapore, Singapore, Singapore; Cancer Science Institute, National University of Singapore, Singapore, Singapore; National University Health System, Singapore, Singapore

**Background:** Small molecule VEGFR inhibitors (VEGFR-I) have failed to improve outcome with chemotherapy in most solid tumors. Continuous administration of a potent VEGFR-I may destroy vasculature and impede drug delivery; in contrast, low-dose, short-course VEGFR-I before chemotherapy may normalize tumor vasculature and enhance drug delivery. **Methods:** We conducted a phase Ib followed by phase II randomized study in patients with measurable primary breast tumors using low-dose sunitinib (Su) for 1 week prior to doxorubicin/cyclophosphamide (AC) and measured tumor blood flow with DCE-MRI and microvessel density and pericyte recovery with CD31 and α-smooth muscle actin (SMA) staining on tumor biopsies, at baseline, after 1 week of Su, and 2 weeks after cycle 1 AC. Patients in phase Ib received 12.5-25mg Su prior to AC; in phase II, patients were randomized to AC+/−12.5mg Su. **Results:** 21 patients have been enrolled, including 3 patients on 25mg Su/AC, 11 on 12.5mg Su/AC, and 7 on AC alone. After 1 week of 25mg Su, 2/3 patients had reduced tumor blood flow on DCE-MRI indicating anti-angiogenic effects. After 1 week of 12.5mg Su, significant increase in tumor fractional plasma volume (Vp) occurred (+28%±28%, p=0.025) suggesting increased perfusion, followed by decrease 2 weeks after AC (-33%±26%, p=0.035) corresponding to mean tumor size change of -17±15%, while no significant Vp changes occurred with AC alone (p=0.823); CD31 expression reduced (20.7 vs 15.7, p=0.173) while SMA/CD31 double staining increased (2.45 vs 7.34, p=0.046) indicating lower microvessel density and normalization of residual vasculature, which was not seen with AC alone (CD31, p=0.434; CD31/SMA, p=0.605). The main toxicity of Su/AC and AC alone was febrile neutropenia (29% vs 43%). 14 patients had surgery with pathological complete response in 1/6 patients who received 12.5mg Su/AC. **Conclusions:** 25mg Su for 1 week can reduce tumor blood flow, suggesting that concomitant standard dose Su may compromise drug delivery. Low dose 12.5mg Su for 1 week is sufficient to normalize tumor vasculature and increase tumor fractional plasma volume, and may potentially improve drug delivery and treatment outcome.
Efficacy of low-dose capecitabine in metastatic breast cancer.

Caitlin Bertelsen, Lingyun Ji, Christy Ann Russell, Darcy V. Spicer, Agustin Garcia, Richard Sposto, Debu Tripathy; Keck School of Medicine of the University of Southern California, Los Angeles, CA; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Children's Hospital Los Angeles, Los Angeles, CA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: The FDA-approved dose of capecitabine (cape) of 1250mg/m² twice daily (BID) is associated with treatment-limiting toxicities. Published reports suggest that lower starting doses of cape can be as effective as the approved dose in treating metastatic breast cancer (MBC). We compared the efficacy of lower than previously published doses of cape with results of registrational Phase III trials using the approved dose. Methods: We performed a retrospective analysis of patients treated at the University of Southern California hospitals who received cape as the first, second, or third line of chemotherapy for MBC to determine the progression-free survival (PFS) associated with low starting doses. The primary endpoint was PFS among patients with measurable disease, and secondary aims were to analyze the relationships between PFS and various clinical characteristics for all patients. Results: Patients (n=84) received a median cape dose of 565 mg/m² BID, often administered as a flat dose (not adjusted for body surface area) of 1000 mg BID. Median PFS among patients with measurable disease (n=62) was 4.1 months (95% confidence interval or CI = 2.9-5.7), which was similar to the median PFS values of 4.4 months (95% CI = 4.14-5.42, n=480) (Sparano et al. JCO 2010;28:3256) and 4.2 months (95% CI = 3.81-4.50, n=377) (Thomas et al. JCO 2008;25:5210) for single-agent cape reported in the major trials with similar eligibility criteria. Among all patients, PFS was shorter in measurable disease, triple negative and HER2− subtypes, and was similar in all lines of therapy. Only two patients (2.4%) discontinued cape due to toxicity. Conclusions: These data support the efficacy of very low doses of cape for MBC. Prospective randomized controlled trials testing lower starting doses of cape are needed to optimize the benefit/risk ratio.

<table>
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<th>Variable</th>
<th>Median PFS (mo)</th>
<th>Multivariate PFS OR</th>
<th>p value</th>
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<tr>
<td>Entire cohort</td>
<td>4.4</td>
<td>Ref; 1.6</td>
<td>0.13</td>
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<td>19.7; 4.1</td>
<td>Ref; 3.2; 2.5</td>
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<td>Ref; 0.42; 0.36</td>
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</tr>
<tr>
<td>No trastuzumab; trastuzumab in HER2+</td>
<td>4.1; 9.6</td>
<td>Ref; 0.31</td>
<td>0.079</td>
</tr>
</tbody>
</table>

OR = odds ratio; DFI = disease free interval; Ref = reference; yr = year.
Early changes in angiogenesis and hypoxia following bevacizumab therapy in primary breast cancer.

Shaveta Mehta, Nicholas Peter Hughes, Adrian M. Jubb, Helen Turley, Chen Han, Sonia Patricia Li, N Jane Taylor, Anwar R. Padhani, Rosemary Frances Adams, Andreas Makris, Adrian L. Harris; University Department of Oncology, Oxford, United Kingdom; Molecular Imaging Program, Stanford University, Stanford, CA; Department of Pathology, Genentech Inc, South San Francisco, CA; Clinical Laboratory Sciences, John Radcliffe Hospital, Oxford, Oxford, United Kingdom; Mount Vernon Cancer Centre, Middlesex, United Kingdom; Paul Strickland Scanner Centre, Mount Vernon Hospital, London, United Kingdom; Mount Vernon Cancer Centre, London, United Kingdom; Oxford University Hospitals NHS trust, Oxford, United Kingdom

Background: Bevacizumab (BV), a monoclonal antibody directed against vascular endothelial growth factor (VEGF), is an approved anti-angiogenic agent, but despite its widespread use, little is known about how tumours develop resistance to BV. We have conducted a window-of-opportunity study in which BV is administered as a short-term first-line treatment for primary breast cancer (PBC) patients, and assessed histological markers of tumour angiogenesis and hypoxia before and after therapy. Methods: 47 patients with locally advanced breast cancer were prospectively enrolled. Informed consent was obtained from all patients. A single infusion of BV (15 mg/kg) was given 2 weeks before starting neoadjuvant chemotherapy. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and core biopsies for immunohistochemistry (IHC) analysis were performed immediately prior to and 2 weeks after BV. 36 patients with invasive ductal carcinoma and good quality MRI scans and core biopsies were included in this analysis. Wilcoxon rank test and Spearman’s correlation test were used for statistical analysis. Results: IHC revealed a significant upregulation of carbonic anhydrase 9 (P < 0.04) and hypoxia inducible factor-1a (P < 0.001) following BV therapy along with a significant reduction in plasmalemma vesicle associated protein (PLVAP) (p=0.01) and Ki67 (p= 0.006). DCE-MRI analysis revealed a significant reduction in vessel permeability and blood flow following BV, as measured by a decrease in the forward transfer constant $K_{\text{trans}}$ (P < 0.0001) and the reverse rate constant $k_{\text{ep}}$ (P < 0.0001). In addition, we found a significant negative correlation between CA9 levels and median $K_{\text{trans}}$ at baseline (Spearman’s rho = -0.46; P = 0.01). Conclusions: Using combined DCE-MRI and IHC analysis, we found that PBC patients treated with single-agent BV showed a decrease in markers of tumour angiogenesis, together with a corresponding increase in tumour hypoxia. Our results suggest that tumour hypoxia may be a key mechanism governing the early onset of resistance to BV therapy, and argue for the use of suitable combination therapies to overcome the resistance and ultimately improve patient survival.

Background: The pathological tumor response in patients with locally advanced breast cancer to NACT is essential for survival and for surgical strategies. Therapy monitoring based on German recommendations is routinely performed by clinical examination, MG and 2DUS. The clinical value of MRI and 3DUS has not been established yet. The aim of the study was to determine the accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) between the different imaging techniques in predicting postoperative histological tumor response after NACT. Methods: Patients with primary breast cancer (cT1-T4, cN0-1, M0) undergoing neoadjuvant chemotherapy between 2005 and 2010 were eligible for this prospective trial. The response was measured by MRI, MG, 2DUS and 3DUS for complete or partial remission versus stable disease after the last cycle of treatment and compared with the final pathological response. Patients with progressive disease were excluded from the study. Statistical analysis was done by calculating the accuracy of each imaging technique and the size difference between imaging and histological tumor size. Sensitivity, specificity, PPV and NPV were calculated for complete or partial pathological response. The study was approved by the local ethic committee (BCD001 194/2004). Results: 103 patients with the mean age of 47.7 (range 24.5 – 71.4) years were evaluated. The accuracy was 0.680 (95%CI: 0.580 -0.768) for MRI, 0.563 (95%CI: 0.453-0.669) for MG, 0.724 (95%CI: 0.618 -0.815) for 2DUS and 0.710 (95%CI: 0.588-0.813) for 3DUS. Sensitivity, specificity, PPV and NPV were 78%, 47%, 75% and 52% for MRI, 61%, 45%, 69% and 36% for MG, 93%, 23%, 74% and 60% for 2DUS, 94%, 19%, 73% and 57% for 3DUS. The mean (standard deviation) size difference was -1.8 mm (14.8) on MRI, 1.5 mm (26.0) on MG, -9.1mm (19.1) on 2DUS and for the volume difference -6916mm3 (15831) on 3DUS. Conclusions: The data suggest that 2DUS is sufficient in predicting tumor response between NACT treatment. MRI and MG are more accurate the 2DUS in predicting the tumor size for surgical planning.
Patient-reported pain and other symptoms as prognostic factors for overall survival (OS) in a phase III clinical trial of patients with advanced breast cancer.

Wei Shen, Ping Wang, Emily Nash Smyth, Lee Bowman, Patrick Peterson, William J. John, Allen S. Melemed; Eli Lilly and Company, Indianapolis, IN

Background: The safety and efficacy of gemcitabine plus paclitaxel versus paclitaxel in advanced breast cancer after anthracycline-based adjuvant therapy has been reported previously (Albain et al. 2008). This post-hoc analysis evaluates the prognostic effect of baseline scores of the Brief Pain Inventory short form (BPI-SF) and the Rotterdam Symptom Checklist (RSCL) on OS. Methods: Patients completed the BPI-SF and the RSCL. BPI “worst pain” item and BPI interference subscale scores range from 0 (no pain or interference with daily living) to 10. Four RSCL subscales were transformed to 0-100, with 100 as best score. Univariate Cox models were used to determine the prognostic effect of each measure on OS. Multivariate Cox models were used to determine the prognostic effect of each measure in the presence of 11 demographic/clinical variables, including Karnofsky performance status, age, and estrogen and progesterone receptor status. Kaplan-Meier curves and log-rank tests were used to compare OS among patient groups categorized using clinically meaningful thresholds and the sample median of the BPI and RSCL scores. Results: Randomized patients were evaluable for this analysis (n=529). In the univariate analysis, significant prognostic effects on OS were observed for baseline scores of both BPI measures (worst pain and interference) (HRs, 1.07 for 1-point increase; all p<0.0042) and three out of four RSCL subscales (activity level, physical distress, quality of life) (HRs, 0.86-0.91 for 10-point increase; all p=0.0120). In the multivariate Cox models, BPI worst pain remained as a significant prognostic factor (p=0.0245), as did RSCL activity level (p=0.0004). The median OS for patients with BPI worst pain score 0 (no pain) was 23.8 months (mos) versus 17.9 mos and 14.8 mos for scores 1-4 (mild) and 5-10 (moderate/severe) (log-rank p=0.0066). The median OS was 23.8 mos for patients with RSCL activity scores greater than or equal to the sample median (≥95.2) versus 14.6 mos for patients with scores <95.2 (log-rank p<0.0001). Conclusions: This retrospective analysis resulted in strong evidence that BPI-SF and RSCL provide distinct prognostic information for OS.
General Poster Session (Board #23D), Sat, 8:00 AM-12:00 PM

Cost-effectiveness analysis using a Markov model assessing the addition of bevacizumab to paclitaxel in HER2-negative metastatic breast cancer patients.

Tamer Refaat, Mehee Choi, Germaine Gaber, William Small, Krystyna D. Kiel; Northwestern University, Chicago, IL; Alexandria University, Alexandria, Egypt; Rush University Medical Center, Chicago, IL

Background: Metastatic breast cancer (MBC) remains an incurable disease despite advances in treatment modalities. In 2008, Eastern Cooperative Oncology Group 2100 trial (E2100) results led to FDA approval for bevacizumab with paclitaxel in the initial treatment of HER2-negative MBC. The addition of bevacizumab to paclitaxel led to a gain of around 2.5 months of progression-free survival (PFS), no significant benefit on overall survival (OS), and increased toxicity. In November 2011, the FDA officially revoked approval of bevacizumab for HER2-negative MBC. However, both the European Medicines Agency (EMEA) and NCCN still endorse bevacizumab for this indication. One of the greatest challenges facing healthcare worldwide is reconciling incremental clinical benefits with exponentially rising costs. This study aimed to assess the cost-effectiveness of bevacizumab with paclitaxel for HER2-negative MBC.

Methods: A Markov decision tree using Data 3.5 (TreeAge Software, Inc.) was created to do decision and cost-effectiveness analyses of using bevacizumab in combination with paclitaxel versus paclitaxel alone as first-line chemotherapy in HER2-negative MBC using efficacy and toxicity data from the E2100 study. Costs were obtained from the Center for Medicare Services Drug Payment Table and Physician Fee Schedule. The model was designed from the patient and payer perspectives and sensitivity analyses were run.

Results: The marginal cost between paclitaxel alone versus bevacizumab and paclitaxel was 86K with a marginal efficacy of 0.369 quality-adjusted life-years and marginal cost effectiveness of 232,720.72 USD. The expected outcome value was 1.86 for bevacizumab and paclitaxel and 1.67 for paclitaxel alone. However, the combination was not cost effective and only a marginal survival advantage that was not significant was observed.

Conclusions: This study demonstrates that, despite a significant PFS advantage, the addition of bevacizumab to paclitaxel is not cost-effective for patients with HER2-negative MBC. Such data could be informative to policymakers who consider the health economics and incremental cost-effectiveness of medical therapies.
Phase I trial of ixabepilone and vorinostat in metastatic breast cancer.

Thehang H. Luu, Suzette Blanchard, Jan Hendrik Beumer, Bean N. Anyang, George Somlo, Joanne E. Mortimer, Arti Hurria, Lixin Yang, Yun Yen; City of Hope, Duarte, CA; University of Pittsburgh Cancer Institute, Pittsburgh, PA

**Background:** VOR, an HDAC inhibitor, induces acetylation of tubulin, and decreases resistance by attenuating downstream activation of AKT, c-Raf and HER-2. Patients (pts) with MBC treated with VOR had a TTP of 8.5 months (range 4-14) and stable disease in 29% (Luu et al., 2008). Our preclinical data showed synergistic effect of IXA and VOR in MDA-MB-231 and MCF7.

**Methods:** The primary aims were to: 1) define the maximum tolerated dose (MTD) based on dose limiting toxicities (DLT), and 2) describe the pharmacokinetics (PK) of 2 schedules of VOR and IXA. Secondary aims were to describe: 1) response rate (RR) and 2) clinical benefit rate (CBR). The study included: 1) pts with MBC; 2) ECOG PS 0-2; 3) adequate marrow and organ functions; 4) no prior IXA or VOR; and 5) grade (gr) 1 neuropathy. Stable brain metastasis were allowed. Pts were randomized to schedule A: VOR (QDx14) + IXA (D2) Q21D; or B: VOR (D1-7 and 15-21) + IXA (D2, 9, 16) Q28D. A modified toxicity probability interval design (target toxicity rate 0.2 and equivalence range -0.05) (Ji et al, 2010) determined dose escalation guidelines. PK were assessed with LC-MS/MS assays.

**Results:** Among 37 pts randomized, 36 were evaluable [median age (55 yrs); median prior chemotherapy regimens (3); ER and/or PR (64%); HER2 (19%)]. In cohort A, 16 pts were treated (1 inevaluable). The MTD was: VOR 300mg (QDx14) + IXA (32mg/m^2 D2) Q21D (dose level 1). DLT was experienced by 27% (4/15) pts [gr 4 neutropenia, gr 3 fatigue/AST, hyponatremia and allergic reaction to IXA]. In cohort B, 21 pts were treated (dose level 1, n=15; dose level 2, n=6). The MTD was VOR 300mg QD (D1-7 and 15-21) + IXA 16mg/m^2 (D2, 9, 16) Q28D (dose level 1), no DLTs were observed. Dose level 2 was closed with 50% (3/6) of pts experiencing DLTs [gr 3 neutropenia, hypertension, and hypokalemia]. Median cycles treated (cohort A: 6, cohort B: 4). Response in cohort A and B respectively was: 1 CR, 2 PR, 7 SD (RR: 20%, CBR: 67%) and 1 CR, 4 PR, 9 SD (RR: 33%, CBR: 93%). VOR and IXA PK were not influenced by the presence of the other drug, clearance values = 220 L/h and 20 L/h/m^2, respectively. **Conclusions:** We established the MTD of VOR and IXA in pts with MBC. The combination demonstrated clinical activity in these heavily pretreated pts. Further studies are recommended.
Outcomes of 47 patients with human immunodeficiency virus infection treated for breast cancer: A 20-year experience.

Roberto Enrique Ochoa, Christos Kyriakopoulos, Judith Hurley; University of Miami, Miami, FL; University of Miami, Miami, FL; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Patients (pts) with Human Immunodeficiency Virus (HIV) are living longer and non-AIDS defining malignancies have been increasingly reported in these patients. Methods: Retrospective review identified 47 pts with breast cancer (BC) and HIV who were seen at the University of Miami Sylvester Comprehensive Cancer Center/Jackson Memorial Hospital between January 1999 and June 2011. Results: Pt characteristics: 46 female, 1 male, mean age 46 years (range 31-65). Race: African American 79%, Caucasian 21%. Ethnic: Hispanics 14%, non-Hispanics 86%. Premenopausal 68% postmenopausal 32%. Tumor characteristics: Stage: Tis 4%, Stage I: 6 %, Stage II: 38%, Stage III: 38%, Stage IV: 9%. ER positive (50%) her-2 positive (15%), Triple negative (21%). HIV characteristics: 36 pts with HIV before or concurrent with the diagnosis of BC. 6 pts diagnosed with HIV within 1 year of BC diagnosis. HIV dx date unavailable in 5 pts. 27% had AIDS. CD4 counts (in cells/µL) were: > 500 (23%); 201-500 (37%), 51 – 200 (20%) < 50 (20%). 15 pts were diagnosed with BC in preHAART era. Of those dx with BC after 1996, 60% were on HAART. BC treatment: 43 pts had localized disease. 32 underwent modified radical mastectomy and 3 pts refused surgery. 26 pts received curative or palliative chemotherapy. Complications of BC treatment: serious side effects were reported in 11 (42%) including neutropenic fever/sepsis (10 pts), ARDS (1 pt). Zoster infection was reported in 12% of the pts. 3 patients developed rapidly progressive and fatal AIDS within 6 months of completion of chemotherapy. Survival: See Table. Conclusions: BC in patients with HIV infection spans the spectrum of BC presentations. Hormonal therapy, surgery and radiation therapy were well tolerated. Infectious complications were common in patients treated with chemotherapy and routine use of growth factors and prophylactic acyclovir should be considered.

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Prognostic impact of weight change during chemotherapy.

Nikola S. Kasprowicz, Philip Gm Hepp, Ulrich Andergassen, Christoph Scholz, Katja Annecke, Arthur Wischnik, Wolfgang Simon, Helmut Forstbauer, Doris Augustin, Thomas Zwingers, Nadia Harbeck, Harald Leo Sommer, Klaus Friese, Marion Kiechle, Wolfgang Janni, Brigitte Kathrin Rack; Department of Gynecology and Obstetrics, Heinrich Heine University, Duesseldorf, Germany; Department of Gynecology and Obstetrics, Ludwig-Maximilians-University, Munich, Germany; Department of Obstetrics and Gynecology, Technical University Munich, Munich, Germany; Zentralklinikum Augsburg, Augsburg, Germany; Robert-Bosch-Krankenhaus, Stuttgart, Germany; Onkologie Troisdorf, Troisdorf, Germany; Klinikum Deggendorf, Deggendorf, Germany; Estimate, Augsburg, Germany; Breast Center, Department of Obstetrics and Gynecology, Ludwig-Maximilians-University, Munich, Germany; Department of Gynecology, Cancer Center of the Ludwig-Maximilians-University, Munich, Germany

Background: Besides established prognostic factors such as tumor size or nodal status, individual host factors of the patient such as obesity, physical activity and diet seem to modulate the course of breast cancer (BC) as well. However, the specific impact of weight change during adjuvant chemotherapy remains unclear. The aim of this analysis was to evaluate the influence of weight change during chemotherapy on BC survival in a large, multi-center prospectively randomized trial. Methods: The ADEBAR trial compares two anthracycline based adjuvant chemotherapy regimen in patients (pts) with lymph node positive (>3 positive) early BC: 4x epirubicin (E) 90 mg/m² + cyclophosphamide (C) 600 mg/m² q3w followed by 4x docetaxel 100 mg/m² q3w versus 6x E 60 mg/m² d1 + d8 and C 75 mg/m² d1-14 q4w. Weight was measured before each cycle. The weight before the 1st and the 6th cycle was assessed. Significant weight change was defined as increase or decrease of >5% of the initial weight. Overall survival (OS), disease free survival (DFS), and BC specific survival (BCSS) were assessed by Kaplan-Meier analysis. Results: In total, 1502 pts were included in the study. 1177 of them completed 6 cycles of chemotherapy. Out of the 350 pts (29.7%) who changed weight 142 pts (12.1%) lost and 208 pts (17.7%) gained weight. There was a significant correlation between weight change and menopausal status (p<0.0001), indicating that more premenopausal pts gained and postmenopausal pts lost weight. All other tumor characteristics were similarly distributed across the groups. Pts with weight change >5% showed a significantly worse outcome with respect to OS (p = 0.0028) and BCSS (p = 0.0258). A difference in DFS was not observed (p = 0.1917). The difference in OS was limited to pts who lost weight (p = 0.0008), whereas pts with weight gain have no significant different OS (p = 0.1246) in comparison to pts with constant weight. Conclusions: Our results suggest that weight loss during anthracycline-based treatment of early stage BC is associated with poorer OS. While weight normalization has shown beneficial effects in lifestyle intervention trials, patients should be advised not to lose weight during chemotherapy.
Phase III trial of first-line treatment with gemcitabine plus docetaxel versus gemcitabine plus paclitaxel in women with metastatic breast cancer (MBC): A comparison of different schedules and treatment.

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Background: Weekly (W) administration of Gemcitabine/Docetaxel (G+D) or Gemcitabine+Paclitaxel (G+P) at low doses may be associated with greater efficacy and/or lower toxicity compared to the standard 3-weekly (3W) schedule. Methods: Patients (pts) (360) with MBC, that relapsed after one adjuvant/neoadjuvant regimen containing an anthracycline (unless contraindicated) that was completed for at least 12 months, were to be randomized equally to a) D 75mg/m² on Day1 + G 1000mg/m² on Days1/8 q3W ; b) P 175mg/m² on Day1 + G 1250mg/m² on Days1/8 q3W ; c) D 30mg/m² + G 800mg/m² on Days1/8/15 qW; or d) P 80mg/m² + G 800mg/m² on Days1/8/15 qW. Primary endpoint was time to progression (TTP). Secondary endpoints were overall survival (OS), overall response rate (ORR) and overall toxicity (T). Results: Due to slow accrual rate, a futility analysis was performed to evaluate the chance of observing a significant result in favour of the alternative hypothesis. The results from this led to early study termination. 241 pts [median age (range) 57.0(31-77) years] were enrolled and randomized to: 3W G+D 60(24.9%); 3W G+P 58(24.1%); W G+D 59(24.5%), of which 18(30.0%), 24(37.5%), 14(24.1%) and 19(32.2%) pts respectively completed the study protocol (i.e. received 6 cycles, extended up to 10 for partial/complete responders). Median TTP [months(95%CIs)] was 8.33 (6.19-10.16) in W and 7.51 (5.93-8.33) in 3W, with 86.3% of pts progressed in each schedule. OS did not significantly differ between treatments and schedules. ORR was comparable between D and P, while it was higher in W than in 3W (50.4% vs. 33.1%; odds ratio 0.44 [95%CI: 0.26-0.75], p=0.003). Grade 3/4 Ts were 69.2% and 71.9% of pts in D and P and showed a higher trend in 3W (75.2%) than in W (65.8%). Neutropenia was the most frequent grade 3/4 T (51.7% and 44.7% in D and P; 39.3% and 56.5% in W and 3W). Conclusions: No substantial differences between treatments were observed in safety and efficacy. W might be associated with lower grade 3/4 Ts and possibly with a better tumour response compared to 3W. These results should be interpreted with caution due to early termination of the study.
Impact of the delivery of adjuvant anthracycline-based nontaxane chemotherapy schedules on the outcome of breast cancer patients: Results from a retrospective database analysis.

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Background: A dose-response effect has previously been observed with CMF and anthracycline-based schedules. The objective of this post-hoc analysis was to give additional information on the impact of chemotherapy delivery on patients’ outcome. Methods: Selection criteria were to have early breast cancer (stage I-IIIA) from Jan 1980 to Dec 2000, to undergo surgery as primary treatment and to receive an anthracycline-based non-taxane schedule in the adjuvant setting. G-CSF support was not given to any patient. Chemotherapy delivery was assessed based on ≥ 2 vs. < 2 delayed cycles, ≥ 15 vs. <15 delayed days and < 85% vs. ≥ 85% of the relative dose intensity (RDI) given. Patients’ outcomes were assessed based on 5- and 10-year disease-free survival (DFS) and overall survival (OS) rates. Results: 793 breast cancer patients with a median age of 51 years (21-79) were analyzed of whom 27% had stage IIIA and 23% had stage I disease. As shown in the table, 5- and 10-year rates of DFS and OS significantly improved when adjuvant chemotherapy was optimally delivered. Conclusions: The dose-response effect is a key factor that should be taken into account when an anthracycline-based non-taxane chemotherapy is administered in the adjuvant setting. Delays and/or reductions of chemotherapy should be avoided in order to achieve the maximal benefit for the patient. This study was partially funded by Amgen SA.
Cancer stem cell markers in locally advanced breast cancer.

Daniel G. Tiezzi, Renata D Sicchieri, Heriton MR Antonio, Larissa R Mouro, Joao Santana da Silva, Jurandyr Moreira de Andrade, Breast Disease Division - FMRP; University of São Paulo, Ribeirão Preto, Brazil

Background: The expressions of CD44/CD24, CXCR4 and ABCG2 have been reported as potential breast cancer stem-like cell (CSLC) markers. The association between the quantity of CSLCs and the response to neoadjuvant chemotherapy (NACT) remains unclear. Methods: We prospectively analyzed the expression of CD44/CD24, CXCR4 and ABCG2 in 20 patients with locally advanced or metastatic (LAMBC) invasive ductal carcinomas of the breast subjected to NACT. The mammosphere assay (Mammocult) was studied in 10 samples. Patients’ mean age was 55.6 ± 8.2 yo. According to clinical stage (CS), 5 patients were IIb, 4 - IIIa, 8 - IIIb and 3 - IV. The mean clinical tumor diameter was 6.3 ± 2.8 cm. The ER, PgR and HER2 positive expression rates were 50%, 45% and 50%, respectively. Ten patients were treated with EC-T, eight were treated with EC-TH (HER2+) and two were treated with FEC75 combination as NACT. The median percentage CD44+/CD24-, CXCR4+, ABCG2+ and ESA+ cells within Lin- cells were determined by flow cytometry in fresh sampled tumors after tissue digestion. The relationship between flow cytometry analyses and clinical and pathological response to therapy was analyzed. Results: Complete clinical response (cCR) and complete pathological response (pCR) was observed in 9 (45%) and 5 (25%) patients. We did not observe a significant association between pCR and ER, PgR or HER2 expression. We observed association between the pCR with percentage of ABCG2+ cells within the tumor and with the number of mammospheres. No correlation between pCR and CD44+/CD24- cell population within the tumor was observed. The median percentage of ESA+/Lin+/ABCG2+ cells within the tumor in pCR patients was 0.6% and 3.5% in patients with no pCR (p = 0.02). The median number of sphere formation was 5/100 cells and 0.9/1000 cells in pCR and non-pCR patients, respectively (p = 0.02). Interestingly, there was a positive correlation between ABCG2 expression and the number of mammosphere formation (r = 0.66; p = 0.03). This correlation was not significant comparing to CD44+/CD24- cells or CXCR4. Conclusions: The percentage of ABCG2+ cancer cells within the tumor and the number of mammosphere formation are predictive factors for pCR in LAMBC patients subjected to NACT. ABCG2 is a potential marker for CSLCs.
EEG for evaluation of “chemobrain.”

Halle C. F. Moore, Michael W. Parsons, Guang H. Yue, Lisa A. Rybicki, Vlodek Siemionow; Cleveland Clinic, Cleveland, OH; Kessler Foundation, West Orange, NJ

**Background:** Cognitive impairment is a poorly understood and worrisome potential complication of adjuvant chemotherapy (CT). We sought to evaluate electroencephalography (EEG) as a means to measure neurophysiologic function in women receiving CT for early breast cancer. **Methods:** Women planning to undergo CT for operable breast cancer and age-similar controls were evaluated at baseline, during CT and at 1 year with neurophysiologic assessments. Testing included a brief fatigue inventory (BFI), brief mental fatigue assessment (BMF), Processing Speed Index (PSI) derived from Digit Symbol Coding and Symbol Search subtests of the Wechsler Adult Intelligence Scale, and a sustained elbow flexion physical task (PT). EEG recordings were obtained at rest and after the cognitive and physical tasks. Data were analyzed using repeated measures of analysis of variance. **Results:** Eight patient/control pairs completed baseline and on-treatment evaluations; 7 pairs also completed the 1 year assessment (1 pair withdrawn due to a second malignancy). Subjective mental fatigue measured by BMF is similar for patients and controls at baseline but BMF scores increase significantly during CT for patients relative to controls (p=0.033), recovering to no difference at one year. Differences in PSI are not observed between patients and controls or at the different time points. BFI scores are greater in patients at all 3 time points but endurance on the PT is no different from controls. During chemotherapy EEG total spectrum amplitudes in patients are greater than in controls at rest (p=0.05) and following both the cognitive (p<0.001) and physical (p<0.001) tasks. EEG activity prior to chemotherapy and at one year is not different between patients and controls. For patients but not controls EEG readings after the cognitive task demonstrate greater amplitude than pre-task readings during the time of CT treatment only (p=0.012) with a similar trend seen for the physical task (p=0.06). **Conclusions:** Patient-perceived mental and physical fatigue during chemotherapy correspond to significant changes in EEG brain activity patterns but not to cognitive testing or physical endurance testing. EEG may offer a sensitive means to measure alterations in brain function associated with CT.
Analysis according to prognostic factors in patients (pts) treated with first-line bevacizumab (BEV) combined with paclitaxel (PAC) for HER2-negative metastatic breast cancer (mBC) in a routine oncology practice study.

Iris Schrader, Frank Gerhard Foerster, Andreas Schneeweiss, Matthias Geberth, Lars Hahn, Claudia Schumacher, Martin Michael Hertz-Eichenrode, Winfried Schoenegg, Matthias Kim Wolfgang, Andreas Kutscheidt, Marcus Schmidt, Bahriye Aktas; Gynäkolog.-onkolog. Gem.Praxis, Hannover, Germany; Schwerpunktpraxis Gynäkologische Onkologie, Chemnitz, Germany; National Center for Tumor Diseases, Heidelberg, Germany; SPGO-Mannheim, Schwerpunktpraxis fuer Gynaekologische Onkologie, Mannheim, Germany; Praxisklinik – Dialysezentrum Herne, Herne, Germany; St. Elisabeth Hospital, Köln, Germany; Gemeinschaftspraxis Hertz-Eichenrode, Remscheid, Germany; Praxis Dr.med. Winfried Schönegg, Berlin, Germany; University Hospital, Bonn, Germany; WisP Clinical Research Organisation, Langenfeld, Germany; Department of Obstetrics and Gynecology, Johannes Gutenberg University, Mainz, Germany; Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany

Background: 1st-line BEV combined with weekly PAC significantly improves progression-free survival (PFS) and response rate (RR) vs PAC alone in HER2-negative mBC, as shown in E2100. We analyzed data from a German routine oncology practice study of 1st-line BEV–PAC according to prognostic factors.

Methods: Pts who had received no prior chemotherapy for mBC received BEV–PAC according to the European label. Efficacy and safety were documented for up to 1 y (or until progression, death, or BEV discontinuation if earlier) with additional long-term follow-up. Efficacy was analyzed in clinically important subgroups. Results: Efficacy data were available for 818 pts. The median duration of follow-up was 11.4 mo. The composition of the pt population with respect to the subgroups below was generally similar to the population treated in E2100, except for a higher proportion of pts with visceral disease or metastases in <3 organs. RR was very similar across all subgroups analyzed. Differences in median PFS and OS were generally in line with the differing prognoses according to clinical characteristics. Conclusions: These data suggest that 1st-line BEV–PAC is typically associated with median PFS >9 mo in the real-life setting, irrespective of baseline characteristics.

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Comparing the outcome between multifocal, multicentric, and bilateral breast cancer and the impact of guideline-adherent adjuvant treatment: A retrospective multicenter cohort study of 5,308 patients.

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**Background:** Beside unifocal-unilateral (UU) breast cancer (BC) there are several subtypes including multifocal, multicentric and bilateral BC. This study tries to answer the following questions: (1) Does localization (multifocal-multicentric/bilateral) influence outcome concerning BC mortality? (2) Is there an impact of guideline-adherent adjuvant treatment in these BC subtypes? **Methods:** This German multi-center retrospective cohort study called BRENDA included 5277 patients obtained from 1992 until 2005. The definition of guideline adherence was based on the German national S3 breast cancer guideline (2004). **Results:** 4085 (77.4%) were UU, 698 (13.2%) multifocal, 282 (5.3%) multicentric and 212 (4.0%) bilateral BC. RFS in multifocal \( p=0.003; \) HR = 1.35 (95% CI: 1.11-1.65), multicentric \( p<0.001; \) HR = 1.76 (95% CI: 1.31-2.34) and bilateral \( p<0.001; \) HR = 2.28 (95% CI: 1.76-2.97) BC was significantly lower compared to unilateral-unifocal BC. Concerning OAS we found only a borderline difference between UU and unilateral-multifocal \( p=0.057; \) HR = 1.22 (95% CI: 0.99-1.48), but a significant difference between multicentric \( p=0.018; \) HR = 1.42 (95% CI: 1.06-1.90) resp. bilateral \( p<0.001; \) HR = 2.87 (95% CI: 2.21-3.74) and UU-BC. There was a significant impact by guideline adherent adjuvant therapy \{UU: \( p<0.001; \) HR = 2.76,95%C.I.:2.25-3.38, \} [unilateral-multifocal: \( p=0.001, \) HR = 2.04,95%C.I.:1.33-3.14], [unilateral-multicentric: \( p=0.020, \) HR = 2.13,95%C.I.:1.13-4.01] and [bilateral: \( p=0.042, \) HR = 2.10,95%C.I.:1.03-4.31]. After stratifying for 100% guideline adherent treatment and adjusting for age, tumor size, nodal status and grading there was no significant difference in RFS/OAS in patients with multifocal \( p=0.282/p=0.610, \) multicentric \( p=0.829/p=0.609 \) or bilateral BC \( p=0.457/p=0.773 \) compared to patients with UU-BC. **Conclusions:** Patients with multicentric and bilateral BC have primarily a worse prognosis in terms of RFS and OAS. However if guideline adherent adjuvant treatment was applied it was no more possible to demonstrate significant differences in survival.

Bevacizumab, etoposide, and cisplatin (BEEP) in brain metastases of breast cancer progressing from radiotherapy: Results of the first stage of a multicenter phase II study.

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Background: With a general prolongation of survival, brain metastasis (BM) has become a common complication of breast cancer. However, management of BM remains a severe challenge. We hypothesized that bevacizumab (BE) could significantly enhance drug delivery of etoposide (E) and cisplatin (P), two of the cytotoxic agents that have moderate activity in BM of breast cancer, to brain tumors and thereby improve the efficacy. Methods: Breast cancer patients (pts) with BM progression after whole brain radiotherapy (WBRT) were enrolled. Pts received BE 15 mg/kg day 1, and E 70 mg/m²/day, days 2-4, P 70 mg/m²/day, day 2, every 21 days for a maximum of 6 cycles. The primary endpoint was a centrally assessed CNS objective response (CNS-OR) defined as a ≥50% reduction in the volumetric sum of all measurable CNS lesions in the absence of increasing steroid use, development of new CNS lesion, or progressive neurologic symptoms. Using a Simon's optimal two-stage design with 15% as a minimum interest in CNS-OR rate (by intent to treat analysis), 11 pts were needed at the first stage; and a total of 31 evaluable for the whole study. Results: Among 16 pts enrolled from Jan 2011 to Jan 2012, 12 pts were evaluable for treatment response at the time of abstract submission. Median age was 55 (range 34-66); 1 pt was ER+/HER2-, 5 pts were HER2+, and 6 pts were ER-HER2-. The median treatment cycles were 4.5 (range 1-6). Nine of 12 pts (75%; 95%CI 42.8-94.5) achieved CNS-OR including 6 pts (50%) with ≥80% and 3 pts (25%) with 50-80% CNS volumetric reduction, respectively. Two pts had non-CNS disease progression while CNS tumors remained under control. The median CNS progression free survival was 6.6 months (95% CI 0.8-12.4). Grade 3/4 toxicities included neutropenia, leukopenia, anemia, and platelet in 13 (25.5%), 6 (11.8%), 2 (3.9%), and 2 (3.9%) cycles, respectively. Seven pts (58.3%) had received dose reduction to E 60 mg/m² and P 60 mg/m². Early reporting of this study was approved by Data and Safety Monitoring Committee due to an extremely promising result. Conclusions: BEEP regimen has a significant anti-tumor effect for BM of breast cancer which progresses after WBRT.
Baseline comprehensive geriatric assessment to predict for toxicity of single-agent chemotherapy in elderly metastatic breast cancer patients: Results from the OMEGA study of the Dutch Breast Cancer Trialists’ Group.

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Background: A comprehensive geriatric assessment (CGA) systematically appraises the somatic, psycho-social and functional health status of elderly patients. If CGA can predict toxicity of chemotherapy in elderly cancer patients, this assessment could be useful in deciding on optimal treatment. In this analysis, we evaluated the association between frailty on CGA or Groningen Frailty Index (GFI), and grade 3/4 toxicity in metastatic breast cancer (MBC) patients treated with first-line chemotherapy. Methods: In the OMEGA study, MBC patients (≥ 65 years) were randomized between PEGdoxo 45mg/m² every 4 weeks or capecitabine 2000 mg/m² on days 1-14 every 3 weeks. Baseline geriatric assessment included functional status (ECOG performance status (PS), IADL), cognition (MMSE), mood (GDS), comorbidity (Charlson), polypharmacy and undernutrition (BMI) and GFI. Frailty on CGA was defined as one or more of the following: IADL ≤13, MMSE ≤23, GDS ≥5, BMI ≤20, ≥5 medications or Charlson ≥2. GFI score for frailty was ≥4. Results: In total, 78 patients were randomized (PEGdoxo 38, capecitabine 40), median age 75 years (range 65-86). ECOG PS was 0-1 in 78% of patients and 2-3 in 22%. So far, 72 patients were evaluable for toxicity and baseline CGA. Overall, 50 patients (70%) were frail on CGA, and 40 (55%) according to GFI. Grade 3/4 toxicity was associated with baseline CGA-fraility (odds ratio (OR) 4.00, 95% confidence interval (CI) 1.77-13.59, p=0.03) while GFI-fraility was not associated with toxicity (OR 1.11, 95% CI 0.85-1.46, p=0.43). Conclusions: In this randomized study on first-line single-agent chemotherapy in elderly MBC patients, baseline CGA demonstrated a good predictive value for grade 3/4 toxicity of chemotherapy but GFI did not.
Sequential treatment with epirubicin/cyclophosphamide, followed by docetaxel versus FEC120 in the adjuvant treatment of node-positive breast cancer patients: Final survival analysis of the German ADEBAR phase III study.

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Background: Based on meta-analytic evidence, taxane-containing adjuvant chemotherapy has been established as standard treatment in breast cancer (BC). However, in the MA-21 study, adriamycin-cyclophosphamide, followed by paclitaxel was significantly inferior FEC120. We prospectively compared a sequential epirubicin-docetaxel chemotherapy regimen to FEC120. Methods: The ADEBAR study was a multicenter phase III trial (n = 1502) to evaluate whether pts with > 3 axillary lymph node metastases BC benefit from a sequential anthracycline-docetaxel regimen (E90C–D: 4 cycles epirubicin [E] 90 mg/m² plus cyclophosphamide [C] 600 mg/m² q21d followed by 4 cycles docetaxel [D] 100mg/m² q21d) compared to dose-intensive anthracycline-containing polychemotherapy (FE120C: 6 cycles E 60 mg/m² d 1+8, 5-FU 500mg/m² d 1+8 and C 75 mg/m² d 1-14, q4w). The observation time (median – 95%CI) was 49.5 (47.4–51.3) m. Results: Treatment was stopped prematurely in 3.7% of the pts in the E90C–D arm and in 8.0% in the FE120C arm due to toxicity (p=0.0009). Antibiotic treatment was given in 10.4% (E90C–D) vs. 19.7% (FE120C), G-CSF support in 39.2% vs 61.4 % and erythropoietin stimulation in 8.7% vs. 20.0%, respectively (p<0.0001). Haematological toxicity (leucopenia, neutropenic fever, thrombocytopenia, anemia) was significantly higher in the FEC-arm. At the time of the current analysis, 369 events of recurrence were observed: 166 events in the FE120C group and 193 in the E90C–D group. The unadjusted hazard ratio (HR) was 0.877 (95 percent confidence interval, 0.722 to 1.065; p=0.3819, log-rank test). Overall survival in the two groups was not significantly different: (131 deaths with FEC vs. 134 with E90C–D (HR 0.996, 0.783-1.267, p=0.9691). Subgroup analyses, stratifying for tumor size, lymph node involvement, hormone receptor and HER2-neu status showed no significant difference between the two arms. Conclusions: Different toxicity profiles given, hematological toxicity in the FE120C group was more severe than in the E90C–D. In contrast to AC-P in earlier studies, EC-Doc provides a feasible and effective option to FEC120.
Participation in adjuvant clinical breast cancer trials: Is there a difference in survival compared to guideline adherent adjuvant treatment? A retrospective multicenter cohort study of 5,326 patients.

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**Background:** Clinical trials (CT) usually compare a standard treatment regime versus innovative new substances or regimens. However participation in CT is available for only few patients and exclusion criteria is usually very strict. Therefore this study tries to answer the following questions: (1) Does participation in adjuvant CT improve survival in breast cancer (BC)? (2) Is there a difference in survival compared to guideline adherence and what is the role of the other treatments surrounding adjuvant breast cancer treatment?

**Methods:** This German multi-center [17 participating hospitals all are certified as breast cancer centers] retrospective cohort study called BRENDA (BRENDA = quality of breast cancer care under evidence-based guidelines) included 5326 patients obtained from 1992 until 2005. The definition of guideline adherence was based on the German national S3 guideline for diagnosis and treatment of breast cancer (2004).

**Results:** 554 (10.4%) patients participated adjuvant clinical trials and 4772 (89.6%) not. There was a trend towards a significantly impaired RFS [p=0.17; HR=0.87 (95% CI: 0.71-1.06)] and OAS [p=0.65; HR=0.84 (95% CI: 0.65-1.09)] when comparing participants (PA) versus non-participants (NPA). When stratifying for guideline adherence (compared to PA-guideline conform in all adjuvant therapies) the outcome was not different in NPA-guideline adherent [RFS: p=0.13; HR=1.25 (95% CI: 0.94-1.67)] [OAS: p=0.83; HR=1.41 (95% CI: 0.96-2.06)]. However survival parameters were significantly impaired in non-guideline conform PA [RFS: p=0.005; HR=1.66 (95% CI: 1.16-2.38)] [OAS: p=0.01; HR=1.83 (95% CI: 1.15-2.92)] and non-guideline conform NPA [RFS: p=0.001; HR=1.70 (95% CI: 1.27-2.26)] [OAS: p=0.002; HR=1.82 (95% CI: 1.24-2.67)].

**Conclusions:** There is a strong association between guideline adherence in adjuvant treatment in BC and survival. PA in clinical trials trended to an improved survival, but only if guideline adherent treatment was applied. Patients who don’t have access to clinical seem to profit substantially of guideline adherent adjuvant treatment.
Randomized phase II study of two doses of pixantrone in patients with metastatic breast cancer (N1031, Alliance).

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Background: Pixantrone (Pix) is a novel aza-anthracenedione with structural similarities to mitoxantrone and promising activity against non-Hodgkin’s lymphoma. Due to the lack of iron binding it is theorized to exhibit less cardiotoxicity than the anthracyclines. Methods: N1031 is a phase II RCT of 2 schedules of Pix, in pts with MBC. Group A pts received 180mg/m2 IV q3 wks, and group B pts 85mg/m2 IV on days 1, 8, 15 q4 wks. Eligibility included prior exposure to anthracyclines and/or taxanes, and 1 to 3 regiments in the metastatic setting (minimum of 2 if no prior adjuvant therapy given). Due to lack of long term cardiac safety data no more than 12 cycles were allowed. Frequent cardiac imaging was performed per protocol. Primary endpoint was RR and secondary endpoints included PFS, OS, safety, and QOL. Planned sample size was 25 pts per group. Results: In total 46 pts were evaluable (23 per group), mean age 55.5 yrs (range 38-79), 37% PS 0, 52% PS 1, and 11% PS 2. 80% of pts had prior exposure to doxorubicin, 72% had prior (neo)-adjuvant therapy, 76% were ER+ and 57% received prior HT. Number of prior metastatic regiments was: 1 (28%), 2 (61%) and 3 (11%). Most common adverse events (%) of any grade were: alopecia (74), anemia (85), nausea (67), ANC decrease (87), and skin disorder (41). Grade 3-4 adverse events (%) at least possibly attributed to Pix and occurring in at least 2 pts were: ANC decrease (57), fatigue (9), increased AST (4%). One pt from each group (4%) had a grade 3 decrease in EF. There were no major differences between the two groups except for more oral mucositis in group A (35% vs 4%). Median number of cycles was 3 in group A (range 1-12) and 2 in group B (range 1-8). There was only 1 confirmed tumor response per group (4%,95% CI: 0.1-22%) prompting early termination of the trial. The median PFS was 2.7 mo (95% CI: 1.8-3.8), and the median OS was 8.9 mo (95% CI: 7.5-N/A). Conclusions: Pixantrone has insufficient activity in patients with MBC exposed to prior anthracyclines and/or taxanes. Adverse events were similar to prior experience with Pix. There were no major differences between the 2 schedules of administration. There was no significant cardiac toxicity seen in this trial. Correlative studies are underway.
Reduction of ovarian reserve in young early breast cancer patients: First data of a prospective cohort study.

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Background: Breast cancer is the most common malignancy in premenopausal women. Sideeffects of chemotherapy are well known nevertheless the precise effects on ovarian function are inadequately studied by now. Premenopausal women undergoing chemotherapy are at risk for symptoms of sexual hormone deficiency and impaired fertility. Searching for predictive parameters of ovarian reserve after chemotherapy this prospective cohort study has been set up. Methods: 36 young patients with primary breast cancer have been included in this trial after written consent (April 2010 to November 2011) and after the study was approved by the local review board. All women were premenopausal (< 46 years). They all received anthracycline based “A” neo- or adjuvant chemotherapy (as FEC) or combinations with taxanes “T” (as TAC or FEC/Dox). Before and 6 and 12 months after initiation of chemotherapy age and chemotherapy related changes in hormone (LH, FSH, E2 and Anti-Müllerian hormone) levels, antral follicle count and amenorrhea as parameters of endocrine function and fertility were assessed. The additional impact of parity, BMI and nicotine use on ovarian reserve was also evaluated. Results: There is a correlation of antral follicle count before and 1 year after chemotherapy and a negative correlation of age and follicle count before and after chemotherapy (n.s.). This analysis shows that patients receiving “T” compared to those with “A” have a significant increase of LH (p=0.025) and FSH (mean:24 vs. 59 IU/l, p=0.021) between visit 1 and 3. The type of chemotherapy has no influence on antral follicle count and AMH levels within the first 3 visits. BMI is negatively correlated with AMH at all time points (n.s.). BMI, nicotine abuse and age have no influence on the duration of amenorrhea, whereas patients with “T” showed 12 months of amenorrhea instead of 9 months in patients with "A" (n.s.). Conclusions: Our study will contribute to a better understanding and prediction of ovarian reserve of young early breast cancer patients undergoing chemotherapy. The 12 months follow up data suggest to offer fertility preserving measures before chemotherapy especially to patients planned for taxane containing chemotherapy.
Methallotionein expression and outcome in patients with metastatic breast cancer (MBC).

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Background: Platinum-based agents are important components of therapy of metastatic breast cancer (MBC) and triple negative breast cancer. Their use can be limited by development of resistance. Metallothioneins (MT) are low molecular weight proteins believed to bind bivalent metal ions such as platinum and zinc. MT expression has been associated with decreased survival in breast cancer patients. A proposed mechanism confers resistance to platinum-based agents by their inactivation or limitation of their activity by MT binding. Methods: MT expression in 99 women with MBC (selected at random from our database of 800 women with MBC) was determined from primary breast cancer tissue (n=80) or metastatic tissue (n=19). MT expression was determined by immunohistochemistry, and graded as negative, weak, moderate or strong. Clinical data was obtained through our database and supplemented by chart review. Overall survival from breast cancer diagnosis (OS), progression free survival for first metastastic regimen (PFS), and time from first metastasis to death or last update (metastatic survival, MS), were calculated through December 2011 using the log rank test. Results: Consistent with prior studies, moderate to strong MT expression was associated with decreased 5-year OS (p=.03). There was no correlation between MT expression and PFS or MS in this cohort. Surprisingly, MT expression at any degree was strongly associated with better MS in patients with MBC that received carboplatin-based regimens in the first line (n=25, p=.0005) or at any line (n=41, p=.0437). Conclusions: Consistent with prior studies, MT expression was associated with decreased survival in patients with MBC. Surprisingly, MT expression was associated with longer MS in patients with MBC that received carboplatin. These findings are inconsistent with the hypothesis that MT expression causes chemoresistance to platinum based agents in patients with metastatic breast cancer. Further studies are needed to elucidate the mechanisms behind these findings.
Amrubicin as second- or third-line treatment for patients with HER2-negative metastatic breast cancer (MBC): A phase II trial of the Sarah Cannon Research Institute (SCRI).

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**Background:** Anthracyclines demonstrate significant activity in breast cancer, but the potential for cardiotoxicity is dose-limiting. Amrubicin is a novel anthracycline with broad-spectrum preclinical activity and low potential for cardiotoxicity. We present phase II results from a phase I/II trial of amrubicin as second/third-line therapy for HER2-negative MBC. **Methods:** Women with measurable HER2-negative MBC with 1 or 2 prior chemotherapy regimens for metastatic disease and normal LVEF were eligible. Prior anthracycline-containing adjuvant therapy was allowed. Amrubicin 110 mg/m² IV every 3 weeks was administered until disease progression or intolerable toxicity. Tumor assessments were performed every 6 weeks and LVEF assessments every 12 weeks. The primary endpoint was progression free survival (PFS); a median PFS ≥ 4.5 months was considered a study result meriting further development of amrubicin. **Results:** 48 evaluable patients (pts) were treated from 1/2010 to 9/2011. Baseline characteristics included median age 57; 23% were triple-negative; 33% had 2 prior chemotherapy regimens for MBC; 38% had anthracycline-containing adjuvant therapy. Median treatment duration was 6 weeks (2 cycles), range 1-12+ cycles. 8 pts (17%) had objective RECIST responses (1 CR, 7 PR); 5 of the 8 responders had received anthracycline-containing adjuvant therapy. 24 additional pts (50%) had stable disease at first reevaluation. The median PFS for all patients was 2.8 months (95% CI 1.6-4.0 months); median PFS was similar for pts with 1 vs 2 previous regimens for MBC (95% CI 2.5 vs 4.0 months). 24% of pts were progression-free at 6 months. Neutropenia was the most common grade 3/4 toxicity (63%; 6% febrile neutropenia). No grade 3/4 non-hematologic toxicity occurred in > 5% pts. No cardiotoxicity occurred. Only 1 pt discontinued amrubicin due to toxicity (grade 2 fatigue). **Conclusions:** Amrubicin had good tolerability, no cardiotoxicity and was active as a second/third-line treatment for HER2-negative MBC, including pts previously treated with adjuvant anthracyclines. The median PFS was comparable to other standard single agents in the MBC setting.
BCL2 protein in prediction of relapse in triple-negative breast cancer (TNBC) treated with adjuvant anthracycline-based chemotherapy.

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Background: Preclinical data show an association of BCL2 expression and resistance to anthracyclines. The absence of BCL2 expression in prechemotherapy samples is associated with a higher probability of pathological complete response to neoadjuvant doxorubicin-based chemotherapy. The aim of our research is identification of markers predicting sensitivity to adjuvant treatment in TNBC. Here we focus on BCL2 protein as a putative predictor of sensitivity to adjuvant anthracycline-based chemotherapy. The objective was to determine whether BCL2 expression predicts relapse in TNBC patients treated with anthracycline-based regimens.

Methods: The study included 187 patients with TNBC, 178 of whom were treated with adjuvant chemotherapy (164 had anthracyclines). BCL2 analysis was performed using IHC, proportion score and intensity score were counted. The data were analysed with software Statistica and R.

Results: High BCL2 expression predicts poor relapse free survival (RFS) in patients treated with adjuvant anthracycline-based regimens (logrank p=.035, hazard ratio, HR 2.37, 95%CI 1.04-5.41). High BCL2 predicts trend to poor overall survival (OS) in patients treated with adjuvant anthracycline-based regimens (logrank p=.075, HR 2.31, 95%CI 0.90-5.97). In univariate analysis of anthracycline treated patients, stage (RFS p=.0004, OS p=.0005), size (RFS p=.003, OS p=.00009) and nodal status (RFS p=.018, OS p=.028) were associated with outcome, as well. In multivariate analysis of anthracycline treated patients, BCL2, size and nodal status had an independent predictive significance for both RFS (p=.005, p=.056, p=.003) (logrank test, p=.0004) and OS (p=.014, p=.006, p=.012) (logrank test, p=0.0007).

Conclusions: This study is the first to prove that high BCL2 expression predicts poor outcome in TNBC treated with adjuvant anthracycline-based chemotherapy. BCL2 expression could facilitate decision making on adjuvant treatment in TNBC patients and its assessment should be included in standard diagnostics. In patients with high BCL2 expression other types of adjuvant treatment should be considered. Grants: IGA NS10286, IGA NS10357-3 and Biomedreg CZ.1.05/2.1.00/01.0030.
Quantitative measures of FDG PET after neoadjuvant chemotherapy to predict breast cancer patient survival.

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Background: In patients with locally advanced breast cancer (LABC), qualitative FDG positivity following neo-adjuvant chemotherapy (NC) has been shown to be inversely associated with survival (Emmering, Annals Oncol, 2008). We investigated quantitative measures of post-therapy FDG uptake, namely standardized uptake value (SUV) and glycolytic flux (Ki), as predictors of breast cancer survival. Methods: Forty-seven patients with LABC underwent dynamic FDG PET scans close to or at the end of NC and prior to surgical resection. Post-therapy FDG uptake at the primary tumor site was measured by mean SUV from 45-60 minutes after FDG injection, maximum SUV (SUVmax) from 50-55 minutes, and FDG glycolytic flux (Ki). Pathologic response (PR) was assessed for at the time of surgical resection. Cox proportional hazards models were used to estimate associations between log-transformed measures of post-therapy FDG uptake, PR and outcome. Results: Median SUVmax was 1.9 (0.9 – 9.2) and median Ki was 2.2 (0.02 – 47.7) mL/min/g. Median follow-up for relapse was 5.7 years with 11 events and 6.3 years for survival with 10 deaths. PR was not significant for DFS (p = .39) or OS (p = .48). Post-therapy FDG uptake measures showed a statistically significant ability to predict survival. SUVmax predicted DFS (p = 0.02) and OS (p = 0.01). Ki was associated with DFS (p < 0.01) and OS (p < 0.01). PET measured hazard ratios were not attenuated in multivariate analysis controlling for known prognostic markers such as primary tumor PR and nodal status. However, multivariate survival models appeared highly influenced by one patient with the shortest survival time (1.3 years) and highest SUVmax and Ki. Without this patient, Ki remained a borderline independent predictor of DFS (p = .08) and OS (p = .07), but SUVmax was no longer significant for DFS (p = .32) or OS (p = .26). Conclusions: Our analysis suggests that quantitative measures of post-therapy FDG PET provide information beyond PR for predicting which LABC patients are at highest risk for relapse and death. This information may be useful in directing post-surgery treatment. Supported by NIH grants CA42045, CA138293, and CA148131.
Evaluation of overall survival (OS), progression-free survival (PFS), or time to progression (TTP) in systematic review of randomized clinical trials (RCT) in patients with metastatic breast cancer (MBC).

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Background: Limited data exists to establish if the introduction of newer agents has been associated with a trend towards an improved OS over time in women with MBC. Methods: Trough a computer-based systematic search of PubMed we identified RCT that treated patients with MBC published between 1980 and 2011. Trials that compared systemic chemotherapy for MBC, and reported a median OS were included. We excluded trials that use concomitant hormonal treatment, investigated only immunotherapy, or if they enrolled only responders to an initial regimen. The data abstracted included: year of publication, number of patients, regimens used, number of patient treated as 1st line vs. refractory patients, median PFS, TTP and OS. Linear regression analysis was used to establish trends. Results: An initial searched revealed 5485 publications, 134 RCT that enrolled 38,090 patients fulfilled our entry criteria and were included. First line therapy was studied in 99 trials and 35 evaluated mostly refractory patients. The use of adjuvant therapy has increased substantially, trials reported in the 1980’s had a mean of 0.07% of patients having had adjuvant chemotherapy compare to a mean of 48% in the last decade. Overall survival has significantly improved; the slope of the fitted line for first line clinical trials was 0.39 (p<0.001), which indicates a 0.39-month increase in median survival time per year. In trials of subsequent lines of therapy this slope was 0.19 (p=0.001). PFS or TTP was reported in 98 trials, interestingly in contrast to OS, this has not significantly changed, the slope for the fitted line has remained almost flat in both first line (0.002, p=0.97) and refractory trials (0.01, P=0.81). Conclusions: Our study is the first of its kind conducted in trials of patients with MBC. It shows that progress has been made in the last 3 decades OS in women affected with MBC, however the lack of change in PFS or TTP appears to indicate that the increase in OS is driven by a combination of newer agents, more subsequent lines of therapy being offered to patients and improved palliative care.
Circulating tumor cells in metastatic breast cancer: Are they a strong and independent predictor of poor progression-free and overall survival?

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Background: Circulating tumor cells (CTCs) are detected in 30–60% of patients with metastatic breast cancer (MBC). The aim of this prospective multi-center study was to evaluate the impact of CTCs on progression free survival (PFS) and overall survival (OS) in a large cohort of 486 patients with progressive metastatic disease. Methods: CTC levels were determined for 486 patients at nine German University Breast Cancer Centers between 12/2007 and 06/2011. Samples of 7.5 ml blood were taken before initiation of a new line of therapy and CTCs were enumerated using the CellSearch System (Veridex LLC, Raritan, NJ, USA). CTC status (≥ 5 CTCs vs. < 5 CTCs per 7.5 ml blood) was assessed as a prognostic factor for PFS and OS using univariate (log-rank test) and multivariate (Cox regression model) statistical methods. Results: CTCs were detected in 205/486 (42%) patients. The median CTC count was 2 (range 0–6380) per 7.5 ml blood. The presence of ≥ 5 CTCs/7.5 ml blood did not correlate with any of the established clinicopathological factors except estrogen receptor status (p = 0.038). PFS and OS were both significantly shorter in patients with ≥ 5 CTCs/7.5 ml than in those with < 5 CTCs/7.5 ml blood. PFS was 5.0 [95% CI 4.1–5.8] months vs. 7.6 [95% CI 5.9–9.3] months, p < 0.001; and OS was 15.0 [95% CI 13.5–16.5] months vs. 18.3 [95% CI 17.4–19.2] months, p < 0.001. In the multivariate analysis considering all clinicopathological factors and the CTC status, independent predictors of reduced OS and PFS were site of metastasis (visceral vs. bone), number of metastatic sites (multiple sites vs. one site), and CTC status. Conclusions: The presence of ≥ 5 CTCs/7.5 ml blood is a strong and independent predictor of poor PFS and OS in patients with MBC.
Validation of NAD(P)H quinone oxidoreductase (NQO1) expression as a predictive factor for adjuvant chemotherapy benefit in patients with early breast cancer.

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Background: NAD(P)H:quinone oxidoreductase-1 (NQO1) has important antioxidant functions by stabilizing p53 from proteasomal degradation. NQO1 knockdown is associated with higher susceptibility to oxidative stress. Polymorphisms suppressing NQO1 are predictors of poor survival in patients with breast cancer (BC) treated with anthracyclines. BC cell lines with impaired NQO1 function showed resistance to epirubicin chemotherapy (CT) independently of p53 status suggesting NQO1 as predictive factor for anthracycline benefit. In this study we hypothesized that lack of NQO1 could predict resistance to anthracycline-containing CT in patients with early breast cancer (EBC). Methods: Patients were identified from two French multicentric trials that randomized patients with EBC to adjuvant anthracycline-based CT vs no CT between 1988 and 1995. NQO1 was determined in TMAs by automated quantitative assessment of immunofluorescence (On-Q-ity Inc, Waltham). Cut-off for positivity was the median value of NQO1 expression. Univariate and multivariate Cox regression models were performed. Treatment effect was assessed on long term overall survival (OS). Results: NQO1 expression was assessed in 600 patients. 75% were postmenopausal, had more often grade II (62%), LN-negative (58%) and ER-positive (67%) BC. Higher NQO1 expression was observed in postmenopausal (P<0.02) patients. No relation with other clinicopathological factors (grade, LN or ER) was observed. Effect of adjuvant CT on death rates was dependant on NQO1 level. Hazard ratio (HR) for treatment efficacy at the four quartiles of NQO1 were 1.07 (95%CI: 0.69-1.7), 0.87 (0.64-1.19), 0.66 (0.45-0.97), 0.46 (0.22-0.95) (interaction test: 0.1). Interaction test was statistically significant (0.02) when NQO1 expression was considered as binary variable with median value taken as cut-off. NQO1 remained predictive among ER+ patients only. HR for OS was 0.61 (0.36-1.02) and 1.25 (0.79-1.99) in patients with high and low NQO1 respectively. Conclusions: This study adds to the existing data suggesting NQO1 expression as an independent predictor of efficacy for adjuvant anthracycline-containing CT.
Analysis of pretreatment nonpharmacologic, pharmacologic factors, and yoga intervention on CINV outcomes in breast cancer patients undergoing adjuvant chemotherapy.

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**Background:** Chemotherapy induced nausea and vomiting (CINV) is affected by both pretreatment patient factors, chemotherapy and antiemetic regimen and psychological interventions. In this study we evaluated the effects of mind body intervention such as yoga in modulating CINV outcomes controlled for the above factors. **Methods:** Chemotherapy naïve breast cancer patients with stage II and III disease participating in a randomized controlled trial comparing yoga (n=45) vs. supportive therapy (n=53) were assessed for CINV outcomes during adjuvant chemotherapy. Morrows Assessment of nausea and emesis was used to assess CINV symptoms including their frequency, severity and anticipatory nature. We developed a multiple regression analyses to test the role of intervention on CINV beyond that explained by the independent prognostic factors [age (<50/≥50 years), stage of disease (II vs III), menopausal status (pre vs post), antiemetic regimen (5HT3 antagonists vs. antidopaminergics), administration of anxiolytics (yes/ no) and type of chemotherapy regimen (FAC vs. CMF)] that were included in model A. Model B includes these six variables plus intervention (yoga vs. supportive therapy) in predicting nausea and vomiting outcomes. **Results:** Intervention emerged as a primary predictor for nausea frequency ($\beta$= -0.38, p=0.002), intensity ($\beta$= -0.44, p=0.001 ), anticipatory nausea frequency ($\beta$= -0.26 , p= 0.04) and intensity ($\beta$= -0.38 , p=0.004 ). Age group emerged as a primary predictor for anticipatory vomiting frequency ($\beta$= -0.39 , p=0.01 ) and secondary predictor for nausea frequency ($\beta$= -0.41 , p= 0.006). Administration of anxiolytics emerged as a primary predictor for vomiting intensity ($\beta$= -0.40, p= 0.001) and secondary predictor for anticipatory nausea frequency ($\beta$= -0.26 , p= 0.05). **Conclusions:** Yoga intervention influences CINV outcomes when controlled for pretreatment and pharmacological factors during chemotherapy in breast cancer patients poorly controlled for nausea and vomiting.
Background: The OPTION trial in premenopausal women tested the ovarian protection effect of goserelin (G) given randomly before and during adjuvant chemotherapy for breast cancer. Methods: Using standard chemotherapy, women were randomised in 2 strata, under 40 yrs and over 40 yrs at diagnosis. 227 patients were recruited by end December 2009. 173 met the criteria for 1 year follow-up for this analysis; 140 patients of these had provided adequate data on menstrual bleeding; 87 patients were aged under 40 and 53 patients were aged over 40 at the time of chemotherapy. Cessation of menstruation during chemotherapy was defined as at least two consecutive cycles with no menstrual bleeding since the previous cycle and no return of menstrual bleeding prior to the final cycle of chemotherapy. Of those patients who had ceased periods during chemotherapy, those with no further menstrual bleeding at 12 months follow up were deemed to be menopausal. Patients were randomised to receive G or no G at start of chemotherapy. Primary endpoint was recovery of menses at 12 months from start of chemotherapy. AMH was measured in 117 women pre-treatment, and at 1 year after starting chemotherapy. Results: There were no differences in pretreatment AMH between control and goserelin-treated groups, thus further analyses were performed on all women grouped together. AMH was lower following chemotherapy (0.40±0.65 vs 1.38±1.82ng/ml; mean±SD; P=0.001)). Pre-treatment AMH was a significant predictor of post-treatment amenorrhoea (P=0.001). By multivariate logistic regression analysis with age and AMH, age remained significant (P=0.003) whereas AMH did not (P=0.07). Grouping pre-treatment and post-chemo AMH into quartiles showed that AMH became undetectable in 94% of women with lowest pre-treatment AMH vs 46.2% of women with the highest pretreatment AMH. We have previously demonstrated in a small cohort that pretreatment AMH can predict long-term (5 year) ovarian activity in women with breast cancer. Conclusions: The present data confirm the value of pretreatment AMH in assessing the likelihood of ongoing ovarian activity after chemotherapy for early breast cancer.
Management of antiangiogenics’ renovascular safety in breast cancer subgroup and intermediate results of the MARS study.

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Background: Hypertension (HTN) and proteinuria (Pu) are class-side-effects of anti-VEGF drugs (AVD), related to the inhibition of the VEGF pathway. The MARS study has been conducted to assess the renovascular tolerance of AVD in the clinical setting. Methods: The MARS study is a multicentric prospective observational study of the renovascular safety of AVD in AVD-naive pts. 7 centres from 2009 to 2011. Data collected included: gender, age, serum creatinine (SCr), diabetes, HTN, hematuria (Hu) and Pu. This sub-group analysis presents the intermediate results for the 1st 155 pts with breast cancer (BC) receiving bevacizumab who completed the 1-year follow-up (f/u) (out of 337 BC pts in total). Results: Median age at inclusion: 62 years. Bone, visceral and cerebral metastasis frequencies were 74.2, 51.6 and 5.2%, respectively. Diabetes and HTN prevalences were 3.9% and 10.3%, respectively. Baseline renal assessment retrieved: Pu 14.2%, Hu 8.4%, aMDRD 98.2 ml/min/1.73m$^2$ and 2 pts with aMDRD<60. The incidence of de novo Pu during f/u was 15% (Table). 59.1% of pts with Pu at inclusion improved. Among pts with de novo Pu, 40.0% afterwards improved/normalized. No grade 3/4 Pu has been reported and no hematuria. 12.9% developed HTN. Moreover, renal function decreased by -3.2 ml/min/1.73m$^2$/year and 4 pts had aMDRD<60 at the end of f/u. 32.2% increased their SCr: 27.1% grade 1, 4.5% grade 2, and 0.6% grade 3. All pts with grade 2-3 returned to normal or grade 1. No thrombotic micro-angiopathy (TMA) has been reported. Conclusions: These results show that 1) TMA remains rare, 2) Pu developed in 15% of pts, with no grade 3/4, 3) less than 13% developed HTN and 4) renal function was only slightly impaired with transient elevations in SCr. Furthermore, in case of a renovascular effect, investigators followed the recommendations from the French Society of Nephrology (Halimi JM. Nephrol Ther 2008) and no treatment withdrawal for unmanageable renovascular toxicity occurred.

<table>
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<tr>
<th>Renovascular effects</th>
<th>Prevalence at inclusion (%)</th>
<th>Incidence during f/u (%)</th>
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<tr>
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* NCI-CTC v4.03.
Neoadjuvant epirubicin, gemcitabine, and docetaxel for primary breast cancer: Survival and prognostic factors in two consecutive neoadjuvant phase I/II trials.

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Background: We previously reported primary end points of two consecutive phase I/II trials which evaluated two different schedules of neoadjuvant gemcitabine (G), epirubicin (E) and docetaxel (Doc) for primary breast cancer. Here we report mature survival data and evaluate prognostic factors for disease-free (DFS) and overall survival (OS).

Methods: 151 patients were treated in two phase I/II trials of G, E and Doc as neoadjuvant chemotherapy (NAC) for T2-4 N0-2 M0 PBC between Feb. '02 and Dec. '04. Patients were treated with six cycles of GEDoc (G 800mg/m$^2$ day (d) 1 + 8, E 60-90mg/m$^2$ d 1, Doc 60-75mg/m$^2$ d 1 every three weeks) or five cycles of G 1250mg/m$^2$ plus E 90-100mg/m$^2$ every two weeks followed sequentially by four cycles of Doc 80-100mg/m$^2$ every two weeks (GEsDoc). Pathologic complete response (pCR), clinical/pathological factors were correlated with DFS and OS.

Results: There was no significant difference in DFS or OS between patients in the GEDoc and GEsDoc trial (DFS: Hazard ratio (HR) 1.13, p=0.67; OS: HR 1.06, p=0.88) with a 5-year DFS and OS of 72 vs 74% and 85 vs 86%, respectively. In an univariate analysis pCR unexpectedly was associated with a worse OS (HR 3.11; p=0.007). HR for DFS showed a similar but non-significant trend (HR 1.78; p=0.1). Molecular subtypes (OS: HR [lum B] 3.17; [triple negative] 5.81; [HER2] 11.5; p=0.002), negative estrogen receptor (ER) status (OS: HR 3.14; p=0.002) and Ki-67 >20% (OS: HR 5.41; p=0.001) were all significantly associated with DFS and OS. The recently published CPS-EG score (Mittendorf 2011) was also significantly correlated with OS (p=0.006) and DFS (p=0.0006). In a multivariate analysis high Ki-67 was the only significant predictor of DFS (HR 10.4; p=0.0026) whereas molecular subtype (p=0.05) and Ki-67 (p=0.04) were significantly associated with DFS.

Conclusions: These results raise caution on the reliability of pCR as a single surrogate marker for survival in trials with small sample sizes. Our results emphasise the role of additional factors, esp. Ki-67 and subtypes. Integrative scores based on clinical and pathologic stage as well as tumor biology, might be more reliable predictors of survival.

Prevention of chemotherapy-induced damage to ovarian reserve by sphingosine-1-phosphate

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Background: Chemotherapy agents such as cyclophosphamide (Cy) and doxorubicin (D) are known to compromise ovarian function. We have previously shown that these agents alter ovarian function by causing apoptotic death of primordial follicles and thereby causing diminishment of ovarian reserve (Cancer Research 2007; Aging 2011). While assisted reproduction techniques exist to preserve fertility there has been no proven approach to pharmacologic preservation of ovarian function. Sphingosine-1-Phosphate (S1P) is a naturally occurring ceramide-induced death pathway inhibitor. Here we investigated whether S1P can prevent Cy or D-induced apoptotic follicle death in mouse ovaries.

Methods: Eight wk old NOD mice (n=23) were treated with Cy (75 mg/kg), Cy+S1P (200 μM), D (10 mg/kg), D+S1P or vehicle only (Control). S1P was administered via continuous infusion using a mini-osmotic pump beginning 3 hours prior to single dose chemotherapy injection for 72 hours. Ovaries were removed 72h later and serially sectioned, and stained with anti-caspase 3 (AC-3) antibody for the detection of apoptosis in primordial follicles. The ratio of apoptotic to total follicles was expressed as percentage in each group.

Results: Both Cy and D resulted in significant increase in apoptotic follicle death compared to controls (48.2±11.6 vs. 28.2±8.9, p=0.016 and 46.4±5.4 vs. 24.8±5.2, p=0.004, respectively). Percentages of apoptotic follicles were similar between Cy and D-treated groups (48.2±11.6 vs. 46.4±5.4, P=NS) indicating that these agents were equally gonadotoxic. S1P treatment resulted in a significant decrease in the percentage of apoptotic follicles both in the Cy (25.6±3.5, P<0.011) and the D group (32.2±10.8, P<0.013) compared to controls. In the S1P-treated groups, the percentages of apoptotic follicles were similar to those in untreated controls indicating that S1P completely blocked Cy and D-induced apoptotic follicle death.

Conclusions: S1P can block apoptotic follicle death induced by highly cytotoxic agents. If targeted delivery systems can be developed, S1P may hold significant promise in preserving fertility by pharmacological means.

A study of sperm-associated antigen 5 (SPAG5) in predicting response to anthracycline (ATC)/platinum chemotherapies (CT) in breast (BC) and ovarian cancers (OVC).

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Background: Recently TOP2A alteration was found to be a predictor for ATC-CT and our neural network analysis of BC gene expression array (GEA) data has revealed SPAG5 gene as a major hubs in both TOP2A and proliferation pathways. In this study the molecular and clinicopathological functions of SPAG5 was investigated in BC and OVC. Methods: (1) A series of 171 BC was evaluated for SPAG5 gene copy number (using aCGH) and mRNA expression (using GEA) which were validated in 5 independent databases. (2) The expression of SPAG5 protein was evaluated pre-clinically in BC and OVC cell lines and in both 40 normal breast tissues and a series of 1650 primary BC and was correlated to clinicopathological and other biomarkers. (3) The association between SPAG5 and response to CT was investigated in a) 350 ER negative BC treated with adjuvant ATC-CT, b) 250 BC treated with neoadjuvant (NEO-A)-ATC-CT, and c) 200 primary OVC treated with cisplatinum based adjuvant CT. Results: (1) 5% and 15% of the 171 BC showed amplification and gain of SPAG5 locus, respectively, at 17q11.2. SPAG5 mRNA expression displayed a significant correlation with its copy number (p < 0.0001). (2) 30% and 20% of ovarian and BC respectively, showed overexpression of SPAG5 protein (+). In BC, SPAG5+ at both mRNA and protein levels showed a significant association with aggressive phenotypes, high mitosis, ER-, high grade, p53 mutation and epithelial mesenchymal transition phenotypes (ps < 0.0001). SPAG5 mRNA (+) was statistically associated with poor survivals (p<0.0001). (3) In ER- BC treated with adjuvant ATC-CT, SPAG5 negative (-)had 7-times higher risk of progression compared with SPRAG+ BC (p<0.0001). SPAG5+ BC received NEO-A-ATC based CT achieved 38% pathological complete response (pCR) vs. 6% of SPAG5- (p<0.0001). After controlling to other predictors for pCR, SPAG5 was an independent predictor (HR; 2.4; p=0.001). Similarly, SPAG5- OVCs were resistant to platinum (p<0.001) and independently associated with poor survival (p<0.001). Conclusions: SPAG5 is an important novel gene implicated in the survival of BC and OVC cells and its protein expression is an independent predictor for anthracycline/ cisplatinum CT.
Phase II trial of sorafenib (S) and vinorelbine (V) in metastatic breast cancer (mBC) with pharmacokinetics (PK) analysis.

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**Background:** S inhibits pathways involved in cancer resistance to treatments (Raf, VEGFR, PDGFR). This phase 2 trial aimed to define tolerability and efficacy of full doses of S and V in mBC. Toxicity data were previously reported: frequent dose reductions were noted, for which we investigated a possible PK interaction. Indeed, the metabolism of both S and V depends on hepatic CYP3A isoenzymes. **Methods:** Patients with measurable (RECIST), HER2 negative mBC received first-line therapy with V (30 mg/m² days 1, 8 every 21) + S (400 mg bid). After 8 cycles patients could be switched to S alone. For PK analysis 6 patients started S on day 4 of cycle 1, to compare plasma levels of V, S and M2 (N-oxide active metabolite of S) when V and S were administered apart from each other versus concomitantly. Plasma samples were collected at time 0 (oral intake of S or right before V infusion), at completion of V infusion and after 0.5, 1, 2.5, 5, 7, 24, 48 and 72 hours from time 0 (cycle 1 day 1 for V and day 21 for S+M2; cycle 2 day 1 for both). Samples were analyzed using validated LC-MS/MS assays. **Results:** 27 patients (median age 57, 35-71) received a median of 8 cycles (1-28), with one patient still on treatment. With repeated cycles 48% of patients required at least 1 dose reduction and 3 patients discontinued therapy for toxicity. 30% of patients had a partial response, 85% had clinical benefit (including stable disease ≥ 4 cycles). Median progression-free survival was 5.7 months (95% CI 4.4-7.6). Plasma levels of V were influenced by S, with a mean Cmax right after the infusion of 1301 ng/mL for V administered alone (cycle 1 day 1) versus 2039 ng/mL with concomitant S (cycle 2 day 1; paired t-test, p=0.004). Plasma levels of S and M2 showed a greater degree of interpatient variability, with no significant difference observed in the presence or absence of concomitant V. **Conclusions:** Combining S with V at full doses is feasible, but not devoid of toxicity. A PK interaction may contribute to the frequent dose reductions. A reasonable option in clinical practice is to start therapy at lower doses of both agents, with a gradual dose increase if well tolerated. Promising efficacy of this combination is documented, with a very high rate of disease control.

Receipt of locoregional therapy among young women with breast cancer.

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Background: Although younger women with breast cancer have the most to gain from receipt of optimal care, few data are available regarding their receipt of locoregional breast cancer treatments. Methods: We identified 318,083 women aged 18-64 who were diagnosed with invasive breast cancer at hospitals reporting to the National Cancer Data Base, a large national cancer registry, during 2004-2008. We used multivariable logistic regression to assess the association of patient age with mastectomy vs. breast-conserving surgery (BCS), radiation with BCS, and post-mastectomy radiation (PMRT) with varying indications, adjusting for patient and tumor characteristics, area-level socioeconomic status, and insurance. Results: Overall, 4% of women were aged ≤35 and 7% were aged 36-40. Women aged ≤35 were significantly more likely to have mastectomy than BCS compared with women aged 56-60 (57% vs. 35%, adjusted odds ratio [OR] 1.97; 95% Confidence Interval [CI] 1.87-2.07) but were less likely to receive radiation if BCS was performed (69% vs. 80%, OR 0.77; 95% CI 0.73-0.82). For those who underwent mastectomy, although overall rates of PMRT receipt were low, women aged ≤35 were more likely to receive postmastectomy radiation (PMRT) despite the presence or absence of clinical indications for PMRT (OR 1.11; 95% CI 1.01-1.22 for strong indications, OR 1.71; 95% CI 1.53-1.91 for borderline indications, and OR 1.49; 95% CI 1.28-1.73 for no indications [all vs. ages 56-60]). Conclusions: Young women with breast cancer may not be receiving optimal locoregional therapy. We observed lower odds of radiation after BCS but higher odds of PMRT for young women regardless of indications for PMRT. Efforts are needed to further understand and improve the receipt of appropriate adjuvant radiation therapy among young women to improve their disease-free and overall survival.

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Background: A recent randomized trial (MA.20) showed that regional nodal irradiation (RNI) in addition to breast irradiation in high risk node negative and 1-3 node positive patients undergoing breast-conserving therapy (BCT) reduced the risk of recurrence and improved disease-free survival. We investigated the trends of RNI use in the United States and related factors for the use of RNI using the National Cancer Data Base.

Methods: This study includes 292,598 stage I-III breast cancer patients without neoadjuvant therapy who underwent BCT from 2003-2007. We investigated pathological, patient, and facility factors related to RNI use, by multivariable logistic regression, with odds ratio (OR) estimations.

Results: The proportion of radiotherapy use after BCT slightly declined from 78.6% in 2003 to 75.6% in 2007. The use of breast irradiation plus RNI decreased from 10.8% in 2003 to 8.3% in 2007 (p<0.0001). The number of tumor positive lymph nodes strongly determined the use of additional RNI: 4.4% patients with negative nodes, 22.8% patients with 1-3 nodes, and 39.7% patients with 4 or more nodes received breast irradiation plus RNI after undergoing BCT (p<0.0001). The proportion of patients undergoing RNI significantly decreased over the study period from 43.3% to 37.2% in the 4+ node positive group, and from 23.6% to 22.0% in the 1-3 node positive group. At comprehensive community cancer centers, 25.5% patients with 1-3 positive nodes were treated with breast irradiation plus RNI (vs. 23.2% in community cancer centers and 21.1% in academic/research cancer centers). Among node negative patients, 11.5% of those with tumor size greater than 5 cm received additional RNI, compared to 4.3% in patients with tumors less than 5cm (p<0.0001). Other significant factors related to RNI use included higher tumor grade, younger age, facility location, and facility volume.

Conclusions: The use of RNI varies by number of tumor positive nodes and facility factors. Only 22.8% of patients with 1-3 positive nodes underwent RNI. Future studies are needed to determine if the use of RNI will increase after publication of the MA.20 trial especially for the 1-3 node positive group.
Primary tumor resection to improve survival and local disease control in stage IV inflammatory breast cancer.

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Background: Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer typically presenting with early metastasis. Optimal outcomes are achieved with multimodality treatment strategies in the non-metastatic setting. Data is limited, however, on the benefit of surgery in patients with metastatic IBC. We evaluated the effect of primary tumor resection on outcomes in patients with newly diagnosed stage IV IBC.

Methods: We reviewed records of 172 patients with metastatic IBC treated at our institution from 1994 - 2009. All patients received systemic therapy with or without locoregional therapy (LRT). Patient demographics, receptor (ER) and HER2-neu status, grade, histology, presence of lymphovascular invasion, margin status, number of distant disease sites, pathologic response of primary tumor and clinical response to systemic therapy (CRS) at distant disease sites were recorded. Overall survival (OS), distant progression-free survival (DPFS), and chest/skin involvement at last follow-up were evaluated. Kaplan-Meier survival analyses, univariate (UV) and multivariate (MV) logistic regression models were used. Chest/skin involvement was compared between groups using Kruskal-Wallis test.

Results: Seventy-nine (45%) patients underwent primary tumor resection. Average age was 51 (22-78). Median live-patient follow-up was 33 months. OS and DPFS were significantly better for patients who underwent LRT versus none (p=0.0001). Factors associated significantly for improved DPFS on MV analysis were ER and HER2-neu status (HR 0.61, 0.60 p=0.02, 0.05 ,respectively), LRT (HR .38, p=0.002) and CRS (HR 0.62, p=0.03). ER status (HR .45, p<0.001), LRT (HR .30, p<0.001) and CRS (HR 0.54, p=0.02) were significant predictors for higher OS on MV analysis. At last follow up, chest/skin involvement was moderate/severe in 11% of patients in LRT group versus 35% of patients in no LRT group (p<0.0001).

Conclusions: This latest retrospective study demonstrates metastatic IBC patients who undergo LRT in addition to systemic therapy may have improved survival and local control outcomes. CRS may be used to guide LRT. A prospective randomized trial is needed to validate these findings.
SPIO-enhanced MR imaging for axillary staging to avoid sentinel node biopsy in patients with breast cancer.

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Background: We previously demonstrated the usefulness of SPIO-enhanced MR imaging for the detection of metastases in sentinel nodes localized by computed tomography (CT) lymphography (CT-LG) in patients with breast cancer (Ann Surg Oncol, 2011). These techniques have evolved and we report our most recent results of axillary staging using them. Methods: Previously unreported 87 consecutive patients with breast cancer and clinically negative nodes were enrolled in this study. Sentinel nodes identified by CT-LG were evaluated prospectively using SPIO-enhanced MR imaging. A node was considered non-metastatic if it showed a homogenous low signal intensity and metastatic if the entire node or a focal area did not show a low signal intensity on MR imaging. Sentinel nodes located by CT-LG were removed, and imaging results and histopathological findings were compared. Results: The mean patient age was 54.9 years (range, 34-77). Sentinel nodes were identified by CT-LG and removed successfully in all patients. The mean number of sentinel nodes identified by CT-LG was 1.16 (range, 1-2). Twenty of 22 patients with positive sentinel nodes definitively diagnosed by pathology demonstrated metastases on SPIO-enhanced MR imaging. Fifty-eight of 65 patients with negative sentinel nodes definitively diagnosed by pathology were non-metastatic on imaging studies. The sensitivity, specificity and accuracy of MR imaging for the diagnosis of sentinel node metastases were 91%, 89%, and 90%, respectively. Two patients whose metastases were not detected had micrometastases. No adverse events were associated with either CT or MR imaging. Conclusions: SPIO-enhanced MR imaging provided accurate axillary staging, and therefore sentinel node biopsy may not be necessary for most patients with breast cancer.
Breast cancer multifocality-multicentricity and survival outcomes.

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**Background:** Studies have consistently shown a correlation between multifocal (MF) and multicentric (MC) breast cancers and the rate and extent of lymph node metastases, but the literature is divided on whether there is a corresponding impact on survival outcomes. In the absence of compelling evidence to dictate otherwise, the convention according to current TNM staging guidelines has been to stage and treat MF and MC cancers according to the diameter of the largest lesions, without taking other foci of disease into consideration. We evaluated a large single institution cohort of MF and MC breast cancers to determine their frequency, clinico-pathological characteristics and effect on survival outcomes. **Methods:** MF and MC were defined pathologically as more than one lesion in the same quadrant and more than one lesion in separate quadrants, respectively. Patients were categorized by presence or absence of MF or MC disease. Kaplan-Meier product limit method was used to calculate relapse-free survival (RFS), breast cancer-specific survival (BCSS) and overall survival (OS). Cox proportional hazards models were fit to determine independent associations of MF/MC disease with survival outcomes. **Results:** Out of 3924 patients, 942 (24%) had MF (n=695) or MC (n=247) disease. MF and MC disease was associated with higher T-stages (T2 26% vs. 21.6%; T3 7.4% vs. 2.3%; P<0.001), higher nuclear grade (grade 3 44% vs. 38.2%, P<0.001), lymphovascular invasion (26.2% vs. 19.3%, P<0.001) and lymph node metastases (43.1% vs. 27.3%, P<0.001). After a median follow up of 51 months, MC but not MF breast cancers were associated with significantly worse 5-year RFS (90% vs. 95%, P=0.02) and BCSS (95% vs. 97%, P=0.01), and a trend towards worse 5-year OS (92% vs. 93%, P=0.08). After controlling for other risk factors, multifocality and multicentricity did not have an independent impact on RFS, BCSS or OS. This was true for the subset of T1N0 breast cancers as well. **Conclusions:** MF and MC breast cancers occurred in 24% of the cases and were associated with poor prognostic factors, but they were not independent predictors of worse survival outcomes. Our findings support the current TNM staging system of using the diameter of the largest lesion to assign T-stage.
Is there a need for sentinel lymph node biopsy in microinvasive breast cancer?

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Background: There is limited data on the long-term outcome of patients with microinvasive breast cancer. Moreover, predictors of lymph node involvement and the impact of multifocal microinvasion are not well understood. We examined the occurrence of nodal metastasis and the significance of multifocality on disease recurrence. Methods: Patients with T1mic breast cancer, defined as tumors ≤1mm, surgically managed at our institute between 1995-2010 were identified. Specimen slides were independently reviewed. Multivariable analysis (MVA) was used to predict lymph node involvement and disease recurrence. Results: Fifty-two patients with T1mic breast cancers were identified. Median patient age was 53 (range 30-92), median size of in-situ disease was 3cm (range 0.1-12cm). Ten patients (19.2%) had multiple foci of microinvasion (range 2-7). The majority of tumors were high-grade (76.9%). When the invasive tumor component was evaluated, 31 of 41 (73.8%) were ER positive, 40.5% were HER2 (15/37), and only one was ER-/PR-/HER2-. Twenty-nine patients (55.8%) had breast conserving surgery and 23 had mastectomies. Lymph nodes were assessed in 48 patients; there was 1 macrometastasis (2.1%), 4 micrometastases (8.3%) and 4 (8.3%) with isolated tumor cells. Seven of 9 patients with lymph node involvement underwent adjuvant chemotherapy. Univariable analysis showed that ER(-) invasive disease and high-grade DCIS tumors were more likely to have involved lymph nodes. On MVA, only negative ER status was a significant predictor of lymph node metastasis (p<0.02). At median follow-up of 83 months (range 6-172 months), 3 patients (6.3%) had disease recurrence (1 local, 1 distant, 1 local and distant) at 8, 17, and 130 months from presentation. All patients with recurrence had negative lymph nodes and only one focus of microinvasion. No factors predicted disease recurrence. Conclusions: Microinvasive breast cancer clearly has the ability to metastasize and recur, but in this series only 2% of patients presented with nodal macrometastasis. The evaluation of lymph nodes in T1mic cancer is unnecessary in the majority of patients. In our cohort, neither lymph node status nor multifocal microinvasion predicts recurrence.
Prognosis of early breast cancer patients treated with sentinel node biopsy: A prospective study from the Japanese society for sentinel node navigation surgery.

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Background: Sentinel node biopsy (SNB) is a new standard of care for clinically node-negative breast cancer patients. Our society conducted a prospective study on SNB for early breast cancer patients from Jul 2004 to Oct 2005 (UMIN000006126). A preliminary result regarding with success rates of multiple mapping methods and the adverse events was presented at the 2007 ASCO. We observed patient’s outcome for 5 years. Methods: Of the 1,411 cases registered, the objects were 1,107 cases excluding cases with bilateral breast cancer, non-invasive breast cancer, past history of other malignancy or failure of SNB and cases treated with primary chemotherapy or endocrine therapy. Adjuvant therapy and breast irradiation were decided by physician’s discretion and patient’s preference. To evaluate the risk of isolated tumor cells or micrometastases in sentinel lymph nodes (SLN), clinicopathological factors were analyzed using the Cox regression model. Results: After a median follow-up of 62 months, there were 85 recurrences and 14 deaths. 5-year Kaplan-Meire estimates for disease-free survival and overall survival (OS) were 92.6% and 97.5% in 848 cases with pN0(sn), 96.2% and 100% in 26 with pN0(i/H11001)(sn), 89.3% and 95.3% in 68 with pN1mi(sn) and 82.8% and 92.0% in 165 with pN1(sn) or greater nodal metastases. No axillary lymph node dissection (ALND) was performed in 809 cases (95.4%), 18 (69.2%), 38 (55.9%), and 24 (14.5%), respectively. Regional node recurrence was found in 8 cases (0.9%), 0 (0%), 2 (2.9%) and 2 (1.2%), respectively. Univariate analysis showed that pN1(sn) or greater nodal metastases, pT2-4, nuclear grade 3, lymphovascular invasion, negative hormone receptor status, SNB followed by ALND, chemotherapy therapy were significant risk factors for OS. However, from multivariate analysis, nuclear grade 3, lymphovascular invasion, negative hormone receptor status, SNB followed by ALND, chemotherapy therapy were significant risk factors for OS. However, from multivariate analysis, nuclear grade 3, lymphovascular invasion and SNB followed by ALND were independent unfavorable prognostic factors (hazard ratio: 3.21, 2.61 and 3.93). Conclusions: Although a non-randomized prospective study, isolated tumor cells and micrometastases in SLN did not affect patient’s survival. ALND should be omitted for early breast patients with those metastases.
Role of axillary ultrasound after neoadjuvant chemotherapy in women with node-positive breast cancer (T1-4, N1-2, M0) at initial diagnosis (ACOSOG Z1071).

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Background: The role of axillary ultrasound (AUS) after neoadjuvant chemotherapy (NAC) to assess for residual nodal disease in patients presenting with node positive breast cancer remains unclear. ACOSOG Z1071 is a prospective multi-institutional trial evaluating sentinel node biopsy in patients with biopsy proven node positive breast cancer (T0-4, N1-2, M0) receiving NAC. Herein we report on the secondary objective evaluating the correlation of lymph node (LN) features on AUS with residual nodal disease.

Methods: AUS images from diagnosis and after NAC were centrally reviewed for cortex size, LN size and LN morphology. Morphologic features were defined as: type I, no visible cortex, type II, < 3 mm hypoechoic cortex, type III, > 3mm hypoechoic cortex, type IV, generalized lobulated hypoechoic cortex, type V, focal hypoechoic cortical lobulation, and type VI, totally hypoechoic node with no hilum. Type I and II are considered normal.

Results: Surgical and imaging data are available on 294 patients. Median age was 50 years (range 23-93 years), mean initial tumor size 3cm (0 to 15cm) and clinical stage II in 64.5% and III in 35.5%. The maximum LN diameter decreased after NAC (mean 22mm pre-NAC to 14mm post-NAC)(p<0.0001); however, there was no significant difference after NAC between the pathologically N+ (13mm, range 5-46mm) and N0 cases (12mm, range 3-32mm)(p=0.13). LN cortical thickness correlated with residual nodal disease after NAC (p-value = 0.04). Using a cutoff point of cortical thickness of 3 mm, the sensitivity was 33% (48/145) and specificity 80% (66/82). AUS morphological features after NAC was associated with false negative rate 62%, false positive rate 28%, sensitivity 38%, and specificity 72%. Conclusions: AUS after NAC is useful to assess nodal response. Cortical thickness was the best predictor of residual nodal metastasis. LN size and morphological features do not reliably exclude residual nodal metastasis in patients after NAC.
Post-neoadjuvant chemotherapy sentinel node biopsy and axillary sampling for node negative (N0) axilla.

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Background: Post neoadjuvant chemotherapy (NACT) sentinel node biopsy (SNB) is not a standard of care due to the wide variability in false negative rate (FNR), varying from 5.7% to 33%. In operable breast cancer (OBC), FNR of less than 10% is acceptable. We attempted to find out the reliability of low axillary sampling (LAS), with dissection limited below the first intercostobrachial nerve, to correctly identify the node negative axilla in the post NACT clinically node negative (N0) patients. Methods: Women with large operable (LOBC) and locally advanced breast cancer (LABC), post-NACT clinically N0, underwent concomitant blue dye-colloid guided SNB and LAS. The identification rate, FNR, and negative predictive value (NPV) of both procedures were compared. Results: Post-NACT 209 eligible women underwent combined LAS and SNB procedure. At presentation, the tumors were large (median 5.0 cm) with 70% clinically palpable nodes. All patients received 4 cycles of neo-adjuvant anthracycline-based chemotherapy and were clinically node negative after chemotherapy. SNB was defined as blue and/or hot node plus palpable node(s). A blue or hot node (median 2 nodes) was identified in 93.8%, and median of 5 sentinel nodes were removed. The false negative rate of SNB was 15.3% (95% CI 8.7%-25.3%). The LAS technique comparatively had nodal yield in 98.5% with median 8 nodes removed; and FNR 8.5% (95% CI, 4.2%-16.6%, p=0.19). Comparative NPV for LAS and SNB were 94.6% and 91.8% respectively. Conclusions: Axillary sampling results for FNR and NPV are similar if not superior to SNB and could be a reliable method of axillary nodal evaluation in advanced breast cancers following neo-adjuvant chemotherapy.
Accuracy of breast MRI in predicting pathologic tumor size.

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Background: MRI use as a preoperative planning tool is increasing in women with breast cancer, yet the correlation between MRI and pathologic size of cancers is unclear. The purpose of this study was to determine the accuracy of MRI in predicting pathologic tumor size, and factors that affect this correlation.

Methods: Clinicopathologic and imaging data from 84 patients diagnosed with invasive or in situ breast cancer from September 2010 to October 2011 who had preoperative MRI were reviewed. 12 patients who had neoadjuvant chemotherapy were excluded. MRI detected 147 lesions in the remaining 72 patients. Concordance between MRI and pathology size was determined using Spearman rho coefficients, and factors affecting the accuracy of MRI in predicting tumor size within ±0.5 cm were determined. Results: There was a modest correlation between MRI and pathology size for all MRI detected lesions (benign or malignant) with a Spearman coefficient of 0.53. Of the 147 MRI detected lesions, 45 (30.6%) had pathologic and MRI size correlating within ±0.5 cm; 76 (51.7%) were overestimated (>0.5 cm) by MRI, and 26 (17.7%) were underestimated (<0.5 cm). 101 (68.7%) of the 147 lesions were found to be malignant (either with invasive disease or DCIS). In this subgroup, 35 lesions (34.7%) had an MRI size within ±0.5 cm of the pathologic size; 40 (39.6%) were overestimated by MRI and 26 (25.7%) were underestimated. Patient age, tumor histology, LVI and grade did not predict concordance between pathologic and MRI size. However, small MRI lesion size more accurately correlated with pathologic tumor size. While 51.1% of tumors that had concordant MRI and pathologic findings within 0.5 cm were <1 cm on MRI, no tumor found to be >5 cm on MRI was within ±0.5 cm on final pathology (p=0.001). Conclusions: MRI accurately predicts pathologic tumor size only when the size of the lesion on MRI is <1 cm.
Magnetic resonance imaging (MRI) evaluation of pathologic complete response (pCR) in different breast cancer subtypes after neoadjuvant chemotherapy (NAC).

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Background: MRI is being used to address treatment response to NAC in breast cancer patients. However, its ability to predict pCR in histologically different tumors remains unclear. We tried to investigate the usefulness of MRI in evaluation of pCR in different breast cancer subtypes after treatment with NAC.

Methods: Serial MRI studies were acquired before, during and after NAC in 75 evaluable patients. MRI interpretation included lesion size, morphology and dynamic enhanced evaluation imaging with initial and late enhancement. On the basis of the final MRI, response was determined to be a clinically complete response (CCR) when no residual tumor and no late enhancement were found. By using immunohistochemistry and fluorescence in situ hybridization (FISH) for human epidermal growth factor receptor 2 (HER2/neu) amplification, tumors were divided into three subtypes: triple negative, HER2 positive, and estrogen receptor (ER) positive/HER2 negative. Every patient received chemotherapy with taxanes and anthracyclines and HER2 positive tumors were treated with trastuzumab. All patients received surgery. pCR was defined as no residual invasive tumor in the surgical specimen. Ductal carcinoma in situ residual disease was considered pCR. Results: 22 of 75 patients (29%) achieved a CCR on the final MRI. Of 22 patients with CCR all 22 (100%) were confirmed pathologically. 19 were pathologic complete responses and 3 showed in situ microscopic residual disease. 12 (55%) were HER2 positive tumors, 4 (18%) were triple negative tumors and 6 (27%) were ER positive/HER2 negative tumors. The negative predictive value of MRI for predicting pCR after NAC was 100%.

Conclusions: Absence of both residual tumor and late enhancement in MRI predict pCR with high accuracy in triple negative, HER2 positive and ER positive/HER2 negative breast cancer after NAC.
Comparison of long-term results of endoscopic video-assisted breast surgery (VABS) between transaxillary retromammary approach (TARM) and periareolar approach.

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Background: The breast conserving surgery (BCS) and the sentinel node (SN) biopsy became to be recognized as the standard treatment for early breast cancers. We have reported about cosmetic effectiveness and lower infestation of the video-assisted breast surgery (VABS) for the breast diseases. We devised the trans-axillary retro-mammary (TRAM) approach of VABS. It needs only one skin incision in the axilla and can treat any tumor of the breast without making any injuries on the breast skin. We evaluated the aesthetic results and the curability of this surgical method. Methods: We have performed VABS on 300 patients since December, 2001. The newly devised TARM was performed on 120 patients of early breast cancer, stage I and II. After endoscopic SN biopsy, we elongated the axillary skin incision to 2.5 cm. We dissected major pectoral muscle fascia to detach retromammary tissue behind the tumor. We cut the mammary gland with clear surgical margin, and removed it through the axillary port. The breast reconstruction was made by filling absorbable oxidized cellulose. The postoperative aesthetic results were evaluated by ABNSW.

Results: BCS was performed on 286 patients (26 after preoperative chemotherapy) and skin-sparing mastectomy on 14. There was no serious complication after surgery. Surgical margin was minimally positive in 2. The original shapes of the breast were preserved well. The follow-up is 126 months at maximum and 74 months on average. There is 3 locoregional recurrences and 14 distant metastases. 5-year survival rate is 97.3%. With regard to TARM, The skin incision only in the axilla made better looks and shapes of the breast. It could be applied for tumors in any area of the breast without tumor nipple extension. The reconstruction with oxidized cellulose needs no excessive detachment of the skin beyond the surgical margin. The postoperative esthetic results were excellent and better. The sensory disturbance was minimal. All patients expressed great satisfaction. Conclusions: VABS can be considered as a good surgical procedure concerning locoregional control and esthetics. TARM is better on the patients without tumor nipple extension.
The impact of primary surgery on stage IV breast cancer.

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Background: The role of primary surgery in metastatic breast cancer is unclear. Herein we have performed meta-analysis on available data to assess the role of surgery on oncological outcome in patients with stage IV breast cancer. Methods: A comprehensive search for published trials that examined outcome following removal of primary disease in stage IV breast cancer was performed using MEDLINE and cross-referencing available data. Reviews of each study were conducted, and data were extracted. Primary outcome was overall survival related to surgical removal of primary disease. Results: We identified 15 relevant studies of which 10 were appropriate for analysis. Data was available on 28,693 patients with stage IV disease, of whom 52.8% underwent removal of the primary carcinoma. Patients undergoing primary surgery in this setting were more likely to be alive at 3 years 40% vs. 22% (OR 2.32 CI 2.08-2.6, p<0.01 (surgery vs. no surgery)). Analysis of subgroups for selection to surgery or not, favoured smaller tumours, fewer comorbidities, fewer metastases (p<0.01). There was no difference between the two groups in location of metastases, grade of tumour or receptor status. Conclusions: Patients undergoing removal of primary carcinoma in the setting of stage IV breast cancer appear to have an improved overall survival. However the available data suggest that these surgical patients probably have better prognosis stage IV disease than those patients not undergoing surgery.
Prognostic impact of local therapy of the primary tumor in metastatic breast cancer.

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Background: MBC is an incurable disease and the treatment aims are palliative. It is not known whether the difference in OS is the result of a selection bias or caused by dissemination of tumor stem cells in patients without surgery. Methods: To identify the impact of surgical therapy of the primary tumor, a monocentric retrospective review from 1990-2006 was done in primary MBC pts. Results: We identified 269 pts. with primary MBC, 63 of whom had received no surgical local treatment. Mean follow up is 65 m for pts., observed mortality 87%. Location of metastases were bone only (36%), visceral or soft tissue (one organ only, 19%), multiple organs (40%) and including CNS metastases (5%). 50% had G3 tumors, 25% negative receptor status, 7% non-resectable local disease and 57% symptomatic metastases. In univariate analysis, pts. without local treatment had a median OS of 14.4m, pts. with local therapy 28.1m (p<0.001). Pts. not receiving local treatment were significantly more likely to have multiorgan or CNS involvement (p<0.001), symptoms at diagnosis (p=0.009), non-resectable tumor (p<0.001) and were more likely to die within the first 30d after diagnosis (p<0.001). In multivariate analysis, local treatment had no significant impact on OS. The only significant variables were: number of involved organs, symptoms at diagnosis, receptor status, grading, and size of the local tumor. The effect of local treatment on OS was not homogenous across subgroups. Local treatment was a significant factor in tumors with only one involved organ or asymptomatic disease. In all other groups, local treatment did not result in an OS benefit. Conclusions: Our cohort showed significantly improved OS in univariate analysis if the breast primary tumor had been removed in metastatic disease. Yet, the decision for local treatment was biased by the extent and presentation of metastatic disease. Pts. with more advanced MBC seem not to benefit from removal of the primary tumor. However, we see significant influence in pts. with limited and asymptomatic MBC. The potential dissemination of tumor stem cells from the breast primary in metastatic but locally untreated disease may only influence prognosis in pts. with limited disease.
Role of breast surgery in T1-T3 breast cancer patients with synchronous bone metastases.

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Background: The role of breast surgery in advanced breast cancer (ABC) is controversial. The main potential advantage of removing the primary tumor is to eliminate the source of further metastatic spread. While previous studies addressed the question in very heterogeneous populations (e.g. patients with any local and distant extension), we have focused on a homogeneous series of ABC patients. Methods: From our institutional Tumor Registry we selected 191 consecutive women diagnosed between 2000 and 2008 with locally operable (T1-T3) ABC, synchronous bone metastases and no other distant sites involved. The progression free survival (PFS) was calculated from diagnosis to the date of progression, defined as either a new site of metastatic disease or clinical/radiographic evidence of increasing tumor burden at a previously known bone metastatic site. Results: Median age was 51 years and 92% of the women had an endocrine-responsive tumor. One-hundred and thirty patients out of 191 (68%) underwent surgery at the time of diagnosis, while 61 (32%) did not. Twenty-six of the operated patients (20%) had previously undergone neoadjuvant chemotherapy; 15 (12%) had positive or undetermined surgical margins. Operated and non-operated patients were similar with respect to age, tumor size, nodal involvement, estrogen and progesterone receptor status, HER2 overexpression and Ki-67, but differed in terms of number of bone metastatic sites: a single metastasis was detected in 34 (26%) operated and 7 (11%) non-operated cases (P=0.02). First-line treatment strategies with endocrine therapy, chemotherapy and Trastuzumab were similarly distributed between the two groups. The 5-year PFS was 22.0% and 10.4% in operated and non-operated patients, respectively. The multi-adjusted hazard ratio was 0.62 (95% confidence interval 0.39-0.98) in favor of surgery. The exclusion of the patients who had received neoadjuvant chemotherapy and patients with positive or undetermined surgical margins did not alter the results. Conclusions: In this large and homogeneous series of ABC patients with synchronous bone metastases, the role of breast surgery had a favorable impact on the progression of the disease, indicating a potential survival benefit.
Postmastectomy radiotherapy for patients with one to three positive lymph nodes: Utilization and benefit.

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Background: The use of postmastectomy radiotherapy (PMRT) for patients with pT1-2pN1 tumors is controversial and ASCO guidelines indicate that there is insufficient evidence to make recommendation. We hypothesized that the use of PMRT in this patient group was low and has minimal impact on survival.

Methods: The study includes 83,742 invasive breast cancer patients from the National Cancer Data Base who underwent mastectomy with pT1-2 and pN1 disease from 1998-2007. Neoadjuvant cases were excluded. We investigated factors related to PMRT use using cross tables and logistic regression. Survival analysis was conducted using Cox models in patients diagnosed from 1998-2002, with a median follow-up of 5.5 years.

Results: The proportion of N1 patients undergoing PMRT remained stable from 1998 to 2007, at approximately 20%. PMRT use increased with larger tumor size (15.4% in T1N1 and 24.4% in T2N1), and with increasing positive lymph nodes (14.6%, 23.7%, and 35.2% for patients with one, two, or three positive nodes, respectively). Age was significantly inversely correlated with PMRT use: the proportion of patients receiving PMRT was 31.3% for age <40 years and 8.2% for 80+ years (p<0.001). Asians are more likely to receive PMRT (25.5%), compared to other races (20.3% white, 20.7% black, and 20.6% Hispanic; p<0.001). PMRT also varied considerably by facility location, the highest in the Northeast at 31.3%, and the lowest in the South at 15.8% (p<0.001). There was only minor difference in PMRT use between different types of cancer centers. Insurance status, income and education level were not associated with PMRT use. After adjusting for prognostic factors in the Cox models, PMRT use was associated with a reduced mortality (hazard ratio=0.87, 95% CI: 0.81-0.93; p<0.001). The multivariable-adjusted 5-year death rate was 16.1% in patients receiving PMRT and 18.1% in patients not receiving PMRT. For pT1N1 tumors the absolute benefit was 1.3% compared to 2.7% for pT2N1 tumors. Conclusions: PMRT use varies with facility and clinicopathologic factors, but not socioeconomic factors. The risks of radiation need to be weighed against the 2% absolute survival benefit when deciding on whether to use PMRT for pT1-2N1 patients.
Patient factors and satisfaction in the choice of contralateral prophylactic mastectomy.

Amanda Kathleen Arrington, Karin London, Steven L. Chen, Courtney Vito, John H Yim, Rebecca A. Nelson, Laura Kruper; City of Hope, Duarte, CA

Background: The percentage of women undergoing contralateral prophylactic mastectomy (CPM) has more than doubled in recent years. The underlying reasons patients choose CPM have not been fully evaluated. Our objective was to survey patients who have undergone a unilateral mastectomy with or without CPM to identify reasons surrounding their decisions. Methods: After obtaining IRB approval, a 30-question cross-sectional validated survey was mailed to 691 patients who underwent mastectomy from 1972 to 2011 and are receiving treatment or surveillance at City of Hope. The questionnaire queried the factors behind the choice of surgery for each patient. Demographic questions were included and patient charts were also reviewed. Results: The overall response rate was 53% (N=368). Patients were classified into those who underwent mastectomy with CPM (N=139, 38%) and those who underwent mastectomy without CPM (no-CPM) (N=229, 62%). Of returned surveys, the median age was 50; 24% of patients reported a family history of breast cancer (42% CPM vs. 13% no-CPM, p=0.0001) and 80% of patients had education beyond the high school level (87% CPM vs. 77% no-CPM, p=0.013). PM patients reported being “very concerned” about breast cancer more often than no-CPM patients (46% vs. 34%, p=0.033). The primary reasons for CPM were: concern of recurrence (55%), cosmetic symmetry (27%), physician recommendation (17%), and unclear pre-operative imaging (9%). When questioned about regrets, the top response was decreased sensation (26%). Although 81% of CPM patients were “very satisfied” with their decision, 32% of no-CPM patients reported the same level of satisfaction with their decision (p<0.0001). For no-CPM patients, the primary reasons for the choice of no-CPM was physician advice and “monitoring is sufficient”; with 18% of the responders still considering a CPM. Conclusions: Patients’ perceived risk of contralateral breast cancer is the primary reason for CPM. CPM patients tend to be more satisfied with their decision compared to no-CPM patients. This may be related to the active decision-making thought processes and education necessary to choose CPM. Further patient education is warranted to minimize the risk of regret in making this decision.
Predictors of recurrence in postmastectomy patients with one to three positive lymph nodes.

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Background: Although the role of post mastectomy radiation therapy (PMRT) is well established in women with ≥ 4 positive axillary lymph nodes (ALN), its indications in patients with 1-3 positive ALN is controversial. A recent large meta-analysis suggested a survival benefit in patients with 1-3 positive ALN who received PMRT. However, because recurrence rates in this group are low, identifying a subgroup of patients at higher risk for locoregional recurrence (LRR) could aid decision-making about PMRT. Methods: From an institutional database, 1,333 breast cancer patients who underwent mastectomy between 1996 and 2006 and had 1-3 positive ALN were identified. Among these, T3/T4 tumors and those who received PMRT were excluded. 926 patients were analyzed. The Kaplan-Meier method and Cox regression was used to explore clinicopathologic features that predicted LRR recurrence. Results: Median follow-up was 7yrs. LRR occurred in 49 patients and DM in 126 patients. LRR and/or DM occurred in 146. On univariate analysis, factors significantly affecting LRR recurrence were increasing tumor size (p=0.04), age <50 (p=0.003), histologic grade (p=0.03), nuclear grade (p=0.008), lymphovascular invasion (LVI) (p<0.0001), and macroscopic ALN metastases (p=0.02). On multivariate analysis, age <50 (p=0.0012) and the presence of LVI (p<0.0001) predicted a higher LRR; increasing tumor size (p=0.0005), age <50 (p=0.04), higher histologic grade (p=0.01), number of positive ALN (p=0.04), LVI (p=0.02), macroscopic ALN metastases (p=0.02), and no chemotherapy (p=0.02) predicted a significantly lower RFR. Conclusions: Pts with T1-2 tumors and 1-3 positive ALN are at low risk of isolated LRR; however, patients <50 and with LVI may have additional risk that warrants consideration of PMRT.
Radiofrequency ablation (RFA) of breast cancer: A multicenter retrospective analysis.

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Background: Local ablative therapy of breast cancer represents the next frontier in the minimally invasive breast-conservation treatment. We performed a retrospective study of ultrasound-guided percutaneous radiofrequency ablation (RFA) of breast cancers to determine safety and complication related to this treatment. Methods: Four hundred and ninety-seven patients with core biopsy proven breast carcinoma in 10 institutions of non-surgical ablaton study group underwent RFA without surgical excision were enrolled in this study. Results: Mean patient age was 54 years (range 22 - 92 years). Mean tumor size was 1.6 cm. Four hundred and twenty-five tumors ( 86 %) were ≤ 2 cm. The median follow-up period was 50 months (range 3 – 92 months). The mean required for ablation was 19 minutes (range, 4- 72 minutes), and the average temperature of the tumor after ablation was 91 degrees Celsius. The local recurrence rate after RFA was higher in tumors of negative estrogen receptor (8 of 78, 10%) than in tumors of positive estrogen receptor (17 of 437, 4%; p<0.05), and was higher in tumors of positive HER2/neu than in tumors of negative HER2/neu (14.9% vs. 3.2%; p<0.01). The local recurrence rate after RFA was higher in tumors of positive node than in tumors of negative node (9.8% vs. 3.6%), and was higher in tumors without irradiation than in tumors with irradiation (18.2% vs. 3.2%; p<0.001). The local recurrence rate after RFA was higher in tumors of > 2 cm (13 of 72, 18%) than in tumors of ≤ 2 cm (11 of 425, 3%; p<0.001). RFA-relating adverse events were observed in 17 patients of local pain, 14 patients of skin burn and 4 patients of retraction of nipple. Conclusions: RFA is considered to be a safe and promising minimally invasive treatment of small breast cancer ≤ 2 cm in diameter. Further studies are necessary to optimize the technique and evaluate its future role as local therapy for breast cancer.

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Background: Sentinel lymph node biopsy (SLNB) is a widely used staging method for patients with early breast cancer. Neoadjuvant Therapy (NT) modifies the anatomical conditions in the breast and axilla, and thus reliability of SLNB after NT remains controversial. The aim of this study is to prospectively evaluate the feasibility and accuracy of this procedure in this particular group of patients. Methods: Between December 2007-2011, 69 patients (mean age 56 years) with locally advanced breast cancer (LABC) were prospectively studied. Patients were T1-4, N0-1, M0. Prior to surgery, 61 patients received chemotherapy (CT) (adriamicin/cyclophosphamide followed by docetaxel) and 8 patients endocrine therapy (ET). Thirty nine patients were initially node-negative (cN0) and 30 patients had clinical/ultrasound node-positive confirmed by cytology (cN1) at presentation. All patients were clinical and ultrasound node-negative after NT. The study contained two groups of patients: group A (validation) included the first 29, associated with an axillary lymph node dissection (ALND) after NT, in order to validate the study, and group B included the last 40, only associated with an ALND when SLNB was positive or not found. Results: Whole SLNB identification rate was 89.9%, and no significant differences were found between patients initially cN0 (92%; 36/39) and initially cN1 (87%; 26/30). Four of 7 patients in whom SLNB was not found had residual nodal metastasis after NT (3 of them were initially cN1). Sentinel lymph nodes were successfully identified in 87% (7/8) of patients after ET and in 90% (55/61) of patients after CT. There was one false negative (FN) case after CT in group A (9% of overall false negative rate, initially cN0) and there were no FN cases after ET. Positive SLNB were higher in initially cN1 group (53%; 16/30) than in initially cN0 group (18%; 7/39). Conclusions: SLNB after NT (CT or ET) is safe and feasible in patients with LABC, not only in initially cN0 but also in initially cN1. It accurately predicts the status of the axilla and avoids unnecessary ALND.
Can primary tumor markers of cancer-initiating cells predict lymph node positivity in breast cancer patients?

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Background: Cancer initiating cells, characterized by ALDH1 positivity and/or colocalization of ALDH1 and CD44, have been shown to be associated with poor prognosis in breast cancer patients. The prognostic value of these tumor markers with respect to prediction of lymph node (LN) status remains unclear. 

Methods: Tissue microarrays from a cohort of 223 breast cancer patients diagnosed between 2003 and 2007 were evaluated using the AQUA method for quantitative immunofluorescence for CD44 and ALDH1. These data, along with other clinicopathologic data, were correlated with LN positivity. 

Results: The median patient age of the cohort was 56 (range; 26-89), with a median tumor size of 1.5 cm. 72 (32.0%) patients were LN positive. The median number of LNs excised was 3 (range; 1-27). Of the LN positive patients, the median number of positive LNs was 1.5 (range; 1-24). Levels of CD44, ALDH1, and ALDH1 colocalizing with CD44 did not correlate with number of positive LNs (Spearman rho coefficients: -0.042, 0.131, and 0.058, respectively), nor overall LN status. Tumor size and lymphovascular invasion (LVI) were the only factors found to be significantly correlated with LN status. 

Conclusions: While ALDH1 colocalized with CD44 has been found to be associated with poor prognosis in breast cancer patients, these markers do not predict LN status. Given that the only factors that reliably predict LN status are tumor size and LVI, further work is required to find primary tumor markers that may predict LN status in order to spare patients axillary surgery.

<table>
<thead>
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<th>Factor</th>
<th>LN -</th>
<th>LN +</th>
<th>P value</th>
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</thead>
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<tr>
<td>Median total CD44</td>
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<td>41.6</td>
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</tr>
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<td>Median total ALDH1</td>
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<td>442.4</td>
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</tr>
<tr>
<td>Median ALDH1 colocalizing with CD44</td>
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<td>454.8</td>
<td>0.562</td>
</tr>
<tr>
<td>Median patient age</td>
<td>53</td>
<td>52</td>
<td>0.083</td>
</tr>
<tr>
<td>Median tumor size</td>
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</tr>
<tr>
<td>LVI+</td>
<td>15.2%</td>
<td>46.7%</td>
<td>&lt;0.001</td>
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<td>85.7%</td>
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<td>69.9%</td>
<td>73.0%</td>
<td>0.738</td>
</tr>
<tr>
<td>HER2-neu+</td>
<td>12.8%</td>
<td>13.2%</td>
<td>1.000</td>
</tr>
<tr>
<td>High-tumor grade</td>
<td>23.1%</td>
<td>27.0%</td>
<td>0.092</td>
</tr>
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</table>
Association of pathologic complete response following neoadjuvant chemotherapy with survival among young women with breast cancer.

Rachel Adams Greenup, Aditya Bardia, Julienne M Buckley, Andrzej Niemierko, Melissa Camp, Suzanne Coopey, Michele Gadd, Lidia Schapira, Alphonse G. Taghian, Barbara L. Smith, Michelle Connolly Specht; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Neoadjuvant chemotherapy is increasingly being used in the treatment of breast cancer, yet data on efficacy and significance of pathologic complete response (pCR) is limited among young women. We sought to determine whether timing of chemotherapy impacted disease-free (DFS) or overall survival (OS), and whether pCR is associated with improved prognosis among young women with breast cancer.

Methods: We performed an IRB-approved review of women ≤40 years old who received treatment for stage I-III breast cancer during 1996-2008 at our institution. DFS and OS were determined through use of state tumor registry, death certificate data, and Social Security Master Death Index. Tumor biology was categorized as hormone receptor positive (HR+), HER-2+, or triple negative (TN) breast cancer. pCR was defined as lack of invasive cancer in the breast and axilla on final pathologic review. Cox regression analyses were conducted to evaluate the hazard ratios (HRs) of the association between chemotherapy and outcomes. Results: 370 women ≤40 years old (median age = 36.5, range: 22-40) were treated with systemic therapy for stage I-III breast cancer. 54.7% of tumors were HR+, 20.9% were HER-2+, and 24.4% were TN. After adjusting for stage, there was no difference in DFS or OS among women who received neoadjuvant versus adjuvant chemotherapy (p=0.6 and 0.5 respectively). pCR following neoadjuvant chemotherapy was higher among HER-2+ (50%) and TN (28.6%) tumors when compared to HR+ tumors (17.6%). Among women who received neoadjuvant chemotherapy, 10-year DFS and OS rates were significantly higher when pCR was achieved when compared to lack of pCR (HR=0.20, p value=0.01 and HR=0.13, p=0.05). pCR with neoadjuvant chemotherapy trended towards higher 10-year DFS and OS when compared to women who received adjuvant chemotherapy (HR=0.30, p value=0.08 and HR=0.20, p=0.1).

Conclusions: pCR after neo-adjuvant chemotherapy is associated with improved disease-free and overall survival in young women with breast cancer. Pathologic complete response may be a valuable surrogate marker for survival, and aid in the evaluation of therapeutic efficacy in young breast cancer patients.
Long-term rates of breast cancer in a population of women with ductal carcinoma in situ treated by breast-conserving surgery.

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Background: Ductal Carcinoma in Situ (DCIS) is a non-invasive form of breast cancer which is often treated by breast-conserving surgery. The addition of radiotherapy to surgery has been shown to reduce the risk of local recurrence (LR), but use of radiotherapy varies. It is not known to what extent women with DCIS are at risk for recurrent cancer due to the omission of radiation therapy. We studied a large provincial cohort of women with DCIS who were treated with breast-conserving surgery for factors which predict local recurrence and estimate the impact of radiotherapy on local recurrence and long-term rates of breast preservation. Methods: All women diagnosed with DCIS in Ontario from 1994 to 2003 were identified. Treatments and outcomes were identified through administrative databases and validated by chart review. Women treated with breast-conserving surgery, alone or with radiotherapy, were included. Survival analyses were used to study local recurrence (DCIS or invasive) in relation to patient characteristics, tumour characteristics and treatment. Results: The cohort included 3975 women who were treated with breast-conserving therapy; of these, 1949 (49%) received radiation. At 10 years median follow-up, 736 developed LR (19%). LR developed in 259 of 1949 women who received radiotherapy (13%) and in 477 of 2026 women who did not (24%; p<0.001). The differences were significant for both invasive LR (7% vs. 14%; p<0.001) and DCIS recurrence (6% vs. 9%; p<0.001). The 10-year cumulative rate of mastectomy was 13% for women who received radiotherapy compared to 17% for those who did not (p<0.01). We estimate that 29% (N=214) of all local recurrences diagnosed in Ontario in women treated for DCIS between 1994 and 2003 would be prevented if all patients received radiotherapy. Conclusions: The omission of radiation therapy after breast-conserving surgery in women with DCIS resulted in a substantial number of local recurrences that might have been avoided and lower rates of breast preservation. Improvements in guidelines that facilitate the selection of women in whom radiotherapy can be avoided are needed.
Clinical findings and outcomes from MRI staging of breast cancers in women.

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Background: For patients diagnosed with breast cancer, case series have shown that staging MRI can detect occult breast cancers in 1-10% of cases. Prevalence and risk factors in underserved populations remain unclear. Methods: We performed a retrospective analysis of all patients, newly diagnosed, with breast cancer who had a preoperative staging MRI seen at Norris Comprehensive Cancer Center and LAC + USC, that cares for an underserved and minority population, from 2006 to 2011. Demographic, clinicopathologic and imaging data were obtained through a review of electronic records. Non index lesions were defined as those not known to be malignant, not presenting with clinical, mammographic or ultrasound findings, in a different quadrant and given an MRI BIRADS score of 4 or 5. Results: A total of 718 patients were analyzed and 148 patients (21%) had a total of 187 non index lesions; 63% were ipsilateral, 26% contralateral and 11% bilateral. As initial evaluation of non-index ipsilateral lesions, 71 (38%) had biopsy, 24 (13%) had excision and 34 (18%) had mastectomy. For contralateral non-index lesions, 41 (22%) had contralateral biopsy, 6 (3%) had excision and 11(6%) had mastectomy. Among all non index lesions, 111 (59%) were benign, 14 (7%) DCIS and 62 (33%) invasive cancer. Occult ipsilateral cancer was detected in 50 (6.9%) of patients and contralateral in 10 (1.4%) and bilateral in 6 (0.8%). Conclusions: The occult cancer detection rate with staging MRI was in this 9.2% of this diverse population. No clear risk factors were identified, with detailed factors, including BRCA status to be updated and reanalyzed.

<table>
<thead>
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<th>Variable</th>
<th>Total series</th>
<th>Non index lesions</th>
<th>Occult cancers</th>
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<td>Hispanic</td>
<td>(304/631) 48%</td>
<td>(63/125) 50%</td>
<td>(18/55) 33%</td>
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<tr>
<td>African American</td>
<td>(50/631) 8%</td>
<td>(10/125) 8%</td>
<td>(3/55) 5%</td>
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<td>Caucasian</td>
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<td>(36/125) 29%</td>
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<td>Asian</td>
<td>(66/631) 10%</td>
<td>(11/125) 9%</td>
<td>(6/55) 11%</td>
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<tr>
<td>Others</td>
<td>(17/631) 3%</td>
<td>(4/125) 3%</td>
<td>(3/55) 5%</td>
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<tr>
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<td>(75/569) 13%</td>
<td>(10/108) 9%</td>
<td>(3/43) 7%</td>
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Overuse of sentinel lymph node biopsy with breast conserving surgery for clinical DCIS.

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Background: The National Comprehensive Cancer Network (NCCN) guidelines recommend against sentinel lymph node biopsy (SLNB) for ductal carcinoma in-situ (DCIS) treated with breast conservation surgery (BCS). SLNB is appropriate with mastectomy because it precludes subsequent SLNB if invasive cancer is identified. However, SLNB is commonly performed with BCS for DCIS. We hypothesize SLNB use in the setting of BCS for DCIS varies and may be overused in some cancer centers. Methods: We examined 6,070 cases with initial biopsy showing DCIS presenting to 13 institutions participating in the NCCN Breast Outcomes Database from 1998-2009. Receipt of SLNB was defined as SLNB performed at any point in primary treatment for those with a final diagnosis of DCIS or at the first surgical procedure for those upstaged to invasive cancer. Results: Of 3,725 treated with BCS, 778 (20.9%) had SLNB. Among 2,345 treated with mastectomy, 1,484 (63.3%) had SLNB. Within BCS, patients presenting with clinical symptoms (vs. screening detected) were more likely to have SLNB (p=0.0006, OR: 1.76; 95% CI 1.31-2.36). For both groups, presence of comedo necrosis, year of diagnosis, and treating institution were predictors of SLNB (p<0.0001). 1,171 (19.3%) were upstaged from DCIS at initial biopsy to invasive cancer on final pathology. 212 (18.1% invasive cancer group) had positive nodes. Use of SLNB increased over time from 1998-2009 in mastectomy group. Among BCS group, SLNB use decreased over the first half of the study period and then remained stable at approximately 15% across all centers. Conclusions: Although use of SLNB has decreased over time, a substantial percentage of patients undergoing BCS for DCIS receive SLNB. Practices vary considerably across centers. SLNB can be performed as a second procedure for those treated with BCS and identified with invasive cancer, thereby avoiding unnecessary risk of significant morbidity. Breast programs should review their practices to curtail the use of unnecessary surgery for women with DCIS.
Axillary lymph node status in breast cancer staging: What patient and tumor factors affect the accuracy of ultrasound-guided fine needle aspiration?

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Background: The purpose of the study is to evaluate the accuracy of ultrasound-guided fine needle aspiration (FNA) of axillary lymph nodes (ALNs) in patients with breast cancer and to determine factors that influence accuracy of ultrasound-guided FNA. Methods: Retrospective review of patients with breast cancer who had FNA of ALNs as well as sentinel lymph node excision or complete axillary dissection. Patients treated with neoadjuvant chemotherapy were excluded. 55 axillary FNAs in 54 patients were included in the final analysis. Pathology reports were reviewed for size of the primary tumor, FNA results, number of positive ALNs, and greatest tumor size in ALNs. FNA was performed if a suspicious lymph node was identified. Surgical sentinel lymph node biopsy or full axillary dissection were the reference standard. Micrometastases (< 0.2 mm) and isolated tumor cells in the lymph node were included in the negative group. Atypical and nondiagnostic FNA results were considered negative cytologic results. Significance was analyzed using the Mann-Whitney test. Results: Size of the primary cancer ranged from 0.3 mm to 8.5 cm. The sensitivity of FNA was 73%, with positive predictive value of 97% and negative predictive value of 52%. The NPV of FNA for primary tumors <1 cm, 1.1-2, 2.1-5 and >5 cm is 100%, 36%, 50% and 66% respectively. Correlation of primary tumor size with sensitivity of FNA was not statistically significant. The sensitivity of FNA for lymph nodes with metastatic deposit < 5 mm, 6-10 mm, 11-15 mm, 16-20 mm, and 21 mm+ is 0%, 57%, 59%, 89%, and 100%, which is statistically significant (p = 0.007). The number of positive ALNs at axillary dissection is not correlated to the sensitivity of FNA. The sensitivity of FNA for 1-3, 4-9 and 10+ positive ALNs is 78%, 64% and 80%. Conclusions: Our findings indicate that FNA of suspicious axillary lymph nodes is valuable even in small tumors, which differs from the literature. The overall negative predictive value of FNA is 52%, so sentinel lymph node biopsy is essential after negative FNA. Sensitivity of FNA increases with the size of the metastatic deposit in the lymph node, but is not correlated to the number of positive ALNs found at dissection.
Background: There is limited literature on breast surgery during pregnancy. We present prospective registry data on 88 breast cancer patients who underwent breast cancer surgery during pregnancy. Methods: The Cancer and Pregnancy Registry is a voluntary international registry that prospectively collects the clinical course, treatment, and disease outcome of women diagnosed with cancer during pregnancy and the perinatal and neonatal outcomes of their children. Results: We identified 88 patients who were diagnosed with breast cancer and had surgery while pregnant. 59 patients (67%) underwent Mastectomy while 29 patients (32%) underwent breast conserving surgery (BCS). Out of 43 patients who underwent BCS as their first surgery 13 patients (30.23%) required subsequent mastectomy during pregnancy. 15 patients (34.88%) from the BCS group and 4 patients (8.69%) from the Mastectomy group had positive margins. There was no significant difference between patients who underwent mastectomy vs BCS based on Age (34.67 vs 34.72 P: 0.97), gestational age at surgery (14.05 vs 16.06 P: 0.23) or ER positivity (47.5% vs 46.4% P: 0.93). 2 patients had neo-adjuvant chemotherapy. 17 patients (19.31%) had sentinel lymph node biopsy. 37 patients (42%) had a pregnancy complication. There was no difference in the rate of complication based on mastectomy vs BCS (45.8% vs 34.5% P: 0.31). There was only 1 patient (from mastectomy group) that delivered within 2 weeks of surgery. Of the 17 patients (19.3%) with spontaneous preterm delivery, there was no difference between Mastectomy and BCS group (22% vs 13.2% P: 0.41). Of the 25 patients (28.4%) with birth complications, there was no significant difference between mastectomy vs BCS (30.5% vs 24.1% P: 0.53). There was also no difference in mean birth weight between the groups (2598 grams vs 2672.3 grams P: 0.57). Conclusions: The data supports the safety of breast cancer surgery during pregnancy. In addition, there were no identified adverse effects in patients who underwent BCS as opposed to mastectomy. Of note, only 19% of patients underwent sentinel node biopsy which is considered the standard of care in early breast cancer patients regardless of pregnancy status.
Phase I/II trial of partial breast irradiation (PBI) with various concurrent chemotherapy regimens.

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Background: Potential benefits of concurrent chemo-radiation include: shorter duration of treatment, smaller interval between surgery and adjuvant therapies, and synergistic effects. We have previously shown that PBI with concurrent dose dense doxorubicin and cyclophosphamide (ddAC) is well tolerated (Zellars JCO 2009). We performed a follow-up feasibility trial of PBI delivered concurrently with other various chemotherapy regimens. Methods: Women with T1-2, N0-1 breast cancer s/p lumpectomy with ≥2 mm margins were eligible. Chemotherapy regimen was at the discretion of the medical oncologist (Table). PBI (40.5 Gy in 15 daily 2.7 Gy fractions) was delivered within the first 2 cycles of chemotherapy. Primary endpoints were hematologic and non-hematologic toxicities graded according to Common Terminology Criteria for Adverse Events manual (v. 3.0). Results: Thirty-four patients enrolled with median f/u of 19.2 mos. (4.0 - 38.6). Mean tumor size was 1.8 cm (+/- 0.7 cm), 71% pN0, 68% HR +, 18% Her2 +. All patients completed concurrent chemo-radiation. Three patients had a 3-8 day delay in chemotherapy (1 grade 2 thrombocytopenia; 1 Grade 2 liver enzymes; 1 T desensitization). There was 1 local (DCIS) and no regional/distant recurrences or deaths. Toxicity: 2 grade 4 neutropenia (ddAC, TCarboH); 1 grade 3 neutropenia (post-AC paclitaxel); 1 Grade 3 hyponatremia and DVT (TC); 1 syncope (TAC). None had > grade 2 radiation dermatitis. Conclusions: PBI and concurrent chemotherapy is associated with minimal toxicity and appears to be well tolerated. These results deserve further investigation. Funded by The Breast Cancer Research Foundation.

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*One patient had 6 cycles of TC, all others had 4 cycles.

Abbreviations: C, cyclophosphamide; P, paclitaxel; T, docetaxel (Taxotere); A, doxorubicin (Adriamycin); Carbo, carboplatin; H, trastuzumab (Herceptin); G-CSF, granulocyte colony stimulating factor.

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) as early imaging biomarker of axillary sentinel lymph node (SLN) status in locally advanced node-positive breast cancer (NPBC) patients (pts) receiving neoadjuvant chemotherapy (NACT).

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Background: Use of FDG-PET in the early evaluation of NACT for NPBC is currently under investigation. The aim of this study is to assess FDG-PET in NPBC pts receiving NACT in order to identify a subset of pts that can be spared axillary lymph node dissection (ALND) in case of response. Methods: All pts (period 2009-2011) had [cT2 (≥3cm)-T4, pN1-3], and no prior BC treatment. All pts received 8 cycles (cy) of NACT +/- trastuzumab. FDG-PET was performed at baseline and after 2 cy. After NACT, mastectomy with SLN and ALND was performed. As primary endpoint, the change in maximum standardized uptake value (SUV_{max}) in the primary tumor (PT) and ALNs was compared with pathological response (Jonckheere-Terpstra test). Logistic regression was used to determine the predictive value of a 50% reduction in SUV_{max} on pathological response and SLN status. Results: Forty-one pts were evaluable for the primary endpoint and 31 pts had successful SN procedures. The median age was 49.8 years (range 27-75). Overall, 9.8% (4/41; 95% CI 2.7 – 23.1) of pts had progressive disease (PD), 7.3% (3/41 ; 95% CI 1.5 – 19.9 ) stable disease (SD), 53.7% (22/41; 95% CI 37.4 – 69.3) partial response (PR), and 21.9% (9/41; 95% CI 10.6 – 37.6) a complete pathological response (pCR). A linear trend existed between pCR and higher decreases in SUV_{max} of the PT site (p=0.008), but not with lymph node SUV_{max} (p=0.294). The odds of achieving a pCR, increased significantly when SUV_{max} of the PT decreased with >50% (OR 10.7; 95% CI 1.2 - 98.0; p=0.03), but not lymph node SUV_{max} (OR 4.75; 95% CI 0.82 - 27.5; p=0.08). Achieving a true negative SLN status was more likely with >50% reductions in PT SUV_{max} (OR 41.2; 95% CI 4.0 - 421.9; p= 0.002). A reduction of >50% in nodal SUV_{max} was not predictive of negative SLN status (OR 3.33; 95% CI 0.66 - 16.8; p=0.1). Conclusions: Early changes in PT metabolism imaged with FDG-PET after only 2 cy of NACT is a promising biomarker in the management of the axilla in NPBC. Molecular imaging of PT biology and to a lesser extent of axillary lymph nodes using FDG-PET warrants further study.
Evaluation of the stage IB designation of the 7th edition of the AJCC Staging System.

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**Background:** Recent data from large cooperative group trials have questioned the relevance of small volume metastases identified in the sentinel lymph nodes (SLN) of early stage breast cancer patients. The 7th ed. of the AJCC staging system differentiates node negative patients (stage IA) from those with micrometastases (stage IB) or macrometastases (stage II or III). This study was undertaken to determine the utility of the stage IB designation. **Methods:** Review of a prospectively maintained database identified 3474 patients who underwent SLN biopsy between 1993 and 2007. Clinicopathologic and outcomes data were recorded and patients staged according to the 7th ed. AJCC system. Recurrence-free (RFS), disease-specific (DSS) and overall survival (OS) were determined using the Kaplan-Meier method and compared using the log-rank test. **Results:** AJCC stage distribution included: 2246 (65%) stage IA, 207 (6%) stage IB, 685 (20%) stage IIA, 209 (6%) stage IIB, and 127 (3%) stage III. For patients with stage IB disease, SLN micrometastasis was identified by H&E in 173 (84%) and immunohistochemistry (IHC) in 34 (16%); suggesting that 16% would have been staged IA if enhanced evaluation had not been performed. Median follow-up was 6.1 yrs (range 0-17.2). The 5-yr RFS,DSS and OS rates for patients with stage IB disease were 98.0%, 99.5%, and 95.9% respectively, which did not differ significantly from patients with stage IA disease who had 5-year RFS,DSS and OS rates of (97.5%, p=.9), (98.8%, p=.7) and (96.2%, p=.8). When all stage I patients (IA and IB) were evaluated by ER status or grade (grade 1 vs 2 vs 3), these biologic factors were able to significantly discriminate patients with respect to RFS, DSS and OS. **Conclusions:** Differentiating patients with micrometastases from node negative patients does not stratify patients with respect to survival. Biologic factors (ER status and grade) are better discriminants of survival than the presence of small volume nodal metastases in patients with early stage disease. These data do not support routine use of IHC or alterations in adjuvant therapy decisions based on identification of SLN micrometastases.
Prospective outcomes trial of immediate, implant breast reconstruction using acellular dermal matrix (POBRAD Trial): Pilot series results.

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**Background:** Acellular dermal matrices (ADM) are biological meshes of dermal origin (allo- or xenografts) stripped of all cellular components leaving a structurally intact and immunologically inert extracellular matrix. They are currently in use as adjunctive subdermal scaffolding during implant breast reconstruction to optimise aesthetic outcome. Despite current use in clinical practice there is no prospective data on their clinical efficacy, associated complication rates and cost-benefit analysis. These are the endpoints of our pilot cohort series, intended to provide baseline event rates to help power a multi-centre prospective, phase II, outcomes cohort study. **Methods:** From July 2011 to January 2012 and with our institution review board’s approval - 20 consecutive patients undergoing immediate, implant breast reconstruction were prospectively accrued to the study. Primary endpoints: 30-day complication rates; Secondary endpoints: cosmetic outcome and cost-benefit analysis. Indications for mastectomy included therapeutic intent and/or risk reduction. The ADM used in all cases was SurgiMend PRS (TEI Bioscience Inc. Boston, MA). **Results:** Preliminary 30 day complication rates are in keeping with peer reviewed estimates for implant based breast reconstruction. Sub-set analysis of cosmetic outcome and cost-benefit ratio’s are currently pending. In overview, ADM’s appear to deliver the aesthetic benefit of autologous- implant cover (eg. latissimus dorsi myocutaneous flap) without the downside of donorsite morbidity and prolonged in-patient admission. **Conclusions:** This is to our knowledge the only prospectively accrued dataset seeking to critically evaluate the clinical efficacy, cost-benefit value and enhanced aesthetic utility of ADMs (SurgiMend PRS) in the immediate breast reconstruction setting. The early results provide new evidence in support of the use ADMs in breast reconstruction and validate our intention to extend the study to a multicentre trial.
Breast cancer in older women.

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**Background:** Recent guidelines recommend minimizing breast cancer screening for women over the age of 75. This study examines the presentation and outcome of older patients with breast cancer to determine if increasing screening among older patients may result in better outcomes. **Methods:** A prospective database at Hackensack University Medical Center was queried for all patients with breast cancer diagnosed between 1/1/2006 and 1/1/2011. Numerical values compared by Student’s t-test; categorical values by Fisher exact test. Median time to events determined by Kaplan-Meier; outcomes compared by log-rank test. **Results:** 2200 patients were identified (> 75 years, n = 335, < 75 years, n = 1865). Among the older cohort, mean age was 81 +/- 4 years (range: 75 – 101); mean tumor size was 2.3 +/- 0.1 cm (range: .1 – 12). Most tumors were invasive and localized (in-situ: 12.7%, localized: 57.3%, node positive: 24.0%, metastatic: 5.8%) and most commonly ductal histology (ductal: 77.0%; lobular: 16.6%, mixed: 6.2%). Only 10.0% of patients with invasive disease and 29.2% with positive nodes received systemic therapy; 90.2% underwent surgical resection. Disease-free and overall 5 year survival was 54.9% and 62.9% (in-situ: 82.2%; localized: 67.1%; node positive: 57%; metastatic 22%). Older patients had larger tumors (2.30 +/- .11 v. 1.91 +/- .04 cm; p<0.001), more locally advanced (T4) disease (6.7% v. 1.7%, p<.001), more invasive disease (89% v. 84%, p<.01). Older patients had less positive family history (21.7% v. 37.3%, p<.0001). There was no difference between the groups in race, presentation with stage IV disease, tumor grade, lymphovascular invasion, histologic subtype, triple negativity, or nodal positivity. Overall and disease free five year survival were significantly worse for older patients (OS: 90.2% v. 63.9%, p<.0001; DFS: 80.9% v. 54.9%, p<.0001). **Conclusions:** Breast cancer among older women leads to worse outcomes compared to younger patients, regardless of histology, invasiveness of disease, hormonal status, nodal status or tumor grade. Older women present with more invasive disease, larger tumors and more locally advanced disease, despite having less family history. This implies that continued screening beyond age 75 may lead to less advanced presentation and better outcomes.
Background: Completion axillary lymph node dissection (ALND) is currently the standard of care in the event of a positive sentinel lymph node biopsy (SLNB). However, result from Z0011 indicate that women with a one or two involved axillary nodes and clinical T1-T2 tumors undergoing lumpectomy with radiation therapy followed by systemic therapy do not benefit from completion of ALND in terms of survival. The purpose of this study was to define possible predictors of having three or more involved axillary node to provide information for surgeons making decision about sparing intraoperative frozen section analysis of sentinel lymph node and completion ALND. Methods: We reviewed the records of 1215 patients with clinical T1-T2 invasive breast cancer. None of these patients were in situ cancer on initial gun biopsy nor received neoadjuvant chemotherapy. Factors associated with having three or more involved axillary nodes were evaluated by univariate and multivariate logistic regression analysis. Results: Among 1215 patients, 321 patients had three or more positive nodes. On a multivariate analysis, having three or more positive nodes was associated with primary tumor size by breast US, axillary LN grade according to cortical thickness by US, presence of axillary LN enlargement on chest CT and age. A scoring system to predict the probability of having three or more nodes based on patients’ data and preoperative image findings was developed from the multivariate logistic regression model. The area under the ROC curve was 0.827 (95% CI: 0.793-0.860), and negative predictive value was 90.2% for a score ≤2.7. Similar findings were observed for a validation dataset of 505 patients. Conclusions: Patients with a low probability of having three or more positive nodes can be identified from preoperative image finding. The scoring system developed will be helpful to surgeons making decision about sparing intraoperative frozen section analysis of sentinel lymph node and completion ALND.
Phase II neoadjuvant trial with carboplatin and eribulin mesylate in patients with triple-negative breast cancer.

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Background: Several neoadjuvant trials have been conducted in triple negative breast cancer (TNBC) with platinum agents with pathologic complete response (pCR) ranging from 16%-32%. Eribulin mesylate, a nontaxane microtubule dynamics inhibitor, has clinical activity as monotherapy in breast cancer and other solid tumors. A recent phase I trial found the combination of eribulin mesylate with carboplatin was well tolerated and showed activity in advanced solid tumors. The recommended dose for future trials was eribulin mesylate 1.1 mg/m\(^2\) and carboplatin AUC6. We proposed a neoadjuvant phase II trial with the combination of carboplatin and eribulin in patients with TNBC. Methods: This is a non-randomized, open-label, multi-center, phase II clinical trial of eribulin and carboplatin enrolling histologically-confirmed TNBC patients. Our primary endpoint is to determine the pCR in TNBC patients treated with the combination of carboplatin and eribulin. Secondary endpoints include determination of the clinical response rate, toxicity evaluation and measurement of stem cell and TLE3 as a biomarker of response to eribulin therapy. To obtain an alpha of 0.10 and a power of 0.90, a sample size of 30 patients is required to detect a pCR rate \(\geq 30\%\). 10 of the planned 30 patients have been enrolled to date. Treatment will be given every 3 weeks for a total of 4 cycles of therapy. There will be an initial safety run-in to evaluate the appropriate dose of eribulin in this population. The first 10 patients will receive eribulin at 1.4 mg/m\(^2\) (intravenously over 2-5 minutes) followed by carboplatin AUC=6 (intravenously over 30 minutes). After the 10th patient has been enrolled, the study will be temporarily suspended pending review; toxicity will be assessed for these first 10 patients (cycle 1 only) to assess whether this dose of eribulin will be used for the remaining patients or if a reduction to a dose of 1.1 mg/m\(^2\) will be required. Definitive surgery will be performed 3-8 weeks after completion of therapy, which will conclude the duration of the study. Clinical Trial Registry Number NCT01372579.
A phase III, randomized trial of docetaxel plus carboplatin (TP) versus epirubicin plus cyclophosphamide followed by docetaxel (EC-T) as adjuvant treatment for triple-negative, early-stage breast cancer in Chinese patients.

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**Background:** Triple-negative [estrogen receptor (ER)-/progesterone receptor (PR)-/HER2-] breast cancer (TNBC) accounts for about 15% of all breast cancers and is associated with very poor prognosis. A combination of anthracycline and taxanes represents the most commonly used adjuvant chemotherapy for TNBC patients. BRCA1, a protein responsible for repair upon DNA damage, is often dysfunctional in TNBC. As a result, TNBC is often sensitive to DNA-damaging agents (e.g., cisplatin and carboplatin). A phase II study of docetaxel plus carboplatin as neoadjuvant treatment for TNBC achieved promising response rate (Chang, CANCER, 2010). Encouraged by this important finding, we are currently conducting a phase III trial to examine docetaxel plus carboplatin as adjuvant chemotherapy in patients with early-stage TNBC (registration number at www.ClinicalTrials.gov: NCT 01150513).

**Methods:** All participants received radical mastectomy or breast-conserving surgery for pT1-3N0-2 breast cancer. All cancers were negative for ER, PR, HER2/Neu. All participants had adequate organ function and performance status. The age ranged from 18 to 70 years. Patients randomly received a TP regimen (docetaxel 100 mg/m$^2$ plus carboplatin AUC=6 on day 1, 21 days a cycle for 6 cycles) or a EC-T regimen (epirubicin 90 mg/m$^2$ plus cyclophosphamide 600 mg/m$^2$ on d1, 21 days a cycle for 4 cycles; followed by docetaxel 100 mg/m$^2$ on d1, 21 days a cycle for 4 cycles). Adjuvant radiotherapy was permitted in both arms. The primary endpoint is disease-free survival (DFS). Secondary endpoints included adverse event and quality of life (QoL). The study planned to recruit 500 subjects over a period of 5 years, with 5-year follow-up (once every 6 months). Target hazard ratio is 0.86 (5 year DFS of 74.0% vs. 71.0%). The estimated power is 0.80; 1-sided type 1 error was set at 0.05. The study was activated in June 2010 with enrollment of 110 subjects.
ANZ1001 SORBET: Study of estrogen receptor beta and efficacy of tamoxifen, a single arm, phase II study of the efficacy of tamoxifen in triple-negative but estrogen receptor beta-positive metastatic breast cancer.

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Background: Targeted therapies are needed for triple negative breast cancer (BC). ERβ is expressed in at least 20% of triple negative BCs. ERβ binds estrogen and tamoxifen with a similar affinity to ERα. ERβ has 5 isoforms but only ERβ1 is fully functional. ERβ expression has been shown to be significantly associated with improved distant disease free survival and better overall survival in tamoxifen treated ERα negative patients in retrospective studies. This “proof of principle” study will determine the efficacy of tamoxifen in patients with triple negative but ERβ positive metastatic BC. Methods: This single arm phase II study, being conducted by the Australia and New Zealand Breast Cancer Trials Group, has a Simon’s 2 stage optimal design. The primary end-point is objective response rate (complete and partial responses). Progression free survival and clinical benefit rate will also be assessed. Eligibility criteria include histologically or cytologically confirmed metastatic triple negative BC (ER and PR absent, HER2 ISH negative or IHC 0 or 1) and measurable disease as per RECIST 1.1. Consenting patients undergo central ERβ testing and confirmation of triple negative status on a metastatic biopsy sample. ERβ positive patients (ERβ1 nuclear staining with Allred score >4) are offered trial participation. To date 12 potentially eligible patients have been screened for ERβ; 4 had Allred score >4 (although 2 of these subsequently proved to be ineligible for the trial), 7 had Allred scores <4 and 1 result is pending. Consenting patients receive tamoxifen 20mg per oral daily until disease progression, unacceptable toxicity or withdrawal of consent. If there are ≥2 responses in the first stage of 28 patients, an additional 38 patients will be accrued. Tamoxifen will be considered worthy of further research if there are ≥6 responses in the total 66 patients recruited. Current accrual is 1. Registered on ANZCTR (12610000506099).
Background: Triple negative breast cancer (TNBC) predominantly clusters with “basal like” subtype on genomic profiling. Over-expression of Secreted Protein Acidic and Rich in Cysteine (SPARC) has been observed in basal like breast cancer (Charaffe-Jaufrett et al. Oncogene 2006; 2273-84). Endothelial transcytosis of nab-paclitaxel occurs via albumin gp60 receptor-caveolin 1 interaction. SPARC entraps the albumin resulting in higher intratumoral accumulation, which may explain the increased efficacy of nab-paclitaxel (Desai et al. Translational Oncology 2009; 59-63). Exploiting this mechanism and the dysfunctional BRCA mediated DNA repair in basal tumors, we hypothesize that nab-paclitaxel + the DNA damaging drug carboplatin would produce high response rates in TNBC. Adding bevacizumab may enhance efficacy by blocking angiogenesis. In TNBC, pathologic complete remission (pCR) to neo-adjuvant therapy correlates with better disease-free survival (DFS). We hypothesize that high pCR rates can be achieved for patients with TNBC with this combination translating to an improved DFS than seen historically. Methods: Patients with palpable and operable TNBC ≥ 2 cm are eligible for this single stage phase II trial. pCR (defined as the absence of invasive tumor cells) in the breast is the primary end point, while pCR in the breast + axillary nodes and pCR + near pCR (residual tumor < 5mm) in the breast are secondary end points. 57 evaluable patients are needed, assuming a pCR rate of 25% vs. 40% for the null and alternate hypotheses respectively. 34 patients have been accrued to date. Patients receive carboplatin AUC 6 day 1 and nab-paclitaxel 100mg/m² days 1, 8 and 15 of a 28 day cycle for 4 cycles and then dose dense AC for 4 cycles. Bevacizumab is given at 10mg/kg Q 2 weeks with chemotherapy for the first 6 cycles. Surgery and radiation are per institutional standards. Bevacizumab is continued postoperatively to complete 1 year of treatment. A core biopsy for collection of fresh tumor tissue is required prior to the start of study treatment. Blood is collected at baseline, and after 4 and 8 cycles for biomarker analysis. Gene expression profiling will be undertaken for correlation with response.
ABT-888 (veliparib) in combination with weekly carboplatin and paclitaxel in advanced solid tumors.

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Background: The combination of paclitaxel and carboplatin is widely used for the treatment of patients with advanced solid tumors of diverse histologies. In breast cancer patients, a weekly regimen of paclitaxel has shown greater efficacy with comparable safety, when compared to every-three-weeks dosing (ECOG 1199). ABT-888 (veliparib) is an oral inhibitor of poly-ADP-ribose polymerase (PARP). Inhibition of PARP has been shown in preclinical studies to potentiate the effect of cytotoxic agents which induce DNA damage, such as platinum agents. The preclinical synergy of carboplatin with veliparib and the efficacy of the combination of paclitaxel with carboplatin supports exploration of this triplet regimen. Methods: This 3+3 phase I trial will seek to determine the maximum tolerated dose (MTD) of the combination of carboplatin (AUC 2), paclitaxel (80 mg/m²), and veliparib in patients with advanced solid tumors. Veliparib will be escalated beginning at 50 mg PO BID to a maximum of 200mg PO BID. Treatment will be given on a weekly basis over a 21-day cycle. There will be an expansion cohort of 6-12 patients with triple negative breast cancer at the maximum tolerated dose. This group of patients will undergo mandatory pre- and post-cycle 1 tumor biopsies. Secondary aims of the study include safety and toxicity of the combination, its pharmacokinetic and pharmacodynamic effects, documentation of any anti-tumor response, and assessment of the characteristics of the tumor specimens obtained in the expansion cohort that may contribute to efficacy. The latter will include whole genome microarray analysis to evaluate expression of genes involved in DNA repair pathways. Currently, the recommended phase II dose has not been determined and enrollment is ongoing on the last planned dose level (veliparib 200 mg BID).
Q-CROC-03: A prospective biopsy driven clinical trial to study the mechanisms of resistance to chemotherapy in triple-negative breast cancer patients.

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Background: Resistance to chemotherapy or targeted agents is the cause of death in most patients dying of breast cancer and one of the major challenges presently faced by oncologists. In triple negative breast cancers (TNBCs), drug resistance emerges quicker than in other breast cancer subtypes and contributes to the poor prognosis seen in these patients. The lack of targeted therapies to treat TNBC highlights the important need to better understand the molecular mechanisms contributing to chemotherapy resistance in order to develop new therapeutic strategies. However, the difficulty in obtaining tissue samples from drug resistant tumors has been one of the limiting factors in this field of study. Methods: We have designed a prospective phase II clinical trial where paired biopsies are collected from chemotherapy resistant TNBCs (NCT01276899). Four needle core biopsies are collected before the initiation of treatment and 2 weeks before surgery or at the time of progression in the neoadjuvant and metastatic settings respectively. Metastatic sites eligible for biopsy include liver, lung, skin and lymph nodes. This study is presently recruiting at 5 major health centers in Quebec and will soon open in the USA. We have currently enrolled 13 patients in the neoadjuvant setting and 2 metastatic patients. Major challenges in patient enrollment will be discussed. We have standardized the methods of collection and processing of tissue and blood specimens to ensure their molecular integrity and compatibility with different genomic and proteomic molecular platforms. Analysis of tumor cellularity has been incorporated into our quality control and we have optimized the extraction of nucleic acids to obtain high yields and optimal quality. Paired biopsies will undergo Next Gen Sequencing, flow sorted aCGH analysis, gene expression and miRNA profiling as well as phosphoproteomic profiling using reverse phase protein arrays. Collection of clinical data will allow molecular profiling data to be linked to clinical response data so as to determine DNA, RNA and protein factors correlated with tumor resistance to chemotherapy.
Phase III open-label, randomized, multicenter study of NKTR-102 versus treatment of physician’s choice (TPC) in patients (pts) with locally recurrent or metastatic breast cancer (MBC) previously treated with an anthracycline, a taxane, and capecitabine (ATC).

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Background: NKTR-102 is a topoisomerase I inhibitor-polymer conjugate that hydrolyzes to provide continuous exposure to SN-38. A phase 2 trial of single-agent NKTR-102 was conducted in pts with 3rd-line MBC; 2 schedules (q14d; q21d) investigated a dose of 145 mg/m². ORR was 29% (including 3% CR) with the prior ATC subset demonstrating an ORR of 31%. Dosing q21d was better tolerated; in this arm, median PFS and OS equaled 5.3m and 13.1m, respectively. Trial Design: Pts will be randomized 1:1 to receive single-agent NKTR-102 or TPC in an open-label, randomized, multicenter phase 3 study in pts with advanced breast cancer. Key Entry Criteria: Adult females, with ECOG 0 or 1 with adequate liver, kidney and marrow function. All pts must have received prior therapy with ATC (these drugs can be administered in the neo/adjuvant or locally advanced/metastatic setting). Prior A is not mandated if contraindicated. Prior toxicities must have resolved to ≤ Grade 1 (except sensory neuropathy ≤ Grade 2; complete resolution of prior diarrhea). Pts with brain metastases may be eligible, if lesions are stable for prior 3 weeks without steroids. Methods: Primary efficacy endpoint is OS. Secondary endpoints include: ORR by RECIST v1.1, clinical benefit rate (ORR+SD > 6 months), PFS and QoL. NKTR-102 is given IV at 145 mg/m² over 90-min every 21 days without premedications. Pts randomized to TPC receive 1 of the following: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel (the agent must be available at the treating institution). Pts are stratified by region, prior eribulin and receptor status (TNBC, Her2+ or Other). Target Accrual: ~840 pts will be required for sufficient events to occur in the planned follow-up time; OS will be compared using a two-sided log-rank test; 1 interim analysis will occur when 50% of the deaths are reported. PK sampling is performed in a subset of pts. CTCs (isolated by Apocell ApoStream technology) are serially assessed for potential predictive markers of response and toxicity. Enrollment is expected to remain open until late 2013.
Randomized controlled trial comparing zoledronic acid plus chemotherapy with chemotherapy alone as a neoadjuvant treatment in patients with HER2-negative primary breast cancer.

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Background: Zoledronic acid (ZOL) is a nitrogen-containing bisphosphonate, and it induces osteoclast apoptosis and inhibits bone resorption by inhibiting the mevalonate pathway. ZOL has also been found to have antitumor effects that include an angiogenesis inhibiting action, an inhibitory effect on tumor cell adhesion to and invasion of the extracellular matrix, and activation of a gdT cells. In addition, it has been found to have a synergistic apoptosis-inducing effect when used in combination with antitumor drugs. In this study we will investigate the pCR rate when ZOL is added to anthracycline followed by taxane to treat T2 and T3 breast cancer patients.

Methods: Women with resectable invasive StageIIA-IIIB (T ≥ a3 cm or T ≥ a2 cm and lymph node positive) breast cancer who are HER-2-negative, between 20 and 70 years of age, and ECOG PS 0-1 are eligible. Patients with distant metastasis, patients who have had received chemotherapy, hormone therapy, or radiotherapy for breast cancer, patients with serious complications, such as heart disease or an infection, patients with a complicating dental or jaw infection or traumatic condition of the teeth, and patients with a history of treatment with a bisphosphonate within the previous 12 months are excluded. A total of 4 courses of FEC100 are administered every 3 weeks followed by weekly paclitaxel for 12 courses. ZOL 4mg is administered every 3-4 weeks a total of 7 times. Patients are randomized 1:1 to chemotherapy + ZOL group or chemotherapy alone group, according to the presence or absence of lymph node metastasis, estrogen receptor (ER) status, and their menopausal status. The primary endpoint is pCR. Secondary endpoints are tumor response rate, the breast-conserving surgery ratio, and disease-free survival (DFS). We calculated the sample size on the basis of a pCR rate of 18% in the chemotherapy alone group and 35% in the chemotherapy + ZOL group, at a one-sided significance rate of 5%, and test power of 80%, and as a result we will target a patient sample size of 180 patients. 162 of planned 180 patients have been enrolled as of January 24, 2012.
NSABP B-47: A phase III trial of adjuvant therapy comparing chemotherapy alone (six cycles of docetaxel plus cyclophosphamide or four cycles of doxorubicin plus cyclophosphamide followed by weekly paclitaxel) to chemotherapy plus trastuzumab in women with node-positive or high-risk, node-negative, HER2-low invasive breast cancer.

Background: Adjuvant studies utilizing trastuzumab in early HER2+ breast cancer demonstrated a large reduction in recurrence and death. Post-enrollment central testing showed HER2 non-amplified participants derived similar benefit. Methods: Selection of one of the two chemotherapy regimens is by physician choice: The non-anthracycline regimen is TC (docetaxel 75 mg/m², cyclophosphamide 600 mg/m²) administered IV every 3 weeks for 6 cycles; the anthracycline regimen is AC followed by WP (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² administered IV either every 3 weeks or every 2 weeks [per investigator discretion] for 4 cycles followed by paclitaxel 80 mg/m² IV weekly for 12 doses). Patients are randomly assigned to receive chemotherapy with or without trastuzumab therapy. For patients receiving the TC chemotherapy regimen, trastuzumab is given every 3 weeks during and following chemotherapy until 1 year after the first trastuzumab dose (8 mg/kg loading dose; 6 mg/kg for the remaining doses). For patients receiving the AC followed by WP chemotherapy regimen, trastuzumab begins with the first dose of weekly paclitaxel and will be given weekly for 12 doses (4 mg/kg loading dose; 2 mg/kg for the remaining weekly doses). Following completion of WP, trastuzumab therapy continues with 6 mg/kg doses given every 3 weeks for a total of 1 year. Eligibility: Eligibility includes: node positive or high risk node negative female breast cancer patients; HER2 IHC 1+ or 2+ scores, but non amplified by FISH Statistical Design: The primary aim is to determine whether the addition of trastuzumab to chemotherapy improves invasive disease-free survival (IDFS). 3260 patients will be enrolled to provide statistical power of 0.9 to detect a 33% reduction in the hazard rate of IDFS using a one-sided alpha level of 0.025. Progress: Protocol was activated in January 2011. As of January 27, 2012, 486 of 3260 patients have been enrolled. Supported by NCI U10-12027, -37377, 69651, 69974, and Genentech, Inc.

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Background: Indibulin (Zybulin, ZIO-301) is a new, synthetic agent that inhibits tumor cell growth at the G2/M phase through destabilization of microtubule dynamics. It binds tubulin at a different site than taxanes and vinca alkaloids. Indibulin does not interact with acetylated (neuronal) tubulins and has not exhibited the neurotoxicity associated with other tubulin binders. Indibulin has potent antitumor activity in human cancer cell lines, including multidrug-, taxane-, and vinblastine-resistant lines. Norton-Simon modeling based on cell line data suggested that dd administration could optimize efficacy while limiting toxicity. Methods: Eligible are patients (pts) with metastatic or unresectable locally advanced breast cancer, measurable or non-measurable disease, and any number of prior therapies. The objective of the Ph I portion is to determine the maximum tolerated dose (MTD) of indibulin when given in a dd fashion (5 days treatment, 9 days rest (14 total) using standard 3+3 dose escalation schema. Ph II will seek to estimate the proportion of pts progression free at 4 months when treated with indibulin at the dose determined in the Ph I. Secondary endpoints are overall response rate, proportion of subjects with stable disease >6 months and toxicity profile of indibulin. Optimal Simon two-stage design with an unpromising rate of pts who have not progressed at four months as 20% and a promising rate of 40% with a type I error of 5% and power of 80% will be used. 13 pts will initially enter the 1st stage of the ph II portion. If there are 3 or fewer pts who do not experience disease progression at 4 months in the first stage of ph II, the study will be terminated and declared to have a negative result. If 4 or more pts do not progress at 4 months, enrollment in the ph II of the study will be extended to 43 pts. A total of 45 pts will be enrolled to allow for a 5% drop out rate to account for pts who may not be evaluable for the primary endpoint due to toxicity or study withdrawal rather than progression of disease or death prior to 4 months. If ≥13 out of 43 pts are progression-free at 4 months, the study will be considered to have a positive result and indibulin would be considered worthy of further testing in this disease.
ARTemis: Randomized trial with neoadjuvant chemotherapy for patients with early breast cancer.

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Background: Bevacizumab is a new humanised monoclonal antibody which targets vascular endothelial growth factor (VEGF) and thereby the neoangiogenic process in cancer. Bevacizumab has shown promising anti-tumour effect when given concurrently with taxane-based chemotherapy in breast cancer. However two neoadjuvant breast cancer trials have produced conflicting results. The NSABP-B40 study showed significant benefit for bevacizumab only in the ER-ve patients (pathological complete response (pCR) in ER-ve population 15.2% vs 23.3%, p=0.008). Whereas the GEPARQUINTO trial reported significant benefit only in the triple negative patients (pCR 27.8% vs 36.4% p=0.021). Methods: ARTemis is a phase III randomised trial to determine whether the addition to neo-adjuvant chemotherapy of bevacizumab is more effective than standard chemotherapy alone in patients with HER2-negative early breast cancer. A total of 400 patients will be randomised into each of the two treatment arms which will allow an absolute difference in the pCR rates in excess of 10% to be detected at the 5% (2-sided) level of significance with an 85% power. Primary outcome is pathological complete response rates after neo-adjuvant chemotherapy, i.e. no residual invasive carcinoma in the breast, and no evidence of metastatic disease within the lymph nodes. Secondary outcomes are disease free survival, overall survival, complete pathological response rates in breast alone, radiological response after 3 and 6 cycles of chemotherapy and rate of breast conservation and toxicities. Results: Recruitment into ARTemis began in April 2009 and as of January 2012 had recruited 469 (59%). ARTemis is due to complete recruitment by Dec 2012 and the first planned interim analysis of the primary outcome will be Dec 2013. Conclusion: The IDSMC reviewed the trial in June 2011 and recommended continuation of recruitment to this important trial given there were no safety concerns, and results from the other neoadjuvant studies (NSABP-B40 and GEPARQUINTO) are conflicting.
A phase II, single-arm, feasibility study of dose-dense doxorubicin and cyclophosphamide (AC) followed by eribulin mesylate for the adjuvant treatment of early-stage breast cancer (EBC).

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**Background:** Randomized trials have confirmed the benefit of the combination of an anthracycline (A) and cyclophosphamide (C) for the adjuvant treatment of EBC. The addition of taxane therapy to AC therapy has further improved survival. Despite the improvement in adjuvant therapies for BC, new approaches for improving outcomes are of significant importance and may involve developing improved combination regimens. Eribulin mesylate has demonstrated antitumor activity and significant improvement in overall survival (OS) in patients with heavily pretreated locally advanced or metastatic breast cancer (MBC) and may improve outcomes in EBC as well. **Methods:** This study will determine the feasibility of eribulin as adjuvant therapy following dose-dense AC for HER2 normal EBC. A completion rate of >80% was set as a threshold for feasibility as established adjuvant regimens have shown feasibility rates ranging from ~65% for trastuzumab to >80%. This is a phase 2, single-center, feasibility study of dose-dense adjuvant chemotherapy in patients with EBC. Dose-dense AC (Doxorubicin 60 mg/m² IV plus C 600 mg/m² IV) on day 1 of every 14-day cycle is given for 4 cycles, followed by 4 cycles of eribulin mesylate at 1.4 mg/m² over 2-5 minutes IV on days 1 and 8 every 21 days. Growth factors are given on day 2 of AC cycles and only for neutropenia events with eribulin treatment. Feasibility is determined by the ability to complete the eribulin portion of the regimen without a dose delay or reduction. Exploratory objectives include efficacy endpoints of 3-year disease-free survival (DFS) and OS. Patients have histologically confirmed HER2 normal stage I-III invasive disease and adequate bone marrow, liver, and renal function. Thirty two of approximately 80 planned patients are currently enrolled. Feasibility rates will be calculated with growth factor support (ie, the successful use of growth factor support following a neutropenia event is not considered a dose delay) and without growth factor support (ie, where need for growth factors is considered a delay). Secondary endpoints include DFS and OS and will be estimated by Kaplan-Meier method.
DETECT III: A multicenter, randomized, phase III study to compare standard therapy alone versus standard therapy plus lapatinib in patients (pts) with initially HER2-negative metastatic breast cancer but with HER2-positive circulating tumor cells (CTC).

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Background: HER2 status may change over the course of disease in breast cancer pts. Approx. 20-30% of pts with initially HER2-negative breast cancer have HER2-positive metastasis (Zidan et al. 2005; Tewes et al. 2009). Determining HER2 status on CTC is one option to re-evaluate HER2 status at the time metastasis is diagnosed. Currently it is unclear if HER2-targeted therapy based on the assessment of HER2 status of CTC reveals a clinical benefit. Methods: This is a randomized, open-label, two arm phase III study to investigate the clinical efficacy of lapatinib, as a HER2-targeted therapy in initially HER2-negative metastatic breast cancer pts with HER2-positive CTC at the time of distant disease. As only half of the pts with HER2-negative metastatic breast cancer show CTC-positivity and of those approx. 32% will exhibit HER2-positive CTC (Fehm et al. 2010), screening of about 1420 pts is required to enroll 228 pts. Main inclusion criteria: metastatic breast cancer with HER2-negative primary tumor tissue and/or biopsies from metastatic sites or locoregional recurrences, evidence of ≥1 HER2-positive CTC and ≥1 measurable metastatic lesion according to RECIST. Eligible pts will be randomized 1:1 to receive standard treatment vs. standard treatment plus lapatinib. Standard chemo- or endocrine therapy must be approved in combination with lapatinib or been investigated in prior clinical trials. Primary endpoint is progression free survival. Secondary endpoints include overall response rate, clinical benefit rate, overall survival and dynamic of CTC. The DETECT III trial is one of the first trials where treatment is based on phenotypic characteristics of CTC. If this trial succeeds in proving efficacy of lapatinib in pts with initially HER2-negative metastatic breast cancer but HER2-positive CTC, this will establish a new strategy in the treatment of metastatic breast cancer.
A multicenter prospective study of image-guided radiofrequency ablation for small breast carcinomas.

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Background: As the management of breast carcinoma evolves toward less invasive treatments, the next step is the possibility of removing the primary tumor without surgery. The most promising noninvasive ablation technique is radiofrequency ablation (RFA), which can effectively kill tumor cells with a low complication rate. Our preliminary studies of RFA followed by standard surgical resection have indicated that this technique is effective for surgical ablation of small (≤ 2cm) breast tumors without extensive intraductal components (EIC). Methods: To determine if RFA is oncologically and cosmetically appropriate for the local treatment of primary breast carcinoma, this multi-center prospective study used RFA as the sole local treatment of breast tumors ≤ 1.5cm in size on ultrasound and MRI. Exclusion criteria include receiving of preoperative chemotherapy, or the presence of invasive lobular carcinoma or invasive ductal carcinoma with suspicious EIC. After confirmation that the standard baseline core biopsy for diagnosis and measurement of tumors markers (ER, PgR, HER-2/neu expression and the presence of the Ki-67 proliferative marker) have been obtained, consent will be obtained and the patient scheduled RFA. All patients received adjuvant radiation therapy. The use and choice of systemic therapy will be based on the information from the baseline core biopsy and imaging studies. The first primary endpoints of this study is successful tumor ablation, as evidenced by negative findings on vacuum-assisted or core biopsies and imaging studies after RFA. The second primary endpoints is the incidence of procedure related adverse events. Forty patients with small tumors that are clearly identifiable and measurable by ultrasound and MRI were enrolled. The response to ablation was evaluated with both vacuum-assisted or core biopsies and imaging studies every 3 months during the first year. The long-term outcomes were assessed using quality of life measurement scales and imaging studies every 6 months thereafter through year 5.
Phase II study of the multikinase inhibitor dovitinib (TK1258) or placebo in combination with fulvestrant in postmenopausal, endocrine resistant HER2-/HR+ breast cancer.

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**Background:** Overcoming endocrine resistance is a critical goal in the treatment of hormone receptor-positive (HR+) breast cancer. Molecular mechanisms associated with endocrine resistance include adaptive “cross-talk” between the estrogen receptor and the fibroblast growth factor receptor (FGFR). Up to 8% of HR+/HER2- breast cancer patients (pts) have amplification of the *FGFR1* gene, which is associated with resistance to endocrine therapy but can be overcome via FGFR1 inhibition in preclinical models. Dovitinib is a potent FGF, VEGF, and PDGF receptor tyrosine kinase inhibitor that demonstrated antitumor activity in heavily pretreated breast cancer pts with FGF pathway amplification (*FGFR1, FGFR2, or ligand FGF3*; Andre et al, ASCO 2011). Dovitinib may reverse resistance to endocrine therapy related to FGF-pathway amplification and is studied here to determine if it can improve outcomes when combined with fulvestrant. **Methods:** Postmenopausal HER2-/HR+ locally advanced or metastatic breast cancer pts (N=150) progressing within 12 months of completion of adjuvant endocrine therapy or after <= 1 prior endocrine therapy in the advanced setting will be enrolled in this multicenter, randomized, double blind, placebo controlled, phase II trial. Pts will prospectively undergo molecular screening to enrich for FGF-amplification (*FGFR1, FGFR2, or FGF3 amplification by qPCR; 45 amplified and 30 non-amplified pts per arm). Pts will be randomized 1:1 to receive fulvestrant (500 mg q4w [with an additional dose 2 wks after the initial dose]) in combination with oral dovitinib (500 mg, 5 days on/2 days off) or placebo until disease progression, unacceptable toxicity, or death. The primary endpoint is progression-free survival, with tumor assessments performed q8w. Secondary endpoints include overall response rate per RECIST v1.1, duration of response, overall survival, ECOG performance status and patient reported outcome scores over time, and safety. The pharmacodynamic effect of dovitinib on FGFR-associated angiogenic pathways in tumor specimens and potential predictive biomarkers of response to dovitinib will be explored.