1000 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

10-yr follow-up results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients.

Thomas B. Julian, Stewart J. Anderson, David N. Krag, Seth P. Harlow, Joseph P. Costantino, Takamaru Ashikaga, Donald L. Weaver, Eleftherios P. Mamounas, Norman Wolmark; National Surgical Adjuvant Breast and Bowel Project; The Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA; National Surgical Adjuvant Breast and Bowel Project Biostatistical Center; University of Pittsburgh Graduate School of Public Health Dpt of Biostatistics, Pittsburgh, PA; National Surgical Adjuvant Breast and Bowel Project; University of Vermont, Burlington, VT; National Surgical Adjuvant Breast and Bowel Project Biostatistical Center, University of Pittsburgh, Graduate School of Public Health, Department of Biostatistics, Pittsburgh, PA; Department of Medical Biostatistics, University of Vermont College of Medicine, Burlington, VT; National Surgical Adjuvant Breast and Bowel Project; Department of Pathology, University of Vermont College of Medicine, Burlington, VT; MD Anderson Cancer Center Orlando, Orlando, FL

Background: NSABP B-32, the largest surgical prospective randomized phase III trial was designed to compare overall survival (OS), disease-free survival (DFS), and morbidity between SNR alone vs SNR + AD in SN negative (-) pts. We present 10 yr outcome data for primary endpoints as well as updated data on the effect of occult metastases, found later in the SN by central, detailed pathologic analysis. **Methods**: 5,611 women with operable, clinically N0, invasive breast cancer were randomized to SNR + AD (Group [Grp] 1) or to SNR alone with AD only if SNs were positive (Grp2). 3,989 (71.1%) of 5,611 pts were SN-. 3,986 (99.9%) of these SN- pts had follow-up information: Grp 1: 1,975, Grp 2:2,011. Median time on study was 9.4 yrs. Cox proportional hazard models adjusting for study stratification variables were used to compare OS and DFS between the two groups. Two-sided p values were used. HR values > 1 indicate a more favorable outcome in Grp 1 **Results**: At 10 yrs, there continues to be no significant difference in OS between the two groups (HR: 1.11, p = 0.27). 10 yr Kaplan-Meier (K-M) estimates for OS are 87.8% for SNR alone and 88.9% for SNR + AD. There continues to be no significant difference in DFS between the two groups (HR: 1.01, p=0.92). 10-yr K-M estimates for DFS were 76.9% for both groups. Occult nodal disease was originally detected in 3,884 pts (15.8%) with SN- on initial H and E analysis. Comparisons between the groups with and without occult disease yielded an adjusted HR for OS: 1.25 (p = 0.08) with an absolute difference at 10 yrs of 2.8% and a HR for DFS: 1.24 (p = 0.018) with an absolute difference of 4.1%. The cumulative incidences of local-regional events were low (10-yr values: SNR 4.0%, SNR+AD, 4.3%) and not significant (HR: 0.95, p = 0.77). **Conclusions**: At 10 yrs there continues to be no significant differences in OS and DFS between SNR and SNR + AD in pts with negative SN. The relative increase in risk of DFS and OS for pts with occult SN metastases remains stable. Support: PHS grants: NSABP: U10CA-12027, U10CA-37377, U10CA-69651, U10CA-69974; VT Ca Cntr: P30 CA22435; DNK: 5RO1CA074137 NCI Dpt HHS. Clinical trial information: NCT00003830.

LBA1001   **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: Final analysis of the EORTC AMAROS trial (10981/22023).

Emiel J. Rutgers, Mila Donker, Marieke Evelien Straver, Philip Meijnen, Cornelis J. H. Van De Velde, Robert E. Mansel, Helen Westenberg, Lorenzo Orzalesi, Willem H. Bouma, Huub van der Mijle, Grard A. P. Nieuwenhuijzen, Sanne C. Veltkamp, Leen Slaets, Carlo G. M. Messina, Nicole J. Duez, Coen Hurkmans, Jan Bogaerts, Geertjan van Tienhoven; Netherlands Cancer Institute, Amsterdam, Netherlands; NKI-AVL, Amsterdam, Netherlands; Leiden University Medical Center, Department of Surgery, Leiden, Netherlands; Cardiff University, Cardiff, United Kingdom; Institute for Radiation Oncology Arnhem, Arnhem, Netherlands; Breast Unit, Careggi University Hospital, Florence, Italy; Department of Surgery, Gelre Hospital, Apeldoorn, Netherlands; Department of Surgery, Nij Smellinghe Hospital, Drachten, Netherlands; Department of Surgery, Catharina Hospital, Eindhoven, Netherlands; Department of Surgery, Amstelland Hospital, Amstelveen, Netherlands; European Organisation for Research and Treatment of Cancer, Brussels, Belgium; EORTC Headquarters, Brussels, Belgium; Department of Radiation Oncology, Catherina Hospital, Eindhoven, Netherlands; Department of Radiation Oncology, Academic Medical Centre, Amsterdam, Netherlands

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Monday, June, 3, 2013, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2013, issue of *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

1002   **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

The effect of surgery type on survival and recurrence in very young women with breast cancer.

May Lynn Quan, Lawrence Frank Paszat, Kimberley Fernandes, Rinku Sutradhar, David R. McCready, Eileen Rakovitch, Ellen Warner, Frances Catriona Wright, Nicole Hodgson, Muriel Brackstone, Nancy Baxter; Foothills Medical Centre, Calgary, AB, Canada; Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; Institute for Clinical and Evaluative Sciences, Toronto, ON, Canada; University Health Network-Princess Margaret Hospital, Toronto, ON, Canada; Institute for Clinical Evaluative Sciences, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada; Juravinski Cancer Centre, Hamilton, ON, Canada; London Health Sciences Centre, London, ON, Canada; Department of Surgery, University of Toronto, Toronto, ON, Canada

Background: Young age has been identified as an independent predictor of recurrence and mortality in women with breast cancer. The equivalence of breast conserving surgery (BCS) with mastectomy remains unclear in this population in an era of multimodal therapy. We sought to determine the effect of surgery type on the risk of recurrence and survival in a large, population based cohort of very young women. **Methods:** All women diagnosed with breast cancer aged ≤35 between 1994 and 2003 in Ontario were identified from the Ontario Cancer Registry, a population based registry of all incident invasive breast cancers in the province. A retrospective chart review was undertaken to identify patient, tumor and treatment variables, as well as locoregional, distant recurrences and death. Univariable and multivariable Cox proportional hazards regression models were fit to determine the effect of primary surgery type on overall survival while controlling for known confounders. To examine time to recurrence in a multivariable analysis, the proportional subdistribution hazards model (Fine and Gray) was used to account for death being a competing risk. **Results:** A total of 1,381 patients were identified; the median age was 33 (range 18 – 35), median follow up was 11 years. Primary surgical treatment was BCS in 793 (57%) patients of which 89% had adjuvant radiotherapy. Of the 588 (43%) having mastectomy, 53% underwent post mastectomy radiation. Overall, 38% of patients sustained a recurrence of any type and 31% had died. After controlling for tumor size, margin status, node status, grade, LVI, ER/PR, HER2 and treatment (chemotherapy, radiation, hormones) there was no difference in overall survival (HR 0.99, 95% CI 0.79,1.26) or recurrence (HR 0.96, 95% CI 0.73,1.26) among women treated with BCS or mastectomy. Predictors of recurrence were size ≥2 cm, ≥ 1 positive node, neoadjuvant chemotherapy, and lack of radiation. Predictors of death were similar and included high grade and presence of LVI. **Conclusions:** Very young women selected for BCS had similar outcomes to those selected for mastectomy after controlling for known prognostic factors for recurrence and death.

1003   **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

PrECOG 0105: Final efficacy results from a phase II study of gemcitabine (G) and carboplatin (C) plus iniparib (BSI-201) as neoadjuvant therapy for triple-negative (TN) and BRCA1/2 mutation-associated breast cancer.

Melinda L. Telli, Kristin C. Jensen, Allison W. Kurian, Shaveta Vinayak, Jafi A. Lipson, Elizabeth A. Schackmann, Irene Wapnir, Robert W. Carlson, Joseph A. Sparano, Bobbie Head, Lori J. Goldstein, Barbara B. Haley, Shaker R. Dakhil, Judith Manola, James M. Ford; Stanford University, Stanford, CA; Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY; California Cancer Care, Greenbrae, CA; Fox Chase Cancer Center, Philadelphia, PA; University of Texas Southwestern, Dallas, TX; Cancer Center of Kansas, Wichita, KS; PrECOG, Philadelphia, PA

Background: TN and BRCA1-deficient breast cancer (BC) cell lines exhibit enhanced sensitivity to DNA damaging agents. This study was designed to assess efficacy, safety and predictors of response to iniparib in combination with GC in early-stage TN and BRCA1/2 mutation-associated BC. **Methods**: This single-arm, phase II study (NCT00813956) enrolled pts with clinical stage I-IIIA (T $\geq$ 1cm by MRI) ER-negative ($\leq$ 5%), PR-negative ($\leq$ 5%), and HER2-negative or BRCA1/2 mutation-associated BC. Neoadjuvant G (1000 mg/m^2; IV; D1, 8), C (AUC 2; IV; D1, 8), and iniparib (5.6 mg/kg; IV; D1, 4, 8, 11) were given every 21 days for 4 cycles, until the protocol was amended to increase the treatment duration to 6 cycles, with enrollment of 80 pts at multiple PrECOG institutions. The primary endpoint is pathologic complete response (pCR), defined as no invasive carcinoma in the breast and axilla. Pathologic response was centrally assessed by the residual cancer burden (RCB) index. Assuming 76/80 eligible and treated pts, the regimen would be deemed effective if the lower bound of a 90% exact binomial CI on the pCR rate exceeded 25%. Secondary endpoints are safety, MRI response, and breast conservation. **Results**: Among 80 eligible pts treated with 6 cycles, median age is 48 years, 19 pts have germline BRCA1/2 mutations (90% tested to date) and clinical stage is I (13%), IIA (36%), IIB (36%), IIIA (15%). Pathologic response data (ITT population) are detailed below. 69 pts completed treatment per protocol: 5 progressed, 5 discontinued due to an AE and 1 mutation carrier was lost to follow-up. Most common G3/4 adverse events are neutropenia (49%), elevated ALT/AST (14%), and anemia (10%). **Conclusions**: Preoperative GC plus iniparib is active in the treatment of early-stage TN and BRCA1/2 mutation-associated BC. Clinical trial information: NCT00813956.

	All pts	BRCA 1/2 wt	BRCA 1/2 mutant	TN BRCA 1/2 mutant
	n = 80[1]	n = 61[2]	n = 19[3]	n = 16[4]
pCR (RCB 0), n (%)	29 (36%)	20 (33%)	9* (47%)	9* (56%)
90% CI	27 – 46%	23 – 44%	27 – 68%	33 - 77%
RCB 0/1, n (%)	45 (56%)	31 (51%)	14 (74%)	12 (75%)
90% CI	46 - 66%	40 - 62%	52 - 89%	52 - 91%

Completed treatment per protocol: [1]69, [2]52, [3]17, [4]14. * One pt with bilateral BC had pCR in both tumors.

1004   **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto).

Gunter Von Minckwitz, Andreas Schneeweiss, Christoph Salat, Mahdi Rezai, Dirk Michael Zahm, Peter Klare, Jens U. Blohmer, Hans Tesch, Fariba Khandan, Sebastian Jud, Christian Jackisch, Keyur Mehta, Sibylle Loibl, Michael Untch, German Breast Group; German Breast Group, Neu-Isenburg, Germany; National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany; Hematology Oncology Clinic, Munich, Germany; Breast Center Duesseldorf, Louis Hospital, Düsseldorf, Germany; Frauenklinik Gera, Gera, Germany; Praxisklinik Krebsheilkunde, Berlin, Germany; Brustzentrum Sankt-Gertrauden-Krankenhaus, Berlin, Germany; Onkologische Gemeinschaftspraxis am Bethanien-Krankenhaus, Frankfurt/Main, Germany; Frauenklinik, St. Markus Krankenhaus, Frankfurt, Germany; Frauenklinik, Universitätsklinikum, Erlangen, Germany; Klinikum Offenbach, Offenbach, Germany; Helios Klinikum Berlin-Buch, Berlin, Germany

Background: Use of carboplatin in neoadjuvant chemotherapy (NACT) has never been prospectively examined in breast cancer. Cohort studies suggest a high sensitivity to DNA-damaging agents (e.g., carboplatin in triple negative breast cancer [TNBC]), which have a high prevalence of BRCA mutations. Two trials examining carboplatin in HER2+ metastatic disease have shown conflicting results, but one was biased by different dosage of docetaxel in treatment arms. GeparSixto investigates the impact of carboplatin in addition to an identical, optimized cytotoxic-targeted regimen on pathological complete response (pCR) in these two breast cancer subtypes. **Methods:** In GeparSixto trial (NCT01426880) patients were treated for 18 weeks with paclitaxel 80mg/m^2 q1w and non-pegylated-liposomal doxorubicin (NPLD) 20mg/m^2 q1w. HER2+ patients received concurrently trastuzumab 6(8) mg/kg q3w and lapatinib 750mg daily. TNBC patients received concurrently Bevacizumab 15mg/kg i.v. q2w. All patients were randomized 1:1 to receive concurrently carboplatin AUC 1.5-2 q1w vs not, stratified by subtype. Primary objective is pCR rates (ypT0 ypN0), secondary objectives are pCR rate in predefined subgroups or by other definitions, clinical response rate, compliance and tolerability of carboplatin. Carboplatin dose was reduced from AUC 2.0 to 1.5 by an amendment after 330 patients due to carboplatin-related toxicity at pre-planned safety analyses. **Results:** 595 patients were recruited (8/2011 - 12/2012) in 51 German centers, 299 did not receive carboplatin. Median age was 47/48 years (no carb/carb), 36.8/36.5% were postmenopausal; 14.0/13.3% had T3, 5.0/3.7% T4, 41.8/37.6% N+, 93.0/92.9% ductal invasive, 64.5/65.3% G3 tumors; 46.2/46.3% had HER2+, 53.8/53.7% TNBC. 225 patients had a SAE (149 no carb/177 carb) and 3 died (postoperative pneumonia; reduced general condition; acute myocardial infarct), all in no carb arms. Final analysis on primary endpoint will be presented. **Conclusions:** This is first study, evaluating efficacy and safety of the addition of carboplatin to anthracycline-taxane containing NACT in patients with primary HER2+ and TNBC. Clinical trial information: NCT 01426880.

1005 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Differential pathologic complete response rates after neoadjuvant chemotherapy among molecular subtypes of triple-negative breast cancer.

Hiroko Masuda, Keith A. Baggerly, Ying Wang, Ya Zhang, Ana M. Gonzalez-Angulo, Funda Meric-Bernstam, Vicente Valero, Brian D. Lehmann, Jennifer A. Pietenpol, Gabriel N. Hortobagyi, William Fraser Symmans, Naoto T. Ueno; Morgan Welch Inflammatory Breast Cancer Program and Clinic, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Vanderbilt-Ingram Cancer Center; School of Medicine Department of Biochemistry, Vanderbilt University, Nashville, TN; Vanderbilt-Ingram Cancer Center, Nashville, TN; Morgan Welch Inflammatory Breast Cancer Program and Clinic, University of Texas M. D. Anderson Cancer Center, Houston, TX

Background: By gene profiling, Lehmann et al. (J Clin Invest 121:2750-2767, 2011) reported that triple-negative breast cancer (TNBC) can be classified into 6 clusters—basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR)—plus an unstable (UNS) cluster. While it is clear that patients with TNBC differently respond to chemotherapy, the clinical relevance of these molecular TNBC subtypes is unknown. **Methods:** We qualitatively reproduced the Lehmann et al. experiments using Affymetrix CEL files from the public datasets. We identified 130 TNBC gene expression microarrays obtained from 03/00 to 03/10. All patients had received neoadjuvant chemotherapy containing sequential taxane and anthracycline-based regimens and had evaluable pathological tumor response data. Median follow-up was 68.1 months. (5.1-147.5). We classified TNBC samples using Lehmann's gene signatures, then performed Fisher's exact test to correlate TNBC subtype and pCR status. To assess the independent utility of TNBC subtype for predicting pCR status, we fit a logistic regression model to our data and used age, clinical stage, treatment regimens, and nuclear grade as potential explanatory factors. We also performed comparison of the subtypes with the PAM50 intrinsic subtypes and RCB index. **Results:** The BL1 subtype had the highest pCR rate (52%); BL2 and LAR the lowest (0% and 10%, respectively). TNBC subtype and pCR status were significantly associated ($p = 0.044$). TNBC subtype was an independent predictor of pCR status ($p = 0.022$) by a likelihood ratio test. The Lehmann's subtype classification better predicted pCR status than did the PAM50 intrinsic subtypes (basal-like vs. non basal-like). **Conclusions:** Dividing TNBC into 7 subtypes predicts high vs. low pCR rate. The 7-subtype classification may lead to innovative personalized medicine strategies for patients with TNBC. There is a need for prospective validation of the hypothesis that pCR rates associated with the seven TNBC subtypes will predict long-term patient outcome.

1006 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Time trends in the use of adjuvant chemotherapy (CTX) and outcomes in women with T1N0 breast cancer (BC) in the National Comprehensive Cancer Network (NCCN).

Ines Maria Vaz Duarte Luis, Rebecca A Ottesen, Melissa E Hughes, Rizvan Mamet, Harold J. Burstein, Stephen B. Edge, Ana M. Gonzalez-Angulo, Sara H. Javid, Beverly Moy, Hope S. Rugo, Richard L. Theriault, Jane C. Weeks, Nancy U. Lin; Dana-Farber Cancer Institute, Boston, MA; City of Hope, Duarte, CA; Roswell Park Cancer Institute, Buffalo, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Washington, Seattle, WA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; University of California, San Francisco, San Francisco, CA

Background: The role of adjuvant CTX in women with small BC is controversial. Here we analyze time trends of CTX use and outcomes in women with T1N0 BC treated at NCCN cancer centers. **Methods:** 8917 women were identified who received surgery or systemic therapy at an NCCN center with T1a, T1b or T1c N0 M0 BC between 2000-09. Tumors were grouped by biologic subgroups by hormone receptor (HR) and HER2 status and T subgroups (T1a, T1b, T1c). Primary endpoints were receipt of adjuvant CTX ($\pm$ trastuzumab) and BC specific survival (BCSS). Chi-square, Cochran Armitage trend, Kaplan Meier estimates, log-rank test and Cox hazard proportional regression were used for analysis. In this report we focus on T1a/b results (N=4113). **Results:** Median follow up time was 5.5 years (range, 0.7-12.7). CTX use differed according to biologic and T subgroups, with significant changes over time (Table). In 2009, more than 50% of patients (pts) with HER2+ and HR-2- T1a/b breast cancers received CTX ($\pm$ trastuzumab). The table lists use of CTX by year and subset and the 5 year BCSS for pts treated and not treated with CTX. **Conclusions:** A high proportion of pts with HER2+ and HR-HER2- T1N0 breast cancers received adjuvant CTX, with a sharp increase in use of CTX among HER2+ over the past decade. Use of CTX is higher in T1b compared to T1a tumors. In this study, women with T1a and T1b tumors have an excellent prognosis without CTX at 5 Yr. Careful examination of cutoffs for absolute benefit sufficient to recommend CTX is warranted.

	Percent of adjuvant CTX ($\pm$ trastuzumab) (%)							
	HR+HER2- (T1a, b, c) N=6789		HR+HER2+ (T1a, b, c) N=738		HR-HER2+ (T1a, b, c) N=364		HR-HER2- (T1a, b, c) N=1026	
	T1a N=984	T1b N=2246	T1a N=135	T1b N=199	T1a N=81	T1b N=105	T1a N=99	T1b N=264
Year of diagnosis	P<0.0001		P<0.0001		P=0.0003		P=0.3600	
2003	3%	10%	13%	36%	50%	76%	18%	70%
2005	1%	11%	25%	50%	38%	77%	31%	50%
2009	2%	13%	47%	100%	56%	100%	50%	69%
5 Yr BCSS								
CTX (95 %CI)	100%*¥	98.8 % (95.4-99.7)	100%*¥	100%*°	100%*¥	96.3% (88.8-98.8)	100%*¥	97.9% (93.6-99.3)
No CTX (95 %CI)	99.9% (99.2-100)	99.4% (98.9-99.7)	98.5% (89.9-99.8)	97.7% (91.1-99.4)	94.9 %¥ (81-98.7)	100%*°¥	95.4% (86.4-98.5)	95.2% (87.6-98.2)

* No BC death as of 5 yr ° 1 BC death occurred after 5 yr ¥n ≤50

1007   **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Comparison of doxorubicin and cyclophosphamide (AC) versus single-agent paclitaxel (T) as adjuvant therapy for breast cancer in women with 0-3 positive axillary nodes: CALGB 40101.

Lawrence N. Shulman, Donald A. Berry, Constance T. Cirrincione, Heather Becker, Edith A. Perez, Ruth O'Regan, Silvana Martino, Charles L. Shapiro, James Atkins, Charles Schneider, Gretchen Genevieve Kimmick, Harold J. Burstein, Larry Norton, Hyman Bernard Muss, Clifford Hudis, Eric P. Winer, Cancer and Leukemia Group B; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Duke Cancer Institute Biostatistics, Durham, NC; University of Chicago, Chicago, IL; Mayo Clinic, Jacksonville, FL; Georgia Cancer Center for Excellence at Grady Memorial Hospital, Atlanta, GA; The Angeles Clinic and Research Institute, Santa Monica, CA; The Ohio State University, Columbus, OH; Southeastern Medical Oncology Center, Goldsboro, NC; Christiana Care Health System, Newark, DE; Duke Cancer Institute, Durham, NC; Memorial Sloan-Kettering Cancer Center, New York, NY; University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC

Background: Determining optimal adjuvant chemotherapy for early stage breast cancer depends on efficacy and toxicity. We sought to determine if T is equivalent to AC but with reduced toxicity. **Methods:** Pts with operable breast cancer with 0-3 positive nodes were enrolled on a 2x2 factorial design study which addressed (1) superiority of 6 vs. 4 cycles of therapy (previously reported, Shulman, *JCO* 2012) and (2) equivalence of single-agent T to standard AC, defined as upper bound of 95% confidence interval (CI) of hazard ratio (HR) of T vs. AC < 1.30 for the primary endpoint of relapse-free survival (RFS). A planned target of 567 RFS events required 4,646 pts with 4 yrs FU. At activation in 2002, T (80mg/m2) was q1wk for 12 or 18 wks and AC (60/600 mg/m2) was q3wk for 4 or 6 cycles. In 2003 (570 pts enrolled) schedules were revised to 4 or 6 cycles q2wk for both T (175 mg/m2) and AC. The 6-cycle arms were dropped in 2008 (3,171 pts enrolled) due to slow accrual. Relative effectiveness of T to AC is shown by hazard ratio (HR). Logrank p-values are measures of discordance but are not relevant for the equivalence question and are not adjusted for multiple comparisons. **Results:** After enrolling 3,871 pts, the study closed in 2010 due to slowing accrual. With a median follow-up of 6.1 yrs there are 437 RFS events. The HR of 1.26 (95% CI: 1.05-1.53; $p = 0.02$) does not allow a conclusion of equivalence of T with AC. With 266 deaths the HR for overall survival (OS) is 1.27 (95% CI=1.00-1.62; $p = 0.05$), favoring AC. The estimated absolute advantage of AC at 5 yrs is 3% (91 vs. 88%) for RFS and 1% (95 vs. 94%) for OS. All 9 treatment-related deaths were in pts receiving AC and are included in the survival analysis. The incidence of Grade 3+ toxicity for AC vs T was 33% vs. 4% for hematologic toxicity and 36% vs 22% for non-hematologic toxicity. **Conclusions:** This trial did not show equivalence of T to AC, a conclusion that is very unlikely to change with additional follow-up. T was less toxic than AC. Clinical trial information: CDR0000069444/NCT00041119.

CRA1008   **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer.

G. Thomas Budd, William E. Barlow, Halle C. F. Moore, Timothy J. Hobday, James A. Stewart, Claudine Isaacs, Muhammad Salim, Jonathan K. Cho, Kristine Rinn, Kathy S. Albain, Helen K. Chew, Gary Von Burton, Timothy David Moore, Gordan Srkalovic, Bradley Alexander McGregor, Lawrence E. Flaherty, Robert B. Livingston, Danika Lew, Julie Gralow, Gabriel N. Hortobagyi; Cleveland Clinic, Cleveland, OH; Cancer Research and Biostatistics, Seattle, WA; Mayo Clinic, Rochester, MN; Baystate Medical Center, Springfield, MA; Lombardi Comprehensive Cancer Center, Washington, DC; Allan Blair Cancer Center, Saskatoon, SK, Canada; Oncare Hawaii, Honolulu, HI; Swedish Cancer Institute, Seattle, WA; Loyola University Medical Center, Maywood, IL; University of California, Davis Cancer Center, Sacramento, CA; LSU Health Sciences Center, Shreveport, LA; Mid Ohio Oncology Hematology, Inc., Columbus, OH; Sparrow Regional Cancer Center, Lansing, MI; Willford Hall Medical Center, Lackland, TX; Wayne State University School of Medicine, Detroit, MI; Arizona Cancer Center, Tucson, AZ; Southwest Oncology Group Statistical Center, Seattle, WA; Seattle Cancer Care Alliance, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX

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1009   **Poster Discussion Session (Board #1), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Use of the FoundationOne next-generation sequencing (NGS) assay to detect actionable alterations leading to clinical benefit of targeted therapies for relapsed and refractory breast cancer.

Jeffrey S. Ross, Massimo Cristofanilli, Sean Downing, Roman Yelensky, Doron Lipson, Geoff Otto, Gary A. Palmer, Siraj M. Ali, Vincent A. Miller, Phil Stephens; Albany Medical College, Albany, NY; Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; Foundation Medicine, Cambridge, MA; Foundation Medicine, Inc., Cambridge, MA

Background: Genomically-informed cancer therapy linking therapeutics targeting the molecular alterations driving the malignancy has the potential to transform the care of patients with metastatic breast cancer (MBC). **Methods**: DNA was isolated from 4 FFPE sections cut at 10 microns from 177 consecutive MBC that had relapsed after surgery, conventional hormonal/chemo and anti-HER2 targeted therapies received by our CLIA lab (Foundation Medicine). DNA sequencing was performed for 3,320 exons of 182 cancer-related genes to average depth of 1017X. Actionable Genomic alterations (GA) were defined as those linked to targeted anti-cancer therapies approved or being evaluated in active registered clinical trials. **Results:** Genomic profiles were generated from 169/177 (95%) BCs identifying 565 GA, averaging 3.34 GAs per tumor (range 0 to 10). 152 (90%) tumors harbored an actionable alteration mean 1.88 per tumor (range 0 to 6). In 124 (73%) tumors, ≥ 1.0 actionable GA was detected that would be missed by current "hotspot assays". Notable GA involved *PIK3CA* (37%), *ERBB2* (14%), *FGFR1/2* (14%), *PTEN* (10%), *MDM2* (7%), *CCND1/CCNE1/CDK4* (7%), *BRCA1* and *BRCA2* (6% each) and *ESR1* and *EGFR* (3% each). Of 23 *ERBB2* GA, 74% were amplifications and 26% were mutation/gene fusion. The frequency of *ERBB2* mutation/fusion was significantly enriched in *CDH1* mutated ILC (~9% of total BC) with a frequency of 19.0% (4/21) compared to other histological types of BCs 1.4% (2/148) [p=0.002]. Significant clinical efficacy included patients with HER2 IHC/FISH negative tumors featuring *HER2* and *EGFR* activating mutations benefitting from lapatinib/trastuzumab and erlotinib respectively. **Conclusions:** Comprehensive genomic profiling with a NGS assay identified actionable GAs in the majority of MBC patients including *ERBB2* and *EGFR* mutations that initiated use of targeted therapies resulting in significant clinical benefit. These data provide a framework for the GAs expected in advanced BC and should facilitate the implementation of molecularly targeted trials supporting the efforts for a modern approach to precision medicine for the disease.

1010   **Poster Discussion Session (Board #2), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Next-generation sequencing to find predictors for chemotherapy response in triple-negative breast cancer (TNBC).

Esther H. Lips, Magali Michaut, Lennart Mulder, Nicolle Besselink, Marlous L. Hoogstraat, Marco J. Koudijs, Emile E. Voest, Rene Bernards, Jelle Wesseling, Lodewyk F. A. Wessels, Sjoerd Rodenhuis; Department of Molecular Pathology, the Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Molecular Carcinogenesis, the Netherlands Cancer Institute, Amsterdam, Netherlands; Center for Personalized Cancer Treatment/ Department of Medical Oncology UMC Utrecht, Utrecht, Netherlands; Department of Pathology, the Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Medical Oncology, the Netherlands Cancer Institute, Amsterdam, Netherlands

Background: In TNBC initial response to chemotherapy is often favorable, but relapse and chemotherapy resistance frequently occur in advanced disease. Hence there is an urgent need for targeted treatments in this breast cancer subtype. **Methods:** To identify biomarkers of chemotherapy resistance and putative directed treatment targets, we performed next generation sequencing (NGS) of 2,000 genes implicated in oncogenesis. DNA from 31 pre-treatment biopsies and matched normal blood was sequenced. Biopsies were derived from patients scheduled to receive neoadjuvant chemotherapy with doxorubicin/cyclophosphamide. For the analysis, the tumors were divided in responders and non-responders, depending on whether or not a pathological complete remission (pCR) was achieved. Two definitions of pCR were employed: either the complete absence of infiltrating tumor cells in the breast (n=18) or a pCR of both the breast and lymph nodes (n=15). Tumors with partial or no responses were grouped in the non-responder category. **Results:** As a positive control, we verified that all patients with a known germline BRCA1 mutation (n=8) could be detected by the NGS analysis. In further analyses, we focused only on somatic mutations. Overall, the mutation rate was slightly higher in the non-responders (per tumor, average=12, range=[3-25]) than in the responders (average=8, range=[3-19]) (p=0.17). The analysis of individual genes did not reveal significant differences between responders and non-responders. However, pathway analysis showed that mutations in phosphatidylinositol signaling (e.g., PIK3CA, CALML5) were significantly more frequent in the non-responders, with mutations present in 10/13 non-responders and 2/18 responders (adjusted p=0.013). The chemokine and integrin signaling pathways also revealed a significantly higher mutation rate in the non-responders. **Conclusions:** Mutations in genes of the phosphatidylinositol pathway occur frequently in TNBCs that do not achieve a pCR on a neoadjuvant chemotherapy regimen consisting of doxorubicin and cyclophosphamide. After validation, alternative chemotherapy regimens and targeted agents should be investigated for these tumors.

1011   **Poster Discussion Session (Board #3), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Molecular identification of basal-like breast cancer through genomic analyses across five cancer types.

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Background: Common molecular alterations in different types of cancer are being identified and these might be successfully targeted regardless of the tumor´s tissue of origin. To better understand the genomic relationships among different types of cancer, we explored global gene expression patterns across breast, lung, ovarian, brain and colorectal cancers. **Methods:** A unified set of 1,707 samples of 5 human cancer types (breast [n=547], lung [squamous and adenocarcinomas, n=249], ovarian [serous carcinoma, n=489], brain [glioblastoma multiforme, n=202] and colorectal [n=220]) from The Cancer Genome Atlas (TCGA) project was evaluated. All microarrays were performed at the University of North Carolina under the same protocol and platform. All samples provided in each publication of TCGA were used, except for lung adenocarcinomas where we used TCGA public data. Consensus clustering was used to identify molecular entities, and breast cancer intrinsic subtyping was performed using the PAM50 predictor. **Results:** A total of 6 distinct and robust molecular entities were identified representing tumors from breast luminal/HER2-enriched, breast Basal-like, lung, ovarian, brain and colorectal cancers. Strikingly, 55%, 26%, 16% of Basal-like breast cancers were found to be more similar to squamous cell lung carcinomas, lung adenocarcinomas and ovarian cancers, respectively, compared to breast luminal/HER2-enriched tumors. Breast cancer intrinsic subtyping identified a Basal-like profile in 55% of squamous cell lung cancers, 53% of ovarian cancers and 8% of lung adenocarcinomas. Finally, single genes and gene signatures tracking cancer-related biological processes such as proliferation, angiogenesis and immune activation were found highly expressed in different proportions across the 6 molecular entities. **Conclusions:** These data suggest that breast tumors of the Basal-like subtype have a distinct cell of origin compared to luminal/HER2-enriched tumors. Clinical trials focusing on tumors with common profiles and/or biomarker expression rather than their tissue of origin are warranted with a special focus on Basal-like breast cancer, squamous cell lung carcinoma and serous ovarian cancer.

1012   **Poster Discussion Session (Board #4), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

NFKBIA deletion in triple-negative breast cancer.

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Background: While effective, target-directed therapies are available for ER-positive and *HER2*-amplified breast cancer, adjuvant therapeutic options for triple-negative breast cancer (TNBC) are limited in the absence of well-defined molecular targets. Constitutive activation of oncogenic nuclear factor kB (NFkB) has been associated with ER-negative or basal-like (BL) breast cancers, but the underlying mechanism of this activation remains undefined. We previously showed that deletion of the endogenous NFkB repressor gene *NFKBIA* associates with *EGFR* non-amplified glioblastoma multiforme and portends unfavorable clinical outcome (Bredel et al. NEJM 2011). **Methods:** We analyzed >5,000 human breast cancers for deletions, mutations and/or expression of *NFKBIA*. We studied tumor suppressor activity of *NFKBIA* and the effect of targeted NFkB inhibition in cell culture with various *NFKBIA* genotypes. We compared molecular results with outcomes of affected persons. **Results:** *NFKBIA* is often (10.8%) deleted but not mutated in breast cancer. *NFKBIA* deletions are significantly associated with TNBC (32.8%) and particularly frequent in the BL subtype (36.7%). Loss of *NFKBIA* exerts a haploinsufficient effect on *NFKBIA* expression and the transactivation of several NF-kB target genes with important roles in breast carcinogenesis. Restoration of NFKBIA expression or pharmacologic NFkB inhibition attenuates the malignant phenotype of cells cultured from TNBC with *NFKBIA* deletion. Deletion and low expression of *NFKBIA* are highly associated with unfavorable overall survival, independent of patient age, tumor stage, nodal status, and tumor subtype. Loss of NFKBIA expression portends significantly poorer disease-specific survival, recurrence-free survival, and distant metastasis-free survival. Moreover, *NFKBIA* expression is significantly associated with duration of metastasis-free survival in subgroups of patients with brain or lung metastases from breast cancer. **Conclusions:** *NFKBIA* is a new, prognostically relevant, molecular target in TNBC, which remains a clinically challenging subtype of breast cancer with limited treatment options.

1013 **Poster Discussion Session (Board #5), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Correlation of intratumor gene expression heterogeneity with chemotherapy sensitivity in breast cancer.

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Background: The goal of this study was to develop a method to quantify intratumor heterogeneity of cancers using gene expression data. We compared gene expression heterogeneity between different molecular subtypes of breast cancer and between basal like cancers with or without pathologic complete response (pCR) to neoadjuvant chemotherapy. **Methods**: Affymetrix U133A gene expression data of 335 stage I-III breast cancers were analyzed. Molecular class was assigned using the PAM50 predictor. All patients received neoadjuvant chemotherapy. We measured tumor heterogeneity by the Gini index (GI) calculated individually for each case over the expression of all probe sets and random subsets. The GI was used as a metric of inequality of gene expression distributions between cases. The higher the GI, the greater the inequality of the expression distribution. **Results**: Basal like cancers (n=138) had greater heterogeneity than luminal cancers (n=197) (mean GI values 24.51 vs 23.05, p<0.001) and luminal B (n=71) cancers had greater heterogeneity compared to Luminal A (n=126) cancers (24.49 vs 22.25, p<0.001). Among the basal-like cancers, those with pCR (n=44) had significantly higher heterogeneity compared to cancers with residual disease (RD, n=94) (26.10 vs 23.77, p<0.001). Significant differences in GI between cancer subtypes remained for as low 2500 randomly selected probe sets. **Conclusions**: Breast cancer subtypes differ in intratumor gene expression heterogeneity. Greater degree of heterogeneity correlate with greater chemotherapy sensitivity. Importantly, among basal-like cancers only the heterogeneity metric differed significantly between cases with pCR or RD but not individual genes expression values or gene signatures.

1014   **Poster Discussion Session (Board #6), Mon, 1:15 PM-5:15 PM and**
4:45 PM-5:45 PM

Proliferation-, estrogen-, and T-cell-related metagenes to predict outcome after adjuvant/neoadjuvant chemotherapy for operable breast cancer in the ECTO trial.

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Background: Predicting recurrence in operable breast cancer (BC) despite optimal chemotherapy would be relevant to new drug development and tailored treatments. **Methods:** A large series (n=3,154) of public Affymetrix gene-expression profiles (GEP) was used to define prognostic/predictive metagenes in different BC subtypes. In ER+/HER2- a proliferation and an ER-related metagene were combined to predict low, intermediate and high risk of recurrence. In TN and in HER2+ a T cell metagene was used to predict low, intermediate and high risk (higher expression associated with lower risk). The metagenes were validated in patients enrolled in the phase III ECTO trial (Gianni L. *JCO* 2009) and treated with the same taxane-anthracycline-CMF regimen as neoadjuvant or adjuvant therapy before endocrine therapy if indicated. The outcome was distant event free survival (DEFS). **Results:** 283 good quality GEPs were obtained (neoadjuvant n=121; adjuvant n=162) from 464 retrospectively collected samples. Median follow-up was 8.9 years. In ER+/HER2- tumors the 10-yrs DEFS was 92.3, 81.2 and 66.6% in low, intermediate and high risk groups, respectively [high vs low HR 4.38 (1.01-19.1) p=.048] according to proliferation and ER-related metagenes. In HER2+ and TN subgroup the 10-yrs DEFS was 97.2, 75.6 and 78.8% in low, intermediate and high risk groups, respectively [high vs low HR 8.73 (1.09-69.8) p=.041]. In TN tumors, the pCR rate was 20% in the high and 61.5% in the low risk group. By combining the predicted risk group in each molecular subtype the 10-yrs DEFS was 95.3, 79.2 and 71.5% in low (24.2%), intermediate (42.7%) and high (33.1%) risk group, respectively [logrank p=0.003; high vs low HR 6.22 (1.87-20.6) p=.002]. ER, PGR, Ki67 and lymphocyte infiltration (LI) by IHC underperformed compared to genomic predictors. **Conclusions:** BC patients at higher risk of relapse despite optimal standard treatment can be identified who should be spared ineffective and toxic therapy and considered for investigational new strategies. In TN and HER2+, high T cell metagene and to a lesser extent LI are prognostic/predictive and associated with an extremely low risk of DEFS after chemotherapy.

1015   **Poster Discussion Session (Board #7), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Neo-tAnGo science: A translational study of PAM 50 sub-typing in sequential fresh tissue samples during neoadjuvant chemotherapy.

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Background: Neo-tAnGo was an NCRI UK neoadjuvant breast cancer study testing the addition of gemcitabine to anthracycline and taxane-based treatment and also the sequencing of chemotherapy. In a translational substudy, sequential fresh tissue was analysed for PAM 50 subgroups. **Methods:** Neo-tAnGo recruited 831 patients. 162 patients were consented for Neo-tAnGo Science, for 3 additional fresh tissue samples to be taken at diagnosis (diag), mid-chemotherapy (CT) and end-CT. Standard methodology was used for PAM 50 subtyping. **Results:** Fresh tissue samples at diag were received from 123 patients (pts). 45 pts (37%) had 2 additional samples provided (at mid- and end-CT). 57 pts (46%) had 1 additional sample provided (34 at mid-CT, 23 at end-CT). PAM 50 subtyping at diag was as follows: 31 (25%) BASAL; 30 (24%) HER2; 39 (32%) LUM B; 13 (11%) LUM A; 10 (8%) NORMAL-like. Pathological complete response rates (pCR: no disease in breast or axillary nodes, n = 121 pts) differed between PAM 50 subtype at diag (p = 0.04): BASAL 11/31 (35%); HER2 8/30 (27%); LUM B 3/37 (8%); LUM A 1/13 (8%); NORMAL-like 3/10 (30%). Of the 94 pts who were not PAM50 NORMAL-like at diag and had 2+ samples, 42 (45%) 'shifted to NORMAL-like'. This was associated with slightly higher pCR rates (24% vs 15% who didn't 'shift to NORMAL-like', p = 0.44) and borderline significantly higher rates of pCR or minimal residual disease (MRD: <10% residual scattered tumour cells) (48% vs. 27% who didn't 'shift to NORMAL-like', p = 0.06). In the 102 pts with 2+ samples, 58 pts (57%) showed a shift to a better prognosis PAM 50 subtype after CT (Group (Gp) 1), 37 (36%) showed no change (Gp 2) and 7 (7%) a shift to a worse prognosis subtype (Gp 3). pCR rates were 26% Gp1, 14% Gp2 and 0% Gp3 (p = 0.05). pCR/MRD rates were 48% Gp1, 22% Gp2 and 0% Gp3 (p = 0.001). **Conclusions:** PAM 50 subtype at diagnosis correlates with pCR to neoadjuvant chemotherapy. Shift to a better prognosis PAM 50 group during neoadjuvant chemotherapy was demonstrated in 57% of pts and was significantly correlated with higher pCR and pCR/MRD rates. Clinical trial information: 78234870.

1016   **Poster Discussion Session (Board #8), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Evaluation of flap endonuclease-1 (FEN1) as a prognostic, predictive, and therapeutic target in breast (BC) and ovarian cancer (OVC).

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Background: FEN1 is a multifunctional protein with essential roles in long patch base excision repair (LP-BER), Okazaki fragment maturation during replication, resolution of tri-nucleotide repeat sequence-derived secondary structures, rescue of stalled replication forks, maintenance of telomere stability and apoptotic fragmentation of DNA. In the current study we have evaluated FEN1 as a prognostic, predictive and therapeutic target in BC and OVC. **Methods:** Clinico-pathological significance of FEN1 mRNA expression was evaluated in a BC training cohort [n=128], test cohort (n=249) and validated in a large cohort of 1,980 BC (METABRIC). Neural network analysis (NNA) was conducted to identify FEN1 interaction genes. FEN1 protein expression was investigated in three consecutive series of BC and OVC: 568 ER negative (ER- BC), 894 ER positive (ER+ BC) and 195 OVC cohorts. Pre-clinically, FEN1 deficient and proficient HeLa cell lines were investigated for chemotherapy sensitization. A high throughput screening (HTS) strategy was developed to identify FEN1inhibitors for therapeutic application. **Results:** FEN1mRNA overexpression is associated with adverse clinicopathological features such as high grade, high mitotic index, and triple negative (ps<0.0001). High FEN1 mRNA expression was highly significantly associated with PAM50 Her2, PAM50 Basal and PAM50 LumB (ps<0.0001) BC. FEN1 mRNA overexpression is associated with resistance to chemotherapy (p=0.019), endocrine therapy (p<0.0001) and independently with poor survival (p<0.0001). NNA revealed novel interaction genes with predominant roles in proliferation, cell growth, DNA repair, differentiation, invasion, migration, metabolism and apoptosis. FEN1 protein overexpression is significantly associated with aggressive clinico-pathological features and independently with poor survivals in ER+ BC, ER- BC and in OVC (ps<0.001). HTS assay has identified novel FEN1 inhibitors for therapeutic development. **Conclusions:** This is the first study to investigate FEN1 in BC and OVC. We provide confirmatory evidence that FEN1 is a promising biomarker as well as a therapeutic anti-cancer drug target for clinical application.

1017   Poster Discussion Session (Board #9), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

10-year outcomes of breast cancer patients with histologically confirmed axillary lymph node metastases and pathologic complete response after primary systemic chemotherapy.

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Background: Pathologic complete response (pCR) of tumors in the breast and axillary lymph nodes (ALN) after primary systemic chemotherapy (PST) is associated with an excellent outcome. A previous analysis showed superior 5-year overall survival (OS) and relapse-free survival (RFS) for patients who achieved an ALN pCR after PST compared to those without a pCR in 5 prospective clinical trials. This study is an expanded analysis of all patients treated with PST at our institution examining the impact of ALN pCR on 10-year OS and RFS. **Methods:** Patients with clinical stage II/III and pathologically confirmed ALN metastases who underwent PST were categorized into 1 of 2 groups: ALN pCR and ALN residual disease. Additional data were collected, including breast cancer subtype, clinical tumor size, and lymph node staging, pathologic tumor (T) stage, and class of PST. RFS and OS were estimated by the Kaplan-Meier product limit method. Subset analyses were performed on patients with HER2-positive cancer. **Results:** 1,600 women diagnosed between 1989 and 2007 were identified. Median follow-up was 79 months (5-277); 454 (28.4%) achieved an ALN pCR. ALN pCR was associated with triple-negative and higher grade cancers, lower clinical stage, and lower pathologic breast T stage. 5-year OS and RFS estimates were similar to prior analysis. The 10-year OS was 85% and 58% and the 10-year RFS 83% and 55% (p < 0.001), for patients who achieved an ALN pCR and those with residual ALN disease. For HER2-positive breast cancers, 67.3% of patients who received HER2-targeted therapy achieved an ALN pCR vs. 32.3% without HER2-targeted therapy (p < 0.001). For patients receiving HER2-targeted therapy for HER2-positive breast cancer (n = 153), the 10-year OS was 92% and 52% (p = 0.006), and the 10-year RFS was 89% and 59% (p < 0.001) for those with and without an ALN pCR. **Conclusions:** ALN pCR is an excellent early surrogate marker for long-term outcome, 10-year RFS and OS. In HER2-positive breast cancers, HER2-targeted therapy is associated with high rates of pCR. Despite the aggressive nature of their disease, patients who achieve ALN pCR with PST have an excellent 10-year prognosis.

1018   Poster Discussion Session (Board #10), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Sentinel node biopsy following neoadjuvant chemotherapy in biopsy proven node positive breast cancer: The SN FNAC study.

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Background: A significant and increasing proportion of patients ($>$30%) with biopsy proven node positive breast cancer will obtain a pathological complete response (pCR) in the axilla after neoadjuvant chemotherapy (NAC). If sentinel node biopsy (SNB) can accurately identify these patients, they could potentially avoid the morbidity of an axillary node dissection. The primary aim of this study is to evaluate the identification rate (IR), false negative rate (FNR) and accuracy of SNB in this setting. The accuracy of post NAC axillary ultrasound and clinical examination are evaluated as secondary endpoints. **Methods:** Patients with biopsy proven node positive breast cancer (T0-3, N1-2, M0) treated with NAC were eligible to participate in this multi-centre prospective trial. Following NAC, axillary ultrasound and clinical examination results were obtained. At time of surgery, all participants underwent both a SNB and a completion node dissection. A SNB IR greater than 90% and a FNR of less than 10% were pre-determined as being optimal. **Results:** From September 2009 to December 2012, 153 patients were accrued to the study. 7 patients were not eligible and 5 patients had not yet undergone surgery at the time of analysis. Axillary pCR rate = 34.0% (48/141). SNB IR = 87.2% (123/141), 95% CI [81.7%-92.7%] and FNR = 9.9% (8/81), 95% CI [3.4%-16.4%]. If only one sentinel node was removed, FNR = 19.0%(4/21); if there were 2 or more sentinel nodes, FNR = 6.6% (4/61) (p $<$ 0.0001). Accuracy of SNB, axillary ultrasound and clinical examination were 93.5%, 63.2%, and 45.5% respectively. **Conclusions:** SNB following NAC in biopsy proven node positive breast cancer is associated with a suboptimal IR. FNR (less than 10%) and accuracy of SNB in this study are comparable to that of patients that present with clinically negative nodes. The FNR decreases when more than one sentinel node is identified. However, in an era where regional nodal radiation is increasingly used, the relevance of leaving residual disease in the undissected axilla after NAC is unknown and remains to be investigated. Clinical trial information: NCT00909441.

1019   **Poster Discussion Session (Board #11), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

The presence and extent of extracapsular extension (ECE) and the need for axillary lymph node dissection (ALND) in patients who meet ACOSOG Z11 eligibility criteria.

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Background: Whether ECE mandates ALND in patients with ≤2 positive sentinel nodes (SN) is controversial. ACOSOG Z11 excluded patients with matted nodes, but did not comment on microscopic ECE. In a prospective, consecutive series of patients, we sought to determine if ECE correlates with the number of positive axillary lymph nodes (LN) and if ECE ≤2mm clinically differs from ECE >2mm. **Methods:** In 8/2010 an institutional treatment algorithm based on the Z11 results was prospectively applied to consecutive patients having BCS. ALND was performed for ≥3 +SNs. The approach to ECE was not specified. Characteristics of patients with and without ECE were compared with Fisher's exact test and the Wilcoxon rank sum test. **Results:** From 8/10-11/12, 2157 invasive breast cancer patients had BCS; 381 had LN metastasis, 287 met Z11 selection criteria, and ALND was avoided in 242 (84%). ECE was present in 111 (39%), of whom 23% had ≥3 +SNs (vs 2% without ECE; p<0.0001) and 35% had ALND (vs 3% without ECE; p<0.0001). The presence of ECE was associated with tumor size (1.9cm vs 1.6; p=.01) but not with age, grade, or receptor status. The degree of ECE was associated with age, grade, number of +SNs, and performance of ALND (Table). In 45 cases, ALND was advised for ≥3 +SNs (n=29) or <3 +SNs with ECE (n=16). 39 patients had ALND and 34 of these had ECE. Additional +LNs were seen in 5/9 patients with ≤2mm ECE and 20/25 with >2mm ECE; median of 1 additional +LN in each group. Seven or more additional +LNs were seen in 6 patients with >2mm ECE; 1 patient with ≤2mm ECE had 6 additional +LNs, the remainder had ≤3. **Conclusions:** The presence of ECE was associated with ≥3 +SNs and the need for ALND. Only a minority of patients with ≤2mm of ECE had ≥3 +SNs, and nodal disease at ALND in this group was limited, suggesting that ≤2mm ECE may not be an indication for ALND.

	≤2mm (n=53)		>2mm (n=58)		
	Median	Range	Median	Range	P value
Age	58	34,84	64	35,92	0.03
pT size	1.8	0.6,4.2	2.1	0.4,5	0.09
	n	%	n	%	
Subtype*					
HR+/HER2-	42	81%	53	91%	
HR+/HER2+	6	12%	1	2%	
HR-	4	8%	4	7%	0.11
Nuclear grade*					
1 (includes lobular)	2	4%	12	21%	
2	33	62%	28	49%	
3	18	34%	17	30%	0.02
≥3 +SNs					
No	46	87%	40	69%	
Yes	7	13%	18	31%	0.04
ALND advised	12	23%	27	47%	0.01

* Missing data for 1 tumor.

1020   **Poster Discussion Session (Board #12), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Predicting nonsentinel lymph node metastases using established nomograms among patients with breast cancer after primary systemic therapy (PST): The transSEN-TINA substudy.

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Background: Recent studies such as the SENTINA trial suggest that performing SLNB in patients with a cN1 status before but converting to a ycN0 status through PST result more often in a false-negative evaluation of LN status compared to SLNB at primary surgery. Therefore, there is a need to predict non-SLN status after PST and tailor axillary staging procedures. We investigated the accuracy of established nomograms to predict non-SLN metastases at primary surgery in patients after PST. **Methods:** The SENTINA trial is a 4-arm prospective multicenter cohort study evaluating an algorithm for the timing of a standardized SLNB in patients undergoing PST. 1,737 pts. from 104 institutions were categorized into four treatment arms according to the clinical axillary staging (including ultrasound examination) before and after chemotherapy. Patients in arm C with a cN1 status prior to PST converting to a ycN0 status but found to have a histologically positive SLN after PST were included. Several published nomograms predicting non-SLN status in patients with a positive SLN at primary surgery were applied (including the MSKCC-, Mayo-, Cambridge-, and Stanford-Nomogram, MDA-Score and Tenon-Score) and Area-under-the-Curve-(AUC)-values were calculated. **Results:**This subgroup comprised 592 patients. Among these, 74 patients had a positive SLN after PST and had all available data to run the nomograms. AUC-values were: MSKCC: 82.3 (95% confidence interval (95%CI) 72.6-91.9), Mayo: 71.8 (95%CI 60.1-83.5), Cambridge: 71.5 (95%CI 59.7-83.2), Stanford 70.6 (95%CI 59.7-83.2), MDA 70.7 (95%CI 59.0-82.5), and Tenon 73.1 (61.5-84.7). **Conclusions:** Analysis of the above nomograms in the post-neoadjuvant setting yielded AUC values comparable to those in the setting of primary surgery. Our results suggest that nomograms predicting non-SLN status in the setting of primary surgery (and particularly the MSKCC nomogram) may be used to avoid full axillary dissection in patients after PST.

1021   **Poster Discussion Session (Board #13), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Effect of margin width on local recurrence (LR) in triple-negative (TN) breast cancer treated with breast-conserving therapy (BCT).

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Background: Positive lumpectomy margins are associated with increased rates of LR after BCT; however, the effect of increasing negative margin distance on LR is controversial. Rates of LR vary by breast cancer subtype, with the highest rates seen in TN cancers. The purpose of this study was to examine the rate of LR in relationship to margin width in TN breast cancers treated with BCT. **Methods:** All women with TN breast cancer who underwent BCT between 1999-2009 were identified from a prospectively maintained database. Margins were defined as positive (tumor on ink), close ($\leq$2mm), or negative (>2mm) for either invasive or in situ cancer. Patients with positive margins (n=46) were excluded. Statistical comparisons were by t tests, Fisher's exact test, and Wilcoxon rank sum test. Cumulative incidence of LR was compared using competing-risks methodology. **Results:** Characteristics of the 535 cancers (in 534 patients) with close (n=71) and negative (n=464) margins are compared in the Table. At median follow-up of 84 months (range, 8-165 months) there were 37 local, 18 regional, and 77 distant recurrences or deaths as first events. 10 patients had LR prior to planned radiation therapy (RT). The cumulative incidence of LR at 60 months for patients with close margins was 7.3% (95% CI, 1.1-13.6), and 5.1% (3.0-7.2) for negative margins. After controlling for use of chemotherapy, there was no significant difference in LR between the entire close and negative margin groups (p=.07) or after exclusion of recurrences prior to RT (p=.06). A difference in the risk of distant recurrence or death was not observed (p=.60). **Conclusions:** Margin width greater than 2mm was not associated with a clinically meaningful reduction in LR risk. This, coupled with reports of similar LR in TN cancers treated with BCT or mastectomy, suggests that larger surgical procedures do not improve outcomes in this high-risk patient subset.

Margin	Close (n=71)	Negative (n=464)	P value
Age at surgery (mean ± stdev)	56.7±12.2	55.2±12.2	0.30
Tumor size (median, IQR)	1.5 (1, 2.2)	1.6 (1.1, 2.3)	0.27
Node positive	25 (35.2%)	130 (28.1%)	0.26
Chemotherapy	54 (76.1%)	398 (85.5%)	0.05
Lymphovascular invasion	19 (26.8%)	110 (23.7%)	0.55

1022   **Poster Discussion Session (Board #14), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Impact of delaying initiation of adjuvant chemotherapy in breast cancer patients.

Debora De Melo Gagliato, Ana M. Gonzalez-Angulo, Xiudong Lei, Sharon Hermes Giordano, Richard L. Theriault, Vicente Valero, Gabriel N. Hortobagyi, Mariana Chavez-Mac Gregor; The University of Texas MD Anderson Cancer Center, Houston, TX; Breast Medical Oncology Department, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The survival benefit of adjuvant chemotherapy in breast cancer is well established. However, the optimal timing to initiation of chemotherapy after definitive surgery is unknown. We evaluated the association between time to initiation of chemotherapy and survival outcomes according to breast cancer subtype and stage at diagnosis. **Methods:** Women diagnosed with stage I–III breast cancer between 1997-2011 who received adjuvant chemotherapy at our institution were included. Patients were categorized according to time from definitive surgery to adjuvant chemotherapy into one of three groups: $\leq$ 30 days, 31–60 days and more than 60 days. Descriptive statistics, Kaplan-Meier statistics and Cox proportional hazards models were used. **Results:** Among the 6,827 patients included, the 5-year Overall Survival (OS), Relapse-Free Survival (RFS) and Distant Relapse-Free Survival (DRFS) estimates were similar for the different time-to-chemotherapy categories. Among patients with stage I, there was no association between outcome and time to initiation of chemotherapy. Patients with stage II disease experienced an 18% and 22% increase in risk of RFS (HR 1.18; p=0.038) and DRFS (HR 1.22; p=0.02), when systemic treatment was started >60 days from surgery. Patients with stage III disease that started adjuvant chemotherapy >60 days after surgery had a 70% increase in the risk of death (HR 1.7; p=0.002), a 32% increase risk of relapse (HR 1.32; p=0.046) and a 34% increase risk of distant relapse (HR 1.34; p=0.044). Time to chemotherapy did not have a significant effect on outcome among Hormone Receptor (HR)-positive patients. Patients with triple negative (TNBC) and HER2-positive tumors treated with trastuzumab who started chemotherapy >60 days after surgery had lower 5 year-OS estimates (HR 1.52; p=0.016 and HR 2.62; p=0.005, respectively). **Conclusions:** Time to chemotherapy did not influence survival outcomes in the overall population. However, patients with stage III, TNBC and HER2-positive tumors treated with trastuzumab, experienced worse outcomes when chemotherapy was delayed. Among patients with tumors with aggressive biology and more advanced stages at diagnosis, early initiation of therapy should be favored.

1023   **Poster Discussion Session (Board #15), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

NCI 8609: Interim fluoro-3'-deoxythymidine (FLT) PET imaging findings from the phase I trial of PARP inhibitor veliparib (V) and carboplatin (C) in advanced breast cancer.

Bhuvaneswari Ramaswamy, Jun Zhang, Nathan Hall, Katharina Schregel, Maryam B. Lustberg, Robert Wesolowski, Ewa Mrozek, Rachel M. Layman, Erin Macrae Olson, Susan Ottman, Andrea Camp, Jeffrey J. Chalmers, Susan Michelle Geyer, Miguel Angel Villalona-Calero, Charles L. Shapiro, Michael R. Grever, Michael V. Knopp; The Breast Program, The Ohio State University Comprehensive Cancer Center and the Stefanie Spielman Comprehensive Breast Center, Columbus, OH; The Ohio State University, Columbus, OH; The Ohio State University College of Medicine, Columbus, OH; The Ohio State University Wexner Medical Center, Columbus, OH

Background: We are currently conducting a phase I trial of PARP inhibitor, V on an intermittent (7 or 14 day) or continuous (21 day) schedule in combination with C in patients (pts) with advanced breast cancer. We are using FLT PET/CT sequentially to assess DNA damage induced by varying dose schedules of PARP inhibitor, where uptake of FLT depends on the proliferation rate of the tumor. **Methods:** Eligible pts received C-AUC 5 Q 3weeks (except dose level 1-AUC 6) plus escalating doses of V, BID on 7, 14, or 21-day schedules based on a standard 3+3 dose escalation design. We performed FLT PET/CT at baseline, cycle 1 day 7 and 14 and after cycle 3. Lesions were track-matched with the FDG PET/CT and semi-quantitatively assessed using 2D ROI placement in a matched, blinded fashion. **Results:** 38 pts have been accrued to 7 dose levels and FLT-PET imaging was successfully obtained in all pts with the proliferative whole body mapping revealing expected bone-marrow, liver and RESuptake. FLT-PET uptake showed a significant (p < 0.001) decrease between baseline and day 7 (N = 25) with an overall trend to rebound nearly to baseline at day 14 for pts that did not show a significant decrease in FLT uptake reduction after cycle 3. The 14-day (n = 15) dosing schedule resulted in more pronounced day 14 reduction in FLT uptake when compared to those on the 7-day (n = 7) schedule. A FLT rebound to baseline level appeared to be associated with limited therapy response. There were no reported toxicities from FLT imaging. **Conclusions:** FLT-PET was consistently obtained with excellent whole body quality. All lesions revealed a FLT (proliferation) uptake that was different from the FDG (metabolism) uptake. FLT uptake indicated an initial reduction of proliferation at day 7, followed by a rebound at day 21 in all patients on the 7 or 14 day schema. The trial protocol was therefore amended to include a 21 day schema which is currently still ongoing. FLT appears to be a promising in-vivo imaging marker that may serve as a guiding tool to optimize dosing schema in addition to assessing/ predicting overall response. Study support- U01 CA076576 /Wright Center of Innovation ODSA TECH09-028. Clinical trial information: NCT01251874.

1024   Poster Discussion Session (Board #16), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Efficacy of the combination of ABT-888 (veliparib) and carboplatin in patients with BRCA-associated breast cancer.

George Somlo, Paul Henry Frankel, Thehang H. Luu, Cynthia Ma, Banu Arun, Agustin Garcia, Tessa Cigler, Gini F. Fleming, Harold A. Harvey, Joseph A. Sparano, Rita Nanda, Helen K. Chew, Timothy Jerome Moynihan, Linda T. Vahdat, Matthew P. Goetz, Arti Hurria, Joanne E. Mortimer, David R. Gandara, Alice P. Chen, Jeffrey N. Weitzel; City of Hope Cancer Center, Duarte, CA; City of Hope Beckman Research Institute, Duarte, CA; City of Hope, Duarte, CA; Washington University School of Medicine in St. Louis, St. Louis, MO; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Southern California, Los Angeles, CA; Weill Cornell Medical College, New York, NY; Alliance for Clinical Trials in Oncology, Chicago, IL; Milton S. Hershey Medical Center, Hershey, PA; Montefiore Medical Center, Bronx, NY; University of Chicago, Chicago, IL; University of California, Davis Cancer Center, Sacramento, CA; Mayo Clinic, Rochester, MN; University of California, Davis Comprehensive Cancer Center, Sacramento, CA; National Cancer Institute, Bethesda, MD

Background: The combination of platinum agents and PARP inhibitors may benefit patients (pts) with BRCA-associated metastatic breast cancer (MBC). We report on the response and clinical benefit rates when combining the PARP inhibitor veliparib (V) and carboplatin (carb) in a phase I trial. **Methods:** BRCA carriers with MBC were eligible. Carb starting at an AUC of 6 was given IV in 21-day cycles (C) and V was given orally twice daily (BID) at dose levels (L) L1 through L5. **Results:** Twenty-eight pts (26 eligible) carrying BRCA1 (12) or BRCA2 (15), or both (1) mutations were accrued between June 2010 and June 2012. The median age (32-66) was 45 years. The number (#) of prior chemotherapy regimens given for MBC was 1 (0-5); 70% of BCs were ER+, and 7% were HER2+. The schema, dose limiting toxicities (DLT) during C 1, median # of Cs on trial, and maximum tolerated dose (MTD) are shown. There were 3 (12%) complete and 9 (35%) partial responses (PR). Unconfirmed PR or stable MBC (median duration: 8 months [6-10+]) were seen in 7 pts (27%); the clinical benefit rate was 74%. The median progression-free survival (PFS) is 7.8 months (95% CI 7.3-9.5). The pt with Fallopian tube cancer had a CR. DLTs with C 1 were seen in 2/6 evaluable pts at L1 (1 pt w/grade 3 hyponatremia and dehydration, and 1pt w/grade 4 thrombocytopenia [PLT]), leading to de-escalation of carb. At L2, 1 pt had grade 4 PLT. At L5, 1 pt had grade 4 PLT, and 2 pts grade 3 PLT (1 pt also experienced grade 4 granulocytopenia [ANC]), defining the MTD at carb AUC 5 and V 150 mg BID (L4). Dose delays and/or dose adjustments due to grade ≥ 2 toxicities for ANC or PLT were seen during the first 3 Cs at L1 (100%), L2 (50 %), L3 (67%), L4 (83 %), and at L5 (67%). **Conclusions:** The combination of carb and V is active, and is associated with substantial clinical benefit rate and managable hematologic toxicities in BRCA carriers with MBC. Further definition of the role of V is warranted.

Dose levels	L1	L2	L3	L4 MTD	L5
Carb AUC	6	5	5	5	5
V in mg	50 BID	50 BID	100 BID	150 BID	200 BID
# of pts	7*^	6	3	6	6
DLTs	2	1	0	0	3
# of Cs given	9 (1-15)	10 (1-12)	12 (9-14)	9+ (4-10+)	7.5 (1-15+)

* One pt ineligible/inevaluable (progressing pre-existing brain metastasis). ^ One pt ineligible (pathology: Fallopian tube cancer).

1025   **Poster Discussion Session (Board #17), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Radiation-induced increases in PARP1 activity to predict for long-term radiosensitization by PARP1 inhibition in preclinical breast cancer models.

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Background: Sustained locoregional (LR) control of breast cancer (BCa) is a significant issue for patients with inflammatory disease or chest wall recurrences. Inhibition of poly(adenosine diphosphate-ribose) (PAR) polymerase 1 (PARP1), a DNA damage response protein, is a promising strategy for radiosensitization (RS). We investigated RS by PARP1 inhibition and aimed to identify early biomarkers (BMs) predictive of long-term treatment efficacy in preclinical BCa models. **Methods:** Clonogenic survival assays in 12 BCa and normal epithelial cell lines were used to determine the degree of RS conferred by the PARP1 inhibitor ABT-888 and to optimize the sequencing of therapy. Immunoblots, immunofluorescent staining, flow cytometery, and xenograft studies were used to evaluate for pre-/intra-treatment BMs predicting for subsequent response to therapy. **Results:** ABT-888 preferentially radiosensitized BCa (vs. normal) cells (enhancement ratios (EnhR) up to 2.3 across different subtypes). The highest EnhRs resulted from concurrent and adjuvant ABT-888. The degree of RS did not correlate with pretreatment markers of PARP1 activity (e.g., PAR levels), DNA damage/repair (e.g. gamma-H2AX & RAD51 foci), or cell cycle distribution. However, increases in PARP1 activity from pretreatment to 24 hours after RT, was associated with long-term clonogenic death after treatment with ABT-888 + radiation (RT) (Spearman's coefficient=0.8, p=0.002). The four cell lines significantly radiosensitized by PARP1 inhibition (EnhR>1.5) averaged a 2-fold increase in PAR levels following RT. Findings were also confirmed in SKBR3 and MDA-231 BCa xenograft models. **Conclusions:** Our study demonstrates that PARP1 inhibition improves the therapeutic index of RT in BCa cell lines. Treatment-induced increase in PARP1 activity 24 hours after RT predicts for long-term radiosensitization by PARP1 inhibition and is a potential biomarker of response. These studies have led to a clinical trial, incorporating intratreatment BM analyses, of PARP inhibitors and RT in BCa patients currently open for accrual through the Translational Breast Cancer Research Consortium.

1026   Poster Discussion Session (Board #18), Mon, 1:15 PM-5:15 PM and
4:45 PM-5:45 PM

Prospective evaluation of *BRCA* mutations in a large triple-negative breast cancer (TNBC) registry: Implications for germline testing.

Priyanka Sharma, Jennifer R. Klemp, Bruce F. Kimler, Anna Ludlow, Larry Geier, Manana Elia, Qamar J. Khan, Carol J. Fabian, Marilee McGinness, Carol Sue Connor, Joshua Mammen, Lori Ranallo, Catie Knight, Andrew K. Godwin; University of Kansas Cancer Center Medical Center, Westwood, KS; University of Kansas Medical Center, Kansas City, KS; University of Kansas Medical Center, Westwood, KS; University of Kansas Medical Center, Kansas City, MO; University of Kansas Medical Center, Lee's Summit, MO

Background: Although current NCCN guidelines recommend genetic testing (GT) for all TNBC patients aged <60 years (regardless of family history) however due to the lack of prospective information on prevalence of mutations in unselected TNBC patients, these guidelines have not been widely adopted by clinicians and insurance carriers (including Medicare). Data on *BRCA* mutations from unselected TNBC cohorts are lacking. Aims: In a large TNBC registry, to prospectively determine the 1) prevalence of germline *BRCA* mutations and 2) validity of current NCCN guidelines for GT. **Methods:** Patients with stage I-III TNBC presenting for treatment at an academic and surrounding community practices were approached for participation in a prospective registry. All patients underwent comprehensive BRAC*Analysis* (Myriad). Detailed FH was collected. Mutation prevalence in the entire cohort and in subgroups stratified by FH and age were calculated. A significant family history (SFH) was defined as 1st-/2nd-degree relatives with breast cancer aged <50 years or ovarian cancer at any age. **Results:** 165 patients with stage I-III TNBC have been enrolled from 2011-2013. Median age 54 (range 24-84yrs), 58% postmenopausal, 29% LN +, 33%, 58% and 9% had stage I, II, III disease respectively. 82% Caucasian, 14% AA, 2% Hispanic, 0.6% Ashkenazi Jewish. Deleterious *BRCA1/2* mutations were identified in 13.1% patients (20/152, 15 *BRCA1*, 5 *BRCA2*; results pending in 13). 27% of patients had a SFH and 64% had any FH. Mutation rates in patients with or without SFH was 32.5% and 6.1%, respectively. When examined by age at diagnosis, the mutation rates were: 16.6% (<60yrs), 21.8% (<50yrs), 10.6% (51-60yrs), and 0% (>60 yrs). If SFH or age <50, were the only criteria used 35% and 30% of mutations would have been missed. All mutations were identified using the NCCN guidelines. **Conclusions:** This is the first study to prospectively evaluate *BRCA* mutations in an unselected TNBC cohort. In this large academic and community registry with negligible Ashkenazi representation, the overall *BRCA* mutation rate was 13%; 16.6% in those <60 years. These results validate GT based on current NCCN guidelines and support its use in routine clinical practice.

1027   **Poster Discussion Session (Board #19), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Randomized phase III study of adjuvant chemotherapy for node-positive early breast cancer (BC) patients (pts) comparing epirubicin plus cyclophosphamide followed by docetaxel (EC-T) versus epirubicin plus docetaxel followed by capecitabine (ET-X): Efficacy analysis of the GEICAM/2003-10 trial.

Begoña Bermejo, Amparo Ruiz, Manuel Ruiz Borrego, Nuria Ribelles, Alvaro Rodriguez-Lescure, Montserrat Munoz-Mateu, Sonia Gonzalez, Mireia Margeli, Agust Barnadas, Manuel Ramos Vazquez, Sonia del Barco, Lourdes Calvo, Cesar Mendiola, Carmen Crespo, Cesar Augusto Rodriguez, Eduardo Martinez, Maria Isabel Casas, M Carmen Camara, Eva Maria Carrasco, Miguel Martin, Spanish Breast Cancer Research Group (GEICAM); Hospital Clinico Universitario Valencia, Valencia, Spain; Instituto Valenciano de Oncologia, Valencia, Spain; Hospital Universitario Virgen del Rocio, Seville, Spain; Hospital Universitario Virgen de la Victoria, Malaga, Spain; Hospital General de Elche, Alicante, Spain; Hospital Clinico de Barcelona, Barcelona, Spain; Hosp Mutua Terrassa, Barcelona, Spain; Institut Català d'Oncologia - Hospital Germans Trias i Pujol, Barcelona, Spain; Hospital de la Santa Creu i Sant Pau, Medical Oncology Department, Barcelona, Spain; Centro Oncológico de Galicia, A Coruña, Spain; Institut Català d'Oncologia Hospital Universitari Josep Trueta, Girona, Spain; Complexo Hospitalario Universitario de A Coruña, A Coruna, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital Ramon y Cajal, Madrid, Spain; Oncology Department, Hospital Universitario de Salamanca, Salamanca, Spain; Hospital Provincial de Castellón, Castellon, Spain; Spanish Breast Cancer Research Group- GEICAM, Madrid, Spain; GEICAM, Madrid, Spain; Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañon, Universidad Complutense, Madrid, Spain

Background: X is an active drug in metastatic breast cancer. GEICAM/2003-10 is an adjuvant trial investigating the integration of capecitabine into an epirubicin and docetaxel containing regimen for node-positive early breast cancer pts. **Methods:** Pts aged 18-70, with T1-T3/N1-3 operable BC were eligible. HER2+ pts were initially allowed. In October 2005, after 803 pts were included in the trial, the study was amended to exclude them. Pts were stratified by site, menopausal status, number of axillary nodes (1-3, 4-9, >9) and hormonal receptor status and randomized to receive EC (90/600 mg/m^2 x4) followed by T (100 mg/m^2 x4) or ET (90/75 mg/m^2 x4) followed by X (1,250 mg/m^2 BID, d1–14, x 4) all every three weeks. The primary endpoint was DFS. The trial was designed to detect an absolute 5-y DFS increase of 7% (72% EC-T, 79% ET-X); a sample size of 1,184 evaluable pts (592 per arm) was required to detect this difference (a=0.05, β=80%). Assuming a drop-out rate of 17%, 1,382 pts were required. The first analysis of DFS was planned after 290 events. **Results**: Between February 2004 and February 2007, 1384 pts (EC-T 669, ET-X 715) were randomized. Patient characteristics were balanced between arms, median age was 51, 84% of pts were HR positive and 11% HER2 positive; 66, 25 and 9% had 1-3, 4-9 and > 9 nodes respectively. The median relative dose intensity was 99% for EC, 99% for T, 99% for ET and 94% for X. The most frequent grade 3-4 toxicities (>5% in either arm) with EC-T vs. ET-X were neutropenia (19% vs. 10%) with 7% febrile neutropenia in both arms, hand-foot syndrome (2% vs. 20%), fatigue (13% vs. 11%), diarrhea (3% vs. 11%), stomatitis (6% vs. 5%) and vomiting (5% vs. 5%). After a median follow-up of 6.6 years and 292 events, the proportion of patients disease free at 5 years is 86% and 82% with EC-T and ET-X (HR for relapse 1.314, 95% CI: 1.042 – 1.657); log-rank p-value=0.0208. Overall survival was not different between treatment arms (HR 1.113, 95% CI: 0.809 – 1.531); log rank p-value=0.511. **Conclusions:** DFS has been in favour of EC-T in pts with node-positive early BC. Clinical trial information: NCT00129935.

1028   **Poster Discussion Session (Board #20), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

NEOZOTAC: Efficacy results from a phase III randomized trial with neoadjuvant chemotherapy (TAC) with or without zoledronic acid for patients with HER2-negative large resectable or stage II or III breast cancer (BC)—A Dutch Breast Cancer Trialists' Group (BOOG) study.

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Background: The role of bisphosphonates when added to the neoadjuvant treatment of BC in enhancing the efficacy of therapy is still unknown. **Methods:** NEOZOTAC is a national, multicenter, randomized study comparing the efficacy of TAC (docetaxel, Adriamycin and cyclophosphamide i.v.) CT followed by G-CSF on day 2 with or without ZA 4 mg i.v. ,q 3 weeks in patients (pts) with stage II/III, measurable, HER2-negative BC and absence of prior bisphosphonate usage. The primary endpoint is the pathologic complete response (pCR) rate in the resection specimen and positive lymph nodes. 228 pts are needed to show an improvement of the pCR rates from 17% to 34% in the experimental arm using a 5% significance level based on the two-sided Fisher's exact test with a power of 80%. Randomization was done by using the Pocock's minimisation technique stratified by cT, cN and estrogen receptor status. pCR rate was analyzed using the Cochran-Mantel-Haenszel test, adjusting for the stratification factors. Analysis was based on intent-to-treat. An unplanned subgroup analysis of postmenopausal women (PMW; FSH >20 and estradiol <110) and baseline vitamin D levels was performed. **Results:** From July 2010 to April 2012, 250 patients from 25 participating sites were randomized. Pathologic response data of 228 patients are currently available. pCR rate did not differ between the two study arms (17% vs 16%, p = 0.81). However, a trend in benefit in favor of ZA was observed in PMW (18% vs 11%, OR 1.90, 95% C.I. 0.52 – 6.88). Patients with severe vitamin D insufficiency (<25 nmol/L) seemed to respond worse to CT numerically (6% vs. 18%). At ASCO pCR and clinical response data of all patients will be reported. **Conclusions:** Previously, we have shown that adding ZA to neoadjuvant CT is safe with good compliance.In this study, treatment with ZA did not result in a pCR benefit in the total study population. However our findings suggest that addition of ZA to neoadjuvant CT might be effective for enhancing response in PMW with BC. Clinical trial information: NCT01099436.

1029   **Poster Discussion Session (Board #21), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

A 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) has been found to have a synergistic anti-proliferative effect when used in combination with antitumor drugs. We investigated the synergistic effect of ZOL, assessed by pathological complete response (pCR) rate, when added to neoadjuvant chemotherapy (CT) in the primary tumor. **Methods:** Women with resectable invasive Stage IIA-IIIB breast cancer who are HER2-negative, between 20 and 70 years of age, and ECOG PS 0-1 were eligible. CT regimen was FEC100 q3w $\times$ 4 cycles followed by weekly paclitaxel for 12 cycles. ZOL 4mg was administered every 3-4 weeks, a total of 7 times. Patients were randomized 1:1 to the ZOL group or CT group, according to the presence or absence of lymph node metastasis, estrogen receptor (ER) status, and menopausal status. The primary endpoint was the rate of pCR defined as absence of invasive disease in the breast at surgery. The planned sample size was 180 patients. **Results:** 188 patients were recruited between March 2010 and April 2012; however 10 patients were excluded from the primary assessment. The overall pCR rate was 14.8% and 7.8% in the ZOL and CT groups, respectively (p=0.160). In the postmenopausal patients, pCR rate was 18.4% and 5.4% in the ZOL and CT groups, respectively (p=0.153). In the triple-negative patients, pCR rate was 35.3% and 11.8% in the ZOL and CT groups, respectively (p=0.225). In the postmenopausal and triple-negative patients, pCR rate was 50.0% and 0% in the ZOL and CT groups, respectively (p=0.077). There was no significant difference in severe toxicity between the two groups. **Conclusions:** The results of this trial suggest that the addition of ZOL to neoadjuvant CT has potential anti-cancer benefit in patients with postmenopausal and triple-negative breast cancer. Further investigation will be warranted. Clinical trial information: 000003261.

1030   **Poster Discussion Session (Board #22), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

The persistence of disseminated tumor cells after systemic therapy and their influence on prognosis in early breast cancer patients.

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Background: Detection of disseminated tumor cells (DTC) in the bone marrow (BM) of early breast cancer (EBC) patients before the administration of systemic therapy is associated with poor outcome. The aim of this study was to evaluate the impact of DTC on overall survival (OS) and disease free survival (DFS) in a large cohort of EBC patients after the administration of systemic therapy. **Methods:** EBC patients receiving systemic therapy (endocrine therapy and/or chemotherapy +/- HER2-directed treatment) either prior to surgery (neoadjuvant systemic therapy, NST) or after surgery (adjuvant systemic therapy, AST) at Tuebingen University Hospital, Germany between 01/2003 and 06/2012 were available for this analysis. BM aspirates were collected during surgery / one year after surgery in patients receiving NST / AST. DTC were identified by immunocytochemistry (pancytokeratin antibody A45/B3) and cytomorphology. Survival was analyzed using univariate (log-rank test) and multivariate analysis (cox regression). **Results:** DTC were detected in 201 of 608 (35%) patients. 175 of 419 (42%) patients treated with NST and 35 of 189 (19%) patients treated with AST were DTC-positive. Chemotherapy / endocrine therapy was administered prior to BM aspiration in 399 (96%) / 19 (5%) of the patients receiving NST and in 99 (52%) / 158 (84%) of the patients receiving AST. On univariate analysis, the detection of DTC was a significant predictor of poor DFS (HR: 2.27, 95% CI: 1.48 – 3.48, p<0.001) and poor OS (HR: 1.89, 95% CI: 1.19 – 3.00, p=0.007). On multivariate analysis (considering all clinicopathological factors and the DTC-status), independent factors for DFS were DTC-status (negative vs. positive), grading (G2-3 vs. G3), nodal-status (negative vs. positive), and the ER-status (negative vs. positive). Independent factors for OS were grading, PR-status (negative vs. positive) and nodal-status. **Conclusions:** The persistence of DTC in the BM of EBC patients after systemic treatment is a strong and independent marker of poor prognosis. Determination of the DTC-status is thus promising to monitor the effect of systemic therapy and to identify patients that are in need of additional adjuvant therapy.

1031   **Poster Discussion Session (Board #23), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

The effect of obesity on prognosis in operable breast cancer patients treated with adjuvant anthracyclines and taxanes according to pathologic subtypes.

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Background: According to observational studies, obesity is an unfavourable prognostic factor in breast cancer (BC), regardless of menopausal status and treatment received. Information collected in clinical trials should confirm this effect and serves to test its homogeneity by pathologic subtype. **Methods:** We retrospectively analysed 5,683 operable BC patients enrolled in four randomized clinical trials (GEICAM/ 9906, 9805, 2003–02, and BCIRG 001) evaluating adjuvant anthracyclines and taxanes. Our primary aim was to assess the prognostic effect of body mass index (BMI) on disease recurrence, breast cancer mortality (BCM), and overall mortality (OM). A secondary aim was to detect differences by BC subtypes (ER/PR-positive/HER2-negative, HER2-positive, triple-negative). Cox models were fitted for each endpoint, adjusted by potential confounders. **Results:** Analyses adjusting for age, tumor size, nodal status, menopausal status, surgery, grade, hormone receptor and HER2 status, chemotherapy regimen, and undertreatment showed that obese patients (BMI 30.0–34.9) had similar prognoses to that of patients with a BMI<25 (reference group) in terms of recurrence (HR 1.08 [95% CI 0.9–1.3]; p=0.41), BCM (HR 1.02 [0.81–1.29]; p=0.85), and OM (HR 0.97 [0.78–1.19]; p=0.747). Patients with severe obesity (BMI≥35) had a significantly increased risk of recurrence (HR 1.26 [1.00–1.59]; p=0.05), BCM (HR 1.32 [1.00–1.74]; p=0.05), and OM (HR 1.35 [1.06–1.71]; p=0.02) compared to our reference group (Table). The prognostic effect of severe obesity did not vary by subtype. **Conclusions:** Severely obese patients treated with anthracyclines and taxanes present a worse prognosis regarding recurrence, BCM, and OM than patients with a BMI<25. The magnitude of the harmful effect of BMI was similar across subtypes.

Variable BMI	Overall mortality			Breast cancer mortality			Recurrence		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
<25	1.00			1.00			1.00		
25-29.9	0.95	0.80-1.12	0.53	1.01	0.84-1.22	0.89	1.03	0.89-1.20	0.65
30-34.9	0.97	0.78-1.19	0.75	1.02	0.81-1.29	0.85	1.08	0.90-1.30	0.41
>=35	1.35	1.06-1.71	0.02	1.32	1.00-1.74	0.05	1.26	1.00-1.59	0.05

1032   **Poster Discussion Session (Board #24), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Body mass index (BMI), tumor subtype, and relapse-free survival (RFS) in CALGB 9741 (Alliance).

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Background: Obesity is a predictor of poor outcomes in women with early-stage breast cancer (BC). Some reports suggest that obesity is associated with aggressive tumor histology. We examined the relationship between BMI at diagnosis and PAM50 subtype, and explored the interaction between BMI and subtype on prognosis in early BC. **Methods**: CALGB 9741 evaluated dose-density and sequence in node-positive BC. All patients received doxorubicin, cyclophosphamide and paclitaxel dosed by actual body weight without cap or dose adjustment. The primary endpoint was RFS. Height and weight at diagnosis were abstracted from patient records; the PAM50 assay was performed using the Nanostring platform. Association between PAM50 and BMI was assessed by a chi-squared test. The prognostic value of BMI conditional on PAM50 was tested as a continuous variable using Cox models for RFS adjusted for number of involved nodes, tumor size, menopausal status, drug sequence, and dose density. **Results:** Baseline height and weight were available for 1909 of 2005 enrolled patients; 1272 also had subtype determination by PAM50. Distribution of subtypes differed significantly by BMI (p=0.03), with all weight groups having similar proportions of Basal and HER-2 Enriched subtypes and with obese patients having lower rates of Luminal A (30 vs 35%) and higher rates of Luminal B (39 vs 26%) tumors as compared to normal-weight individuals. In multivariate analyses, BMI and subtype were independent predictors of RFS (p=0.011 and p<0.001, respectively). Exploratory analyses did not show a significant interaction between subtype and the relationship between increased BMI and RFS (p=0.15), although largest differences were seen among Luminal cancers (Table). **Conclusions:** Biologic subtypes were distributed differently in obese and non-obese individuals. The association between BMI and RFS did not differ significantly by subtype in this study. More work is needed to further explore the interaction of BMI and subtype, especially in a larger cohort of Luminal tumors.

BMI and RFS within PAM 50 subtypes.

Subtype	10-unit change in BMI (32 kg/m^2 vs 22 kg/m^2)	
	HR	95% CI
Basal	1.23	0.94-1.64
HER2-enriched	1.19	0.88-1.56
Luminal A	1.49	1.14-1.96
Luminal B	0.94	0.69-1.28

1033   **Poster Discussion Session (Board #25), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

Effect of metformin versus placebo on weight and metabolic factors in initial patients enrolled onto NCIC CTG MA.32, a multicenter adjuvant randomized controlled trial in early-stage breast cancer (BC).

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Background: MA.32 investigates effects of Metformin vs. Placebo, in addition to standard care, on invasive disease free survival and other outcomes. Metformin may improve obesity and metabolic factors [insulin, glucose, leptin, C-reactive protein (CRP)] that have been associated with poor BC outcomes. Maintaining blinding of investigators to outcomes, we conducted a planned, DSMB approved, analysis of the effect of Metformin vs. Placebo on weight and metabolic factors at 6 months, including examination of interactions with baseline body mass index (BMI), in the first 498 subjects with paired fasting plasma samples. **Methods:** 498 non-diabetic subjects with T1-3, N0-3, M0 BC meeting defined entry criteria who had completed surgery and adjuvant chemo (if given) provided fasting blood samples at randomization and 6 months (while on study drug). Glucose was measured locally; blood was aliquoted, frozen and stored at -80°C then shipped to NCIC CTG (Kingston, Canada). Paired plasma aliquots were shipped to Mount Sinai Hospital (Toronto, Canada) for analysis of Insulin (Dako), hsCRP (Roche Elecsys) and leptin (Luminex). Statistical analysis used the Wilcoxon signed rank test. **Results:** Mean age was 52.4 ±9.2 years. Arms were balanced for ER/PgR (63% pos), BMI, prior adjuvant chemo (89%), T and N status, grade, mastectomy/ lumpectomy and radiation. **Conclusions:** Metformin significantly improved weight, insulin, glucose, leptin and CRP at 6 months. Effects did not vary by baseline BMI. Funded by: NIH, CCSRI, CBCF, BCRF, Apotex Canada (drug & placebo - in kind). Clinical trial information: # NCT01101438.

	Baseline			Change (6 months-baseline)			Interaction of change with baseline BMI
	Metformin	Placebo	P	Metformin	Placebo	P	P
Weight (kg)	75.6±15.4	76.3±16.7	0.88	-1.96±3.5	+0.37±3.1	<0.0001	0.42
BMI (kg/m^2)	28.2±5.4	28.5±5.9	0.91	-0.74±1.3	+0.14±1.3	<0.0001	—
Glucose (mmol/L)	5.3±0.6	5.2±0.6	0.24	-0.1±7.0	0.03±0.61	<0.0001	0.74
Insulin (pmol/L)	67.7±51.8	71.3±63.4	0.88	-7.74±50.9	-1.46±55.5	0.017	0.98
Leptin (ng/ml)	15.7±13.2	16.2±13.2	0.78	-1.52±7.4	1.42±6.5	<0.0001	0.61
CRP (mg/L)	2.73±3.93	2.64±3.68	0.72	-0.20±4.0	0.80±7.8	0.007	0.23

1034   **General Poster Session (Board #18A), Sat, 1:15 PM-5:00 PM**

Analysis of recurrence risk by subtype in ≤1 cm breast tumors.

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Background: Triple-negative breast cancers (TNBC) comprise 15% of breast cancers and lack ER, PR, and HER2 expression. TNBC is biologically aggressive with high rates of recurrence, but little is known about the prognosis of small (≤1cm) TNBCs compared to similarly sized breast cancers with other receptor profiles. The role of adjuvant chemotherapy for TNBC that is ≤1cm remains unclear. **Methods:** Electronic medical records of all women aged ≥ 18 years with ≤1 cm, node negative, invasive breast cancer from 1997-2007 diagnosed or treated at Vanderbilt or Wake Forest were reviewed. Tumor grade, receptor status, treatment details, and follow up and recurrence information were tabulated. Rates of local and distant recurrence among three different receptor subtype categories, ER+ or PR+, HER2 negative; ER-/PR-, HER2 negative; or any ER/PR, HER2 positive were compared using chi-square tests. **Results:** 437 women with ≤1cm breast tumors were identified. Women with TNBC not given chemotherapy were more likely to have distant recurrence at 9% compared to 2% for ER+ or PR+, HER2 negative and 4% for any ER/PR, HER2 positive. There were no recurrences among the 14 women with ≤1cm TNBC who received chemotherapy. **Conclusions:** Based on our two institution review, women with ≤1 cm TNBC are at an increased risk for distant recurrence compared to other subtypes when not treated with adjuvant chemotherapy. Further studies to determine the benefit of adjuvant chemotherapy in this population are needed.

Recurrence among women with node-negative ≤1cm tumors.

	ER+ or PR+ HER2 negative (n=331)	Any ER/PR HER2 positive (n=57)	ER/PR/HER2 negative (n=49)	Combined (n=437)	
Age	60 (51-69)	56 (45-60)	56 (48-63)	59 (45-69)	
T1a	26% (87)	33% (19)	22% (11)	27% (117)	
T1b	74% (244)	67% (38)	78% (38)	73% (320)	
Grade1/2	90% (297)	72% (41)	37% (18)	81% (356)	
Grade 3	7% (24)	23% (13)	63% (31)	16% (68)	
All patients					
Local recurrences	6% (19)	9% (5)	6% (3)	6% (27)	P=0.680
Distant recurrences	2% (7)	4% (2)	6% (3)	3% (12)	P=0.258
No chemotherapy	n=323	n=42	n=35	n=400	
Local recurrences	5% (17)	7% (3)	9% (3)	6% (23)	P=0.668
Distant recurrences	2% (5)	5% (2)	9% (3)	2% (10)	P=0.025
Adjuvant chemotherapy	n=8	n=15	n=14	n=37	
Local recurrences	25% (2)	13% (2)	0% (0)	11% (4)	P=0.177
Distant recurrences	25% (2)	0% (0)	0% (0)	5% (2)	P=0.022

1035   **General Poster Session (Board #18B), Sat, 1:15 PM-5:00 PM**

The prognostic implications of redox protein expression in stage I-III triple-negative breast cancer.

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Background: It is well known that increased reactive oxidative stress (ROS) in cancer cells correlates with poor prognosis and aggressiveness of tumor cells. The aim of this study is to investigate the expression of redox proteins in triple-negative, early breast cancer (TNBC) which shows aggressive phenotype among breast cancer and to demonstrate relationships between expression of ROS markers and clinical outcomes. **Methods:** Tissues from 135 cases of TNBC from curative surgery at Severance Hospital, Seoul, Korea, from December 2005 to January 2008 were analyzed. Immnunochemical (IHC) staining for redox proteins including thioredoxin reductase, glutathione S-transferase (GST) α, catalase, vitamin D-up-regulated protein 1 (VUDP), and manganese superoxide dismutase (MnSOD) was performed to evaluate the difference between clinicopathological parameters. The mono-carboxylate transporter 4 (MCT4) in stroma was done by IHC staining, too. **Results:** The median age of 135 TNBC patients was 48 (range 27-76). TNM staging were as follows; T1 (n=52, 38.5%), T2 (n=81, 60%), T3 (n=2, 1.5%), N0 (n=88, 65.2%), N1 (n=35, 25.9%), N2 (n=8, 5.9%), N3(n=4, 3.0%). Median follow up was 59 months (range 12-99). Samples were divided into high or low ROS expression level semi-quantitatively. The catalase high expressed group was tend to have lower N stage (p=0.016), lower tumor recurrence (p=0.02) as well as longer overall survival rates (p=0.05). Higher expression of MTC4 in stroma was strongly associated with higher MnSOD expression group analysis (p=0.015) and had significantly longer overall survival (p=0.032). **Conclusions:** This study shows the expression of ROS proteins could contribute defining aggressiveness of TNBC as well as the prognosis. Considering the lack of targeted molecules as well as molecular heterogeneity of TNBC, ROS markers may provide clues to clinical outcomes in TNBC.

1036   **General Poster Session (Board #18C), Sat, 1:15 PM-5:00 PM**

Activity and duration of chemotherapy (CT) in different biologic subtype (BS) in metastatic breast cancer (MBC) patients (P).

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Background: In MBC P the benefit of CT after the 1st line (L) is poorly defined. We evaluated activity of subsequent L of CT in different BS of MBC. **Methods:** MBC P treated in our center from 2007 to 2012 with ER, PgR and HER2 on primary tumor and at least 1 L of CT for MBC were evaluated. P were classified as Luminal A (ER and/or PgR +, HER2 -, Ki67≤14%), Luminal B (ER and/or PgR +, HER2 -, Ki67>14%), HER2+ (HER2+, any ER/PgR) and Triple-Negative (ER-, PgR- and HER2-). Time on CT was calculated from the start of the 1st L to the end of the last L. Statistical analyses included Chi-square and Kruskal-Wallis tests, Kaplan-Meier curves and log-rank tests, and multivariate logistic regressions. **Results:** 207 P were identified, 52 were excluded because HER2 was unknown (19) or they did not receive any CT (33). Median follow-up was 31.4 months (m). The median number (N) of CT L was 2 (range 1-10). N of CT L and clinical benefit (CB) for every BS were reported in table. CB was inferior in TN P as compared with the other ones in 1st and in 2nd L (p=.068 and p=.084 respectively in 1st and 2nd L). From 3rd L onward all P showed the same CB independently from BS. Time on CT related to median survival (S) for every BS was the same. At multivariate analysis the characteristics independently associated with a greater probability of receiving more than 4 CT L were age < 50 years (p=.021), HER2+ or TN disease (p=.027) and site of metastasis other than lung (p=.047). **Conclusions:** Our analysis showed that, despite the same time spent on CT, TN P received less benefit from 1st and 2nd L CT than other BS. On the other hand, young HER2+ P were more likely to receive multiple L of CT with a significant impact on median S (p=.044).

	Luminal A	Luminal B	HER2+	TN
N P	38	73	29	15
Median S, m	50.88	44.37	69.17	39.77
Median CT L	2	2	3	3
N CT L (%)				
1	38 (100)	73 (100)	29 (100)	15 (100)
2	23 (60)	43 (59)	21 (72)	10 (66)
3	15 (39)	21 (28)	15 (51)	8 (53)
4	8 (21)	12 (16)	12 (41)	3 (20)
5	7 (18)	4 (5)	6 (20)	3 (20)
6	2 (5)	1 (1)	5 (17)	2 (13)
7	1 (2)		3 (10)	2 (13)
8			2 (6)	
9			1 (3)	
10			1 (3)	
Median CT duration, m	10.49	9.76	16.90	8.05
Time on CT related to median S, %	21	22	24	20
CB for CT L (%)				
1	30 (86)	51 (79)	25 (92)	7 (58)
2	13 (65)	24 (65)	16 (76)	2 (25)
3	8 (61)	8 (50)	6 (43)	3 (50)
4	5 (71)	7 (70)	3 (30)	1 (50)
5	2 (33)	2 (66)	3 (50)	-
6	1		3 (75)	1
7			1	1
8			1	
9			1	
10				

1037   **General Poster Session (Board #18D), Sat, 1:15 PM-5:00 PM**

Increased expression of folate receptor-α (FRA) in triple-negative breast cancer: A potential therapeutic target.

Jennifer A. Crozier, Brian M. Necela, E Aubrey Thompson, Xochiquetzal Geiger, Alvaro Moreno-Aspitia, Ann E. McCullough, Barbara A. Pockaj, Heather Cunliffe, Zhifu Sun, Krishna R. Kalari, Jennifer M. Kachergus, Daniel J. O'Shannessy, Julia D. Maltzman, Karla V. Ballman, Cathy A. Andorfer, Edith A. Perez; Mayo Clinic, Jacksonville, FL; Mayo Clinic, Scottsdale, AZ; Mayo Clinic, Phoenix, AZ; Translational Genomics Research Institute, Phoenix, AZ; Mayo Clinic, Rochester, MN; Morphotek, Exton, PA

Background: Folate receptor alpha (FRA the product of the FOLR1 gene) has been identified as a potential prognostic and therapeutic target in a number of cancers. A correlation has been shown between intense expression of FRA in breast tumors and poor prognosis, yet little is known about FOLR1/FRA expression across clinically relevant breast cancer subtypes. **Methods:** 131 breast cancer tumors including 4 benign, 33 ER+, 26 HER2+, and 68 triple negative (TN) were constructed into tissue microarrays (TMAs). FRA expression was analyzed by immunohistochemistry (IHC) using a high affinity FRA antibody. Tumor membrane staining intensity was scored by a pathologist as negative (0), weak (1+), moderate (2+) and strong (3+). The percent of cells within each tissue core stained at each intensity was recorded to calculate an an H-score. The H-score is a weighted score that captured both the proportion of positive staining and intensity for each tumor. H-score values can range from zero (no membrane staining) to a maximum of 300 (100% membrane staining at 3+). H-scores for each patient sample were averaged over 3 TMA cores. The mean H-scores for each tumor subtype and the percentage of 3+ staining in >30% of tumor cells were compared by a Mann-Whitney test. The distribution of FOLR1 mRNA was completed using a TCGA RNA-seq dataset from 691 breast tumors classified as ER+, HER2+ and TN. FOLR1 levels of TN versus ER+ and HER2+ were compared by a Mann-Whitney test. **Results:** The mean H-score for the benign tumors was 0, ER+ (13.31), HER2+ (39.36), TN (119.02). The median H-score for the benign tumors was 0, ER+ (0), HER2+ (7.5), TN (127.5). The TN tumors mean and median H scores were significantly higher than benign, ER+ or HER2+ (p<0.001). The largest percentage of 3+ staining in >30% of tumor cells was observed in TN tumors (36.7%) and lowest in ER+ tumors (0%) (p<0.001). TN tumors had significantly higher levels of FOLR1 mRNA compared to ER+ and HER2+ subtypes (p<0.0001). **Conclusions:** Our data indicate that expression of FRA is highly prevalent in TN tumors and is supported by FOLR1 mRNA levels. Anti-FRA therapy may represent an important therapeutic intervention in TNBC who to this point have no active targeted treatment options.

1038　　　　　　　　　**General Poster Session (Board #18E), Sat, 1:15 PM-5:00 PM**

A retrospective comparison of the characteristics and recurrence outcome of triple-negative and triple-positive breast cancer.

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Background: Triple-negative (estrogen/progesterone-receptors negative and HER2-negative; TNBC) and Triple-positive (estrogen/progesterone-receptors positive and HER2-positive; TPBC) breast cancers are very distinctive in terms of tumor behavior as well as disease management. Due to lack of an effective targeted therapy, the treatment options are limited for TNBC. We conducted a retrospective review to compare various characteristics and recurrence outcome in TNBC and TPBC. **Methods:** Over 3000 non-consecutive female breast cancer patients (diagnosed between 2000-2012) were reviewed. Of these, 406 patients (206 TNBC, 200 TPBC) were included. The following data at diagnosis were studied: age, tumor size, stage, grade, lymph node involvement, distant metastases and smoking history. Analyses are performed using R statistical software (Version 2.15.2). Numeric data are summarized by median and quartile with comparisons between groups performed by Wilcoxon Rank Sum Tests. Categorical data are summarized by frequency and percentage and comparisons between groups are performed by chi-square tests. Statistical significance is determined by a p-value ≤ 0.05. **Results:** Both TNBC and TPBC were diagnosed at similar median ages of 56.5 and 55 years respectively (p= 0.059). TNBC were more likely to have poorly differentiated histology (75.63%) whereas TPBC were more often moderately differentiated (54.79%) (p< 0.001). At diagnosis, Triple-Positive (TP) tumors were larger (median 2.4 cm) compared to Triple-Negative (TN) tumors (median 2 cm) (p= 0.013). However, there were no significant differences with respect to lymph node involvement and distant metastases in the two groups. Importantly, recurrences were more common in TNBC 33.85% (65/192) compared to TPBC 4.21% (8/190) (p < 0.001) and there was no association found with smoking history or active smoking status. **Conclusions:** TN tumors although smaller in size compared to TP were more likely to have poorly differentiated histology, showed higher recurrence rates and therefore were more aggressive in behavior. Both TNBC and TPBC were diagnosed at similar median age and exhibited no recurrence association with smoking history.

1039   **General Poster Session (Board #18F), Sat, 1:15 PM-5:00 PM**

Discordant ER, PR, and HER2 status between primary and metastatic breast cancer as prognostic factor.

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Background: The receptor status including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) of metastases may be different from that of the primary breast cancer. This discordance of receptor status may influence patient prognosis. We investigated discordance of receptor status between primary breast cancer and distant metastases in the same patients and its effect on prognosis. **Methods:** ER, PR, and HER2 status in metastases were available in 173 patients. The receptor status was compared between primary tumors and metastases. Tumors were classified as triple-negative breast cancer (TNBC) or non-triple-negative breast cancer (non-TNBC) according to receptor status and as concordant and discordant depending on the difference of receptor status between primary and metastatic breast cancer. Survival analysis was performed depending on concordant or discordant receptor status. **Results:** Discordance for ER, PR, and HER2 was 18.5%, 23.7%, and 10.4%, respectively. Concordant non-TNBC and TNBC between primary tumors and metastases was 69.9% and 17.9%, respectively. Discordant TNBC was 12.1%. On multivariate analysis, patients with discordant TNBC had unfavorable survival compared with patients with concordant non-TNBC (relative risk 2.544, 95% confidence interval, 1.220-5.303, $p = 0.013$). The median survival after recurrence was 41.8 months for patients with concordant non-TNBC, 20.7 months for patients with concordant TNBC, and 19.9 months for patients with discordant TNBC ($p < 0.0001$). **Conclusions:** The change of ER, PR, and HER2 status between primary and metastatic tumors occur and discordant TNBC is associated with poor survival.

1040   **General Poster Session (Board #18G), Sat, 1:15 PM-5:00 PM**

Efficacy of first-line bevacizumab (BEV)-based therapy for metastatic triple-negative breast cancer (TNBC): Subgroup analysis of TURANDOT.

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Background: The randomized phase III TURANDOT trial compared first-line BEV plus paclitaxel (PAC) vs BEV plus capecitabine (CAP) in HER2-negative metastatic BC (mBC). BEV-based regimens are often favored in TNBC [Dawood 2012] because of efficacy in subgroup analyses and a lack of effective treatments. We performed an exploratory subgroup analysis of TURANDOT to provide more data on BEV-based therapy in TNBC. **Methods:** Patients (pts) with HER2-negative mBC who had received no prior chemotherapy for mBC were randomized to either BEV–PAC (BEV 10 mg/kg d1 and 15 + PAC 90 mg/m^2 d1, 8, and 15 q4w) or BEV–CAP (BEV 15 mg/kg d1 + CAP 1000 mg/m^{2}bid d1–14 q3w). The primary endpoint was overall survival (OS); secondary endpoints included objective response rate (ORR), progression-free survival (PFS), and safety. **Results:** Of 561 pts treated, 130 had TNBC. Baseline characteristics were typical of a poor-prognosis population and generally balanced between treatment arms, although fewer pts receiving BEV–PAC than BEV–CAP had ECOG PS 1/2 (25% vs 40%, respectively), positive lymph nodes (56% vs 72%), metastatic disease at first diagnosis (19% vs 30%), and liver metastases (27% vs 43%). Median age was 54 vs 56 years, respectively. At data cut-off, median follow-up was 21.4 vs 19.2 mo for BEV–PAC and BEV–CAP, respectively. The safety profiles in the TNBC subgroup were similar to the overall population. The predominant grade ≥3 AEs were hematologic AEs and neuropathy with BEV–PAC and hand-foot syndrome and diarrhea with BEV–CAP. **Conclusions:** One-year OS rates up to 78% in TURANDOT are among the highest seen in TNBC. BEV-based therapy is a valid option in a setting with limited active treatments. BEV–PAC may be favored based on 1-year OS, PFS, and ORR. Clinical trial information: NCT00600340.

Endpoint	BEV–PAC (n=63)	BEV–CAP (n=67)
OS		
Events, n (%)	28 (44)	34 (51)
HR (95% CI)[a]	1.33 (0.80–2.19)	
Adjusted HR (95% CI)[b]	1.17 (0.69–1.98)	
1-year OS, % (95% CI)	78 (68–88)	63 (51–75)
ORR, n (%)	31 (49)	13 (19)
Difference, % (95% CI)	30 (14–45)	
PFS		
Events, n (%)	50 (79)	54 (81)
Median, mo	9.0	5.6
HR (95% CI)	1.37 (0.93–2.02)	

[a] Univariate Cox proportional hazard model (CPHM). [b] Multivariate CPHM, treatment effect adjusted for ECOG PS, bone metastases, lymph nodes, and menopausal status.

1041 **General Poster Session (Board #18H), Sat, 1:15 PM-5:00 PM**

Molecular biomarkers as predictive factors of pCR for early triple-negative breast cancer.

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Background: Early triple-negative breast cancer (TNBC) patients (p) without pathologic complete response (pCR) after neoadjuvant chemotherapy (NCT) have unsuccessful prognosis. Predictive factors for pCR are necessary in order to improve the treatment choice. The aims of the study are to determine the expression of different biomarkers (BM) in the initial biopsy (IB) of TNBC, to analyze the relationship between the BM expression and pCR, and to determine the expression changes of BM after NCT. **Methods:** We reviewed retrospectively the medical records of 49 TNBC p treated with NCT between 2001 and 2011 at two institutions. Expression of 14 BM in the IB and after NCT was independently analyzed by inmunohisto-chemistry by two pathology specialists. Staining intensity 0-1 + was considered as negative expression, and 2-3-4 + as positive. Ki 67>13% was interpreted as positive. **Results:** Forty-nine p with a median age of 47 years (27-79) were evaluated. Twenty-seven p (55%) had grade 3. Tumor stages were T1(2%), T2(26%), T3(39%), and T4(33%). 38p (77%) were node positive. Five p (10%) received anthracyclines and 42p (86%) anthracyclines plus taxanes. Fourteen p (29%) presented pCR, 27p (55%) partial response, 4p (8%) stable disease, 2p (4%) progressive disease, and 2p (4%) were not evaluable. The BM expression in the IB was: CD44 (88%), CK 5/6 (27%), EGFR (0%), Ki 67 (73%), Wt-1 (10%), p-Akt (24%), HER2 (19%), NY-ESO-1 (11%), MAGE A1 (0%), HER3 (14%), BRCA1 (84%), PTEN (12%), IGFR1 (12%) and AR (14%). Diferentially expressed BM in IB for p with and without pCR, respectively, were p-Akt 0/8(0%) vs 5/13(38%) p=0.11, CK 5/6: 4/9 (44%) vs 2/15 (13%) p=0.15 and Ki 67: 7/7(100%) vs 10/17(59%) p=0.06. The Table shows the BM expression before and after NCT for p without pCR. **Conclusions:** Tumor samples of TNBC show high expression of CD44, ki67, and BRCA1. Most of BM has a decrease in expression after NCT. CK 5/6, Ki 67, and p-Akt could be predictive factor for pCR, although larger prospective studies are needed.

Biomarker	n	Pre-NCT n (%)	Post-NCT n (%)
CD44	15	12 (80)	10 (67)
CK 5/6	13	1 (8)	1 (8)
EGFR	15	0	0
Ki 67	15	9 (60)	6 (40)
Wt-1	7	1 (14)	0
p-Akt	10	3 (30)	0
HER 2	13	3 (23)	1 (8)
NY-ESO-1	12	0	1 (8)
MAGE A1	13	0	0
HER 3	6	0	0
BRCA1	9	7 (78)	5 (56)
PTEN	7	1 (14)	2 (29)
IGFR1	14	1 (7)	0
Androgen R (AR)	14	3 (21)	0

1042   **General Poster Session (Board #19A), Sat, 1:15 PM-5:00 PM**

RAD001-carboplatin combination in triple-negative metastatic breast cancer (TNMBC): A phase II trial.

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Background: Triple negative breast cancer cells often show genetic instability and inability to repair DNA damage rendering them sensitive to platinum agents. Rapamycin enhances platinum- induced apoptosis in breast cancer cell lines. We sought to explore the activity/toxicity of the of carboplatin with RAD001 in TNMBC. **Methods:** The primary objective of this study was to estimate clinical benefit rate/CBR (complete remission (CR) + partial remission (PR) + stable disease (SD) lasting >6 months) and the toxicity of this combination in women with TNMBC who have had 0-3 prior chemoregimens for MBC. 25 subjects were recruited. This design had > 80% power to test the null hypothesis that the CBR is ≤10% vs. alternative hypothesis that CBR is ≥ 30% (≥6 would need to achieve a clinical benefit). Prior Carboplatin was allowed. Women with treated brain metastasis were eligible. Originally, Carboplatin AUC 6 was administered q3 weeks with daily 5mg of RAD001 with a 3 patient run-in, then 10 mg daily. Due to excessive thrombocytopenia, the dose of Carboplatin was first amended to AUC 5 and then to AUC 4 with 5 mg of RAD001 (no escalation to 10 mg). **Results:** All 25 patients have been recruited. Median age is 58.There have been 1 CR, 6 PR's, 2 SD's lasting >6 months and 6 PD's. 3 patients were not evaluable. One SD achieved in a patient progressing on single agent Carboplatin. The estimated CBR is 36% (95% C.I.: 17%-55%). Median PFS is 3.3 months (95% C.I.: 2.4-7.7 months) from start of treatment. 7 patients (28%) had grade 3 or 4 thrombocytopenia and 3 (12%) had grade 3 neutropenia (no bleeding/ febrile neutropenia). Since amendment of Carboplatin to AUC 4 the regimen has been very well tolerated with only 11% grade 3 hemetoxicity. The grade 3 non-heme toxicities included nausea/ vomiting (n=1), mucositis (n=1) and dehydration (n=1). Grade 3 insomnia (n=1) and dyspnea (n=1) were thought to be unrelated to the treatment (no grade 3 fatigue/ interstitial lung disease). **Conclusions:** The study has achieved the primary end point of demonstrating clinical benefit in TNMBC. Dose limiting thrombocytopenia was an unexpected side effect requiring protocol amendment. Clinical trial information: NCT01127763.

1043 General Poster Session (Board #19B), Sat, 1:15 PM-5:00 PM

A phase I study of neoadjuvant chemotherapy (NCT) with the gamma secretase (GS) inhibitor RO4929097 in combination with paclitaxel (P) and carboplatin (C) in women with triple-negative breast cancer (TNBC).

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Background: Notch receptors are overexpressed in TNBC. Notch activation involves the cleavage of Notch ligand/receptor complex by GS. RO4929097 (RO) is an oral inhibitor of GS. We are conducting a phase I NCT trial of intermittent RO in combination with P and C in TNBC to determine the dose limiting toxicity (DLT) and the maximum-tolerated dose (MTD) of RO. Because RO induces CYP3A4/5, plasma P and RO are quantified in real time to ensure P AUC exposure is not decreased. **Methods:** Women $\geq$ 18 years with clinical stage II/III TNBC received C AUC=6 on day 1 and weekly P 80 mg/m2 in combination with RO on days 1-3, 8-10 and 15-17 for six 21-day cycles. The starting dose of RO was 10 mg and escalated according to the 3+3 rule. DLT was defined as grade $\geq$3 (G3) non-hematologic toxicity (n-HT), grade 4 (G4) thrombocytopenia (TCP) or G4 neutropenia (NP) during cycle#1 (c1). Plasma specimens were analyzed for PK by a validated LC-MS/MS assay. **Results:** 13 pts were enrolled. Two pts enrolled at 10 mg RO with C AUC 6 developed G3,4 TCP during c1. The study was amended; the dose of C was decreased to AUC 5. No DLTs were observed with 10 mg RO and C AUC 5. Only 1 DLT (G3 HTN) occured with 20 mg RO, but all 4 pts enrolled on this cohort required dose reductions of RO during subsequent cycles. The RO dose was de-escalated to 10 mg, additional 3 pts were treated with 10 mg RO. G$\geq$3 HT included: G4 NP in 2 pts, G4 TCP in 1 pt, G3 NP in 6 pts, G3 anemia in 4 pts and G3 TCP in 5 pts. G$\geq$3 n-HT included: G3 sensory neuropathy in 3 pts. G3 HTN, G3 fatigue and G3 depression occured in 1 pt each. There were no hospitalizations for treatment-related toxicities. PK studies indicate that P AUC ranged from 80% to 134% on week 3 compared to week 1. Ten pts completed 6 cycles of NCT, 3 are still receiving NCT. Five of 10 (50%) pts had complete pathologic response (pCR) in breast and axilla and 3 (30%) pts had minimal residual cancer in breast. **Conclusions:** The MTD of intermittent RO administered in combination with P and C is 10 mg. This MTD does not result in decreased P exposures. The pCR (50%) and minimal residual disease (30%) suggests this regimen is active in TNBC. Supported by the NCI/NIH Award Number U01CA076576. Clinical trial information: NCT01238133.

1044   **General Poster Session (Board #19C), Sat, 1:15 PM-5:00 PM**

Use of adjuvant chemotherapy and outcomes in women age 70 and older with HER2-positive (HER2+) or triple-negative (TN) breast cancer (BC).

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Background: Chemotherapy use decreases with increasing age. There is a stronger rationale for adjuvant chemotherapy in HER2+ and TN BC due to a higher risk of recurrence, known benefit of trastuzumab with chemotherapy and lack of other systemic options. Aims: 1) Characterize and compare outcomes of resected HER2+/TN BC in older women (age ≥70) (OW) vs. younger women (age 50-69) (YW) 2) Determine chemotherapy use in OW vs. YW 3) Compare outcomes in OW based on receipt of chemotherapy. **Methods**: Women ≥ 50 years old with newly diagnosed resected HER2+ or TN stage I-III BC in British Columbia between 2003 and 2006 were included. Demographic, prognostic and treatment characteristics were compared in OW vs. YW using Chi-Square and t-tests. Kaplan-Meier curves for relapse-free survival (RFS), breast cancer-specific survival (BCSS) and overall survival (OS) were calculated in the various cohorts. **Results**: OW (n=292) had larger tumors (p=0.002), more often had mastectomy and less often had adjuvant radiation (p<0.001) than YW (n=946). There were no differences in nodal or receptor status. OW vs. YW were less likely to receive chemotherapy (28.1 vs. 81.3%, p<0.001); odds decreased with increasing age (OR 15.9 and 7.4 for women age 50-59 and 60-69 vs. ≥70, p<0.001). OW had worse 5-year RFS (75.4 vs. 83.2%, p=0.002), local RFS (93.2 vs. 95.5%, p=0.05) and distant RFS (77.5 vs. 85.5%, p=0.001). Both 5-year BCSS (79.5 vs. 88.1%, p<0.001) and OS (63.7 vs. 85.8%, p<0.001) were worse in OW vs. YW. OS, but not BC-specific outcomes (RFS, BCSS), was significantly better in those who received chemotherapy compared to those who did not (Table). **Conclusions**: OW with HER2+ and TN BC are less likely to receive adjuvant chemotherapy than YW. No difference in BCSS was noted in OW based on receipt of chemotherapy, possibly due to a small sample size. Differences in OS based on receipt of adjuvant chemotherapy suggest that oncologists in British Columbia are accurately identifying women with limited life expectancy less likely to benefit from chemotherapy.

	5 yr RFS %	P value	5 yr BCSS %	P value	5 yr OS %	P value
Overall						
OW	75.4	0.002	79.5	<0.001	63.7	<0.001
YW	83.2		88.1		85.8	
OW						
Chemo	76.5	0.87	80.1	0.86	74.4	0.003
No chemo	75.0		79.4		59.5	

1045 General Poster Session (Board #19D), Sat, 1:15 PM-5:00 PM

A multicenter phase I-II trial of weekly paclitaxel and carboplatin plus bevacizumab in women with triple-negative metastatic breast cancer.

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Background: Triple-negative breast cancer cells are unable to repair double stranded DNA breaks and hence have sensitivity to platinum agents. The combination of carboplatin and paclitaxel administered weekly is active and well tolerated. Bevacizumab when added to paclitaxel prolonged progression-free survival in metastatic breast cancer (MBC). We investigated the activity and toxicity of paclitaxel plus carboplatin and bevacizumab in triple-negative MBC. **Methods:** The study's primary objective was to estimate the objective response rate [complete (CR) + partial remission (PR)] and toxicity of the combination in women with triple negative MBC who had no prior chemotherapy for metastatic disease. The study followed the Simon's two-stage optimal design with 16 patients initially evaluated for response and toxicity and then expanding to a total of 46 patients. The null hypothesis that the objective response rate is ≤40% could be rejected if the number of CR/PR was ≥23. Paclitaxel 90mg/m^{2}and Carboplatin AUC 2 were administered on days 1, 8, and 15 every 4 weeks, preceded by bevacizumab 10 mg/kg on days 1 and 15. **Results:** 45 women with triple negative MBC have been recruited thus far. Of them, 12 were premenopausal and 27 had prior (neo-)adjuvant chemotherapy. The median cycles administered were 5 (range 1-8). Of 38 evaluable patients we observed 7 CR, 22 PR's for an objective response rate 76%. Seven patients achieved stable disease, while two had disease progression. Median duration of response was 8.1 months with median time to progression 9.2 months. Neutropenia grade 3 and 4 was experienced by 13 and 6 patients, respectively, with one toxic death due to febrile neutropenia. Other grade 3 toxicities included anemia/ neurotoxicity (n=2), thrombocytopenia/diarrhea (n=1). **Conclusions:** Although still ongoingthe study has achieved the primary objective of demonstrating clinical activity for weekly carboplatin and paclitaxel in combination with bevacizumab in triple negative MBC. We believe that this triplet combination merits further evaluation in this patient population for whom there is no standard treatment. Clinical trial information: NCT00691379.

1046 General Poster Session (Board #19E), Sat, 1:15 PM-5:00 PM

TGFb signature at 2 weeks to predict response to preoperative therapy (PT) with bevacizumab (B) and chemotherapy (CT) in early breast cancer (EBC).

Nicole Williams, Vinay Varadan, Aditi Vadodkar, Kristy Miskimen, Hannah L. Gilmore, Nicholas Beckloff, Simone Edelheit, Dhivya Prabhakar, Angel Janevski, Nila Banerjee, Sitharthan Kamalakaran, Maysa M. Abu-Khalaf, William M. Sikov, Nevenka Dimitrova, Lyndsay Harris; University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; Philips Research North America, Briarcliff Manor, NY; University Hospital/Case Western Reserve University, Cleveland, OH; Case Western Reserve, Cleveland, OH; Yale University School of Medicine, Yale Comprehensive Cancer Center, New Haven, CT; Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI; Case Western/Seidman Cancer Center, Cleveland, OH

Background: Gene expression profiles from core biopsies taken during PT for EBC may identify markers associated with benefit. B was recently shown to improve pathologic complete response (pCR) to CT in two randomized trials, but is associated with increased toxicity. Predictive signatures are critical to optimizing benefit. We have shown that changes in TGF-β pathway activity after one dose of B are associated with pCR. To confirm these results and understand the mechanism of alteration of the TGFb pathway, we evaluated the 61-gene TGFb signature by RT-PCR, measured markers of TGFb pathway activation and assessed TGFb gene mutations. **Methods:** Real-time PCR was performed on paired (pre/post) core biopsy RNA samples from 21 patients (pts) who received B, trastuzumab (T) or nab-paclitaxel prior to combined CT and targeted therapy using Custom RT2 Profiler PCR Arrays (384-well plate, 64x6 format) containing 60 genes from our TGF-beta signature and 3 housekeeping genes, IPO8, ALAS1, and SDHA. RT- PCR reactions containing Qiagen RT^{2}SYBR Green qPCR Mastermix and 5 ng of amplified cDNA were run on a Roche LightCycler480 machine. Cp values were determined using the Roche LightCycler480 software. Antibodies to p-Smad2, TGFBR1 and TGFBR2 were analyzed in FFPE IHC pre and post therapy. TGFb pathway genes with known mutations in TCGA were assessed using an Illumina Custom Amplicon and miSeq next generation sequencing. **Results:** The log 2 FPKM value of the 60 genes correlated well with the ΔC_P values calculated normalized to ALAS1 housekeeping gene. The $\Delta\Delta C_P$ values was determined by subtracting the 60 gene ΔC_P values of baseline samples from post-exposure samples. Patients were clustered using the $\Delta\Delta C_P$. Pts exposed to B who achieved a pCR showed down-regulation of signatures genes, in contrast to a strong non-pCR cluster. Signature evaluation showed no association with response in the T arm. TGFb pathway protein expression and mutation frequency is under analysis. **Conclusions:** TGFb signature predicts response to B containing chemotherapy after one dose of B and is validated by RT- PCR as a potential predictive tool. TGFb pathway activation and gene mutation analysis will be presented. Clinical trial information: NCT00617942.

1047   **General Poster Session (Board #19F), Sat, 1:15 PM-5:00 PM**

A randomized phase II trial comparing docetaxel plus cyclophosphamide with epirubicin plus cyclophosphamide followed by docetaxel as neoadjuvant chemotherapy for hormone receptor-negative breast cancer: Kanagawa Breast Oncology Croup (KBOG) 1101 study.

Takashi Ishikawa, Daisuke Shimizu, Mikiko Tanabe, Mari S.Oba, Takeshi Sasaki, Satoshi Morita, Kumiko Kida, Shuichi Nawata, Masatoshi Mogaki, Takako Doi, Koichiro Tsugawa, Haruki Ogata, Yoshimasa Kosaka, Norihiko Sengoku, Yasuhiro Suzuki, Akihiko Suto, Takashi Chishima, Yasushi Ichikawa, Itaru Endo, Yutaka Tokuda, KBOG Study Group; Department of Breast and Thyroid Surgery, Yokohoma City University Medical Center, Yokohama, Japan; Breast and Thyroid Surgery, Pathology, and Biostatistics, Yokohama City University Medical Center, Knagawa, Japan; Breast and Thyroid Surgery, Pathology, and Biostatistics, Yokohama City University Medical Center, Kanagawa, Japan; Yokohama City University Medical Center, Kanagawa, Japan; Surgery, Yokosuka Kyosai Hospital, Kanagawa, Japan; Breast Surgery, Shonan-kinen Hospital, Kanagawa, Japan; Breast and Endocrine Surgery, St. Marianna University School of Medicine, Kanagawa, Japan; Surgery, Kitasato University, Kanagawa, Japan; Tokai University School of Medicine, Isehara Kanagawa, Japan; Clinical Oncology and Gastrointestinal Surgery, Yokohama City University, Kanagawa, Japan; Yokohama City University Hospital, Yokohama, Japan; Tokai University School of Medicine, Kanagawa, Japan

Background: Taxane-based regimens have been widely used to treat breast cancer. Accordingly, it has become important to identify subgroups in which anthracyclines are indispensable. Thus, we initiated a randomized phase II neoadjuvant chemotherapy (NAC) study to compare taxane with and without anthracycline in hormone-negative subtypes. **Methods:** Eligibility criteria were hormone-negative, an age younger than 80 years and ECOG PS0-1. According to HER2 status, patients were randomly assigned to TC ($75/600$ mg/m^2) q3wks $\times 6$ or FEC ($500/100/500$ mg/m^2) q3wks $\times 3$ followed by D (100 mg/m^2) q3wks $\times 3$. The primary endpoint was the rate of pathological complete response (pCR; Grade 3 and Quasi-pCR; Grade $3+2$b). Secondary endpoints were safety, breast-conserving surgery ratio, disease-free survival, overall survival, and predictive factors (HER2, Ki-67, P-53, CK5/6, EGFR, and TOP2A by IHC and TOP2A by FISH) for each regimen. **Results:** 97 out of 103 patients were successfully analyzed (47 for TC6 and 50 for FEC-D). Severe adverse events (Grade ≥ 2) were frequently observed in FEC-D-treated patients with statistical significance (poor appetite, nausea/vomiting: $p<0.001$; febrile neutropenia: $p=0.016$). The pCR rate tended to be higher in FEC-D-treated patients compared with that of TC6-treated patients (pCR: 36.0 vs. 25.5%, n.s.; Quasi-pCR: 46.0 vs. 40.4%, n.s.). There was no significant difference of pCR rates in the HER2 and triple negative (TN) subtypes between each regimen. Among predictors, only positive markers CK5/6 and EGFR predicted the superiority of the FEC-D treatment ($p=0.05$). **Conclusions:** TC6 was safe and relatively active even in HER2 subtype patients. Therefore, the concurrent use of trastuzumab with TC could be a reasonable option for NAC in HER2 subtype patients. However, anthracyclines are required to treat basal-type TN cancer. Clinical trial information: UMIN000002215.

1048^　　　　　　　　**General Poster Session (Board #19G), Sat, 1:15 PM-5:00 PM**

Phase II study of neoadjuvant chemotherapy with a metronomic regimen of paclitaxel + cyclophosphamide + capecitabine followed by 5-fluorouracil + epirubicin + cyclophosphamide in operable triple-negative breast cancer (JBCRG-13 study).

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Background: Triple-negative breast cancer (TNBC) is generally associated with a poor prognosis. Combination therapy with anthracyclines and taxanes is widely used as preoperative systemic chemotherapy (PST), but pathological complete response (pCR) rate is ≤50%. We conducted metronomic PST in TNBC patients. **Methods:** Patients had primary breast cancer (T1C-3N0M0 or T1-3N1M0) with low ER expression (<10%) diagnosed with either a triple-negative or HER2-negative invasive tumor. They received 4 cycles of a metronomic PCX regimen followed by 4 cycles of 5-fluorouracil (500 mg/m^2, q3w) + epirubicin (100 mg/m^2, q3w) + cyclophosphamide (500 mg/m^2, q3w) (FEC regimen). The metronomic PCX regimen includes weekly administration of paclitaxel (80 mg/m^2; days 1, 8, 15), cyclophosphamide (50 mg/body; po, days 1-21) and capecitabine (1200 mg/m^2; po, daily), with one cycle set to 21 days. Primary endpoint was pCR rate. **Results:** Between March 2010 and September 2011, 41 patients were enrolled and 40 patients were treated. Characteristics of these 40 pts (ITT population) were: median age 52 years (range, 33-69), median tumor size 23.7 mm (range, 3.5-82), N(+) in 16 pts (40%), and estrogen receptor weakly positive (ER;1-9%) in 7 pts (17.5%). Median dose intensity for paclitaxel, cyclophosphamide and capecitabine was 89.7%, 92.1% and 89.8%, respectively. Five pts requested discontinuation of PST during PCX and 2 during FEC, primarily due to adverse events, leaving a per protocol population of 33 pts. pCR (ypT0/Tis ypN0) rate was 54.5% (18/33). 22 pts achieved CR, and ORR was 93.9% (95% CI, 79.8-99.3) as assessed by MRI or CT. Breast conservation rate was 72.7% (24/33), and 5 of 13 pts changed to partial resection from pre-planned total mastectomy. Grade 3-4 adverse events were neutropenia (35%), febrile neutropenia (25%), leucopenia (25%), and hand-foot syndrome (7.5%). There was no SAE report, and most pts completed treatment as outpatients. **Conclusions:** Metronomic PCX followed by FEC provided a high pCR rate and was manageable as PST in patients with TNBC. Clinical trial information: UMIN000003570.

1049^   **General Poster Session (Board #19H), Sat, 1:15 PM-5:00 PM**

A phase III, open-label, randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer (MBC) previously treated with anthracyclines and taxanes: Subgroup analyses.

Peter Andrew Kaufman, Javier Cortes, Ahmad Awada, Louise Yelle, Edith A. Perez, Jantien Wanders, Martin S. Olivo, Yi He, Corina Dutcus, Christopher Twelves; Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH; Vall d'Hebron University Hospital, Barcelona, Spain; Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium; University of Montreal, Montreal, QC, Canada; Mayo Clinic, Jacksonville, FL; Formerly of Eisai Limited, Hatfield, United Kingdom; Eisai Inc., Woodcliff Lake, NJ; Leeds Institute of Cancer and Pathology, and St James's Institute of Oncology, Leeds, United Kingdom

Background: This phase III study, comparing eribulin versus capecitabine, showed a non-significant trend for superior overall survival (OS; hazard ratio [HR] 0.88 [95% confidence interval (CI) 0.77, 1.00]; p = 0.056) but not progression-free survival (PFS; HR 1.08 [95% CI 0.93, 1.25]; p = 0.31). Pre-specified exploratory subgroup analyses previously presented showed that patients with triple-negative, ER-negative or HER2-negative disease may have a greater benefit in OS with eribulin compared with capecitabine. Here we present further pre-specified exploratory analyses of OS and PFS. **Methods:** Patients (eribulin n=554; capecitabine n=548) with locally advanced or MBC had received ≤3 prior chemotherapy regimens (≤2 for advanced disease), including an anthracycline and a taxane. Patients were randomized (stratified for geographic region and HER2 status) 1:1 to 21-day cycles of eribulin mesylate 1.4 mg/m^2 i.v. on days 1 and 8 or capecitabine 1.25 g/m^{2}BID orally on days 1-14. Further pre-specified exploratory subgroups included: age; receptor status; number and setting of prior chemotherapy regimen(s); sites of disease; number of organs involved; and time to progression after last chemotherapy. **Results:** From analyses for OS, patients with only non-visceral disease (HR 0.51; 95% CI 0.33, 0.80), with >2 organs involved (HR 0.75; 95% CI 0.62, 0.90), who had progressed >6 months after last chemotherapy (HR 0.70; 95% CI 0.52, 0.95), or who had received an anthracycline and/or a taxane in the metastatic setting (HR 0.84; 95% CI 0.72, 0.98), appeared to benefit more from treatment with eribulin compared with capecitabine. For OS, in no subgroup was a trend favoring capecitabine seen. Data for other pre-specified subgroups for both OS and PFS will be presented. **Conclusions:** In addition to patients with triple-, ER-, or HER2-negative disease, further pre-specified exploratory analyses suggest that other patient subgroups may particularly benefit from treatment with eribulin; further studies are warranted to address these hypotheses. Clinical trial information: NCT00337103.

1050^   **General Poster Session (Board #20A), Sat, 1:15 PM-5:00 PM**

Quality of life (QoL) in patients (pts) with locally advanced or metastatic breast cancer (MBC) previously treated with anthracyclines and taxanes who received eribulin mesylate or capecitabine: A phase III, open-label, randomized study.

Javier Cortes, Ahmad Awada, Peter Andrew Kaufman, Louise Yelle, Edith A. Perez, Galina Velikova, Jantien Wanders, Martin S. Olivo, Yi He, Corina Dutcus, W. Robert Simons, Christopher Twelves; Vall d'Hebron University Hospital, Barcelona, Spain; Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium; Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH; University of Montreal, Montreal, QC, Canada; Mayo Clinic, Jacksonville, FL; Leeds Institute of Cancer and Pathology, and St James's Institute of Oncology, Leeds, United Kingdom; Formerly of Eisai Limited, Hatfield, United Kingdom; Eisai Inc., Woodcliff Lake, NJ

Background: In a phase III trial comparing eribulin (E) vs. capecitabine (C) in pts with locally advanced or MBC, a trend for improved OS was observed but a statistically significant superiority was not demonstrated with E vs. C for OS or PFS. The AE profiles were consistent with known side effects. We now report QoL results from this trial. **Methods:** Pts received eribulin mesylate 1.4 mg/m^2 on Days 1 and 8, or C 1.25 g/m^2 BID orally on Days 1-14, of a 21-day cycle. Eligible pts had received prior therapy including an anthracycline and taxane, and were receiving study drug as 1st-, 2nd-, or 3rd-line therapy for advanced disease. QoL, a secondary objective, was assessed using EORTC QLQ-C30 and QLQ-BR23 questionnaires at baseline, 6 weeks, 3, 6, 12, 18, and 24 months after starting treatment (or until progressive disease or treatment change), and at unscheduled visits. Longitudinal analyses were carried out using weighted generalized estimating equations adjusted for non-random attrition due to death within 12 months. Model covariates were time (visit), region, and baseline QoL. The primary endpoint was change from baseline for Global Health Status (GHS)/overall QoL; exploratory endpoints were change from baseline for each functional domain, and signs/symptoms. **Results:** 1,102 pts were randomized (E 554; C 548). GHS/QoL scores were low at baseline for E (56.3) and C (54.7) on a scale of 0 (worse) to 100 (best). GHS/QoL and cognitive functioning improved significantly more in pts receiving E vs. C, (6.5 [p=0.048] and 15.3 [p<0.001], respectively). Emotional functioning improved significantly for pts receiving C vs. E (3.3; p=0.033). Pain was comparable at baseline, and was lower at subsequent visits with both treatments. Patient-reported signs/symptoms in favor of E included nausea and vomiting (E1.9; p=0.043) and diarrhea (-3.7; p=0.001); systemic side effects (5.2; p<0.001) and upset by hair loss (9.3; p=0.023) favored C. **Conclusions:** GHS/QoL scores improved more in pts receiving E than C. E showed advantages in terms of gastrointestinal effects while C had advantages in relation to hair loss. Clinical trial information: NCT00337103.

1051 **General Poster Session (Board #20B), Sat, 1:15 PM-5:00 PM**

Next-generation sequencing (NGS) in patients with advanced metastatic breast cancer: Identification of molecular alterations and analysis of associations with treatment on phase I studies at MD Anderson Cancer Center.

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Background: Matching molecular alterations in patients with breast cancer to targeted therapy may increase response rates. **Methods:** We analyzed 22 sequential breast cancer patients with next generation sequencing (NGS) profiling of their tumors profiling (FoundationOne) treated on Phase I trials at the Clinical Center for Targeted Therapy at MD Anderson Cancer Center. Objectives included: (1) characterize molecular alterations including mutations, amplifications and deletions, (2) evaluate associations between molecular alterations and response to therapy. **Results:** Twenty-two breast cancer patients, all female with median age 56 years were included. Twenty-one of 22 of patients (95%) analyzed demonstrated at least one molecular alteration. Twenty-one of 22 patients were evaluable for response to therapy (1 patient had not yet reached restaging). Sixteen patients were treated on Phase I trials with targeted therapy that was either directly or indirectly associated with a molecular alteration. Seven of these 16 patients (44%) achieved stable disease (SD) ≥ 6 months/partial response (PR)/complete response (CR) including 3 patients with PR and 1 patient with CR. Examples of molecular alterations include: mutations in *PIK3CA* (8 patients), *PIK3R1* (2 patients), *PTEN* (1 patient), *cMET* (1 patient), *NF1* (one patient); amplifications in *CCND1* (8 patients), *FGFR1* (4 patients), *MYC* (3 patients), *MCL1* (3 patients), *IRS2* (2 patients) and *CCNE1*(1 patient). **Conclusions:** A majority of patients with advanced or metastatic breast cancer whose tumors underwent NGS profiling demonstrated molecular alterations. Of the 9 patients who had either SD≥ 6 months/PR/CR on Phase I treatment, 7 (78%) had molecular alterations, either directly or indirectly associated with therapy. Further investigation of larger cohorts of patients with NGS is ongoing.

1052   **General Poster Session (Board #20C), Sat, 1:15 PM-5:00 PM**

TBCRC 019: An open label, randomized, phase II trial of nanoparticle albumin-bound paclitaxel (nab-PAC) with or without the anti-death receptor 5 (DR5) monoclonal antibody tigatuzumab (TIG) in patients with metastatic triple negative breast cancer (TNBC).

Christos Vaklavas, Vandana Gupta Abramson, Nancy U. Lin, Minetta C. Liu, Hope S. Rugo, Rita Nanda, Anna Maria Storniolo, Tiffany A. Traina, Yufeng Li, Sujata Patil, Daniel F. Hayes, Catherine H. Van Poznak, Julie R. Nangia, William Johnson Irvin, Helen Krontiras, Jennifer F. De Los Santos, Paul Haluska, Antonio C. Wolff, Andres Forero-Torres, on behalf of the Translational Breast Cancer Research Consortium (TBCRC); University of Alabama at Birmingham, Birmingham, AL; Vanderbilt-Ingram Cancer Center, Nashville, TN; Dana-Farber Cancer Institute, Boston, MA; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; University of California, San Francisco, San Francisco, CA; University of Chicago, Chicago, IL; Indiana University Simon Cancer Center, Indianapolis, IN; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Rush University Medical Center, Houston, TX; University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Mayo Clinic, Rochester, MN; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: TIG, an agonistic anti-DR5 monoclonal antibody, triggers apoptosis in DR5+ human tumor cells without the aid of crosslinking. TIG has shown strong in vitro and in vivo activity against basal-like breast cancer cells that is enhanced by chemotherapy like paclitaxel. **Methods:** Randomized 2:1 phase II trial of nab-PAC with/without TIG in TNBC patients. Patients stratified by prior exposure to chemotherapy in the metastatic setting. Patients received nab-PAC weekly x 3 and TIG every other week, every 28 days. Primary endpoint was overall response rate (ORR). Secondary objectives were safety, progression free survival (PFS), TIG immunogenicity, and PK. Biopsies and circulating tumor cells were collected. The trial was not powered to compare arms but allowed early stopping for futility and was sized to estimate ORR with 95% CI. **Results:** 64 patients enrolled, 60 treated; 39 in the combination arm and 21 in the nab-PAC arm. Of the 39 in the combination arm, there were 2 CR, 9 PR (1 near CR, 96% tumor reduction), 11 SD and 17 PD; ORR 28% (95% CI 14%-42%). Of the 21 in the single agent arm, there were no CR, 8 PR, 4 SD and 9 PD; ORR 38% (95% CI 17%-59%). Higher ORRs were seen in the chemotherapy naïve patients (58% vs. 15% combination and 42% vs. 35% single agent). 2 patients with CR, 1 near CR, and 1 PR in the combination arm are still on therapy (602+, 531+, 466+, 460+ days). PFS was similar in both groups (3.6 months); higher in chemotherapy naïve patients. Combination was well tolerated (most toxicities grade 1/2); the most common AEs were fatigue, alopecia, peripheral sensory neuropathy, anemia, neutropenia, nausea, thrombocytopenia, anorexia, diarrhea, and vomiting. No grade 4 or 5 toxicity. No apparent added toxicity with TIG was seen. **Conclusions:** Combination therapy with nab-PAC + TIG was well tolerated, without apparent improvement in ORR relative to nab-PAC alone; however, 4 subjects treated as first-line had prolonged clinical benefit with the combination, and correlative studies will investigate markers that might predict clinical outcome (Next-Gen genomic analysis). Clinical trial information: F101004001.

1053   **General Poster Session (Board #20D), Sat, 1:15 PM-5:00 PM**

Claudin-1 as a novel transcriptional target of hedgehog signaling and a predictor for outcome in breast cancer.

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Background: Hedgehog signaling is important in the development of a number of malignancies. We have recently shown that the Hedgehog (Hh) signaling pathway is associated with a poor outcome and is a novel therapeutic target in triple negative breast cancer. Gene expression profiling of M6 murine cell line mammary xenografts overexpressing Hh ligand revealed a series of genes potentially regulated by Hh in breast cancer. We explored the expression patterns of one of the candidates, Claudin-1, an adhesion molecule, and its association with Hh pathway markers and outcome in 292 invasive ductal carcinomas. **Methods:** Immunohistochemistry for Claudin-1 was performed and scored by two observers for membranous and cytoplasmic localization. Membranous or cytoplasmic expression were scored and its associations with patient outcome were assessed using Kaplan Meier and Cox Proportional hazard model analyses. Correlations with clinicopathological features and Hh pathway protein expression were undertaken using chi squared analysis. **Results:** Claudin-1 was expressed both in the cytoplasm and at the plasma membrane of breast carcinoma cells. Cytoplasmic predominant expression of Claudin1 was associated with a favorable prognosis (HR 0.59 (95% CI: 0.36, 0.97), p = 0.039. In contrast, membranous predominant expression was associated with larger tumors, histological grade 3, a high Ki67 index and a poor outcome (HR 1.66 (95% CI: 1.064, 2.60), p = 0.026). Importantly, membranous Claudin-1 directly correlated with Hh ligand (p < 0.0001) and paracrine pathway activation as indicated by high epithelial Hh ligand expression (p < 0.0001) and high Gli1in the peritumoral stroma (p=0.027). There is a strong correlation between paracrine hh/gli (p = 0.001) and membrane predominant claudin confirming our in vivo findings. **Conclusions:** Claudin-1 is an important component of the tight junction in epithelial cells. We have shown for the first time that Claudin-1 is a direct target of Hh pathway activation. Furthermore, we report that the subcellular localization of Claudin-1 shows distinct association with outcome in breast cancer. These findings provide insight into potential mechanisms of metastatic spread of breast cancer.

1054   **General Poster Session (Board #20E), Sat, 1:15 PM-5:00 PM**

Preclinical studies with neratinib in triple-negative breast cancer.

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Background: Currently, one of the most urgent problems in breast cancer therapeutics is the validation of targeted therapy for triple-negative breast cancer (TNBC). Neratinib is an irreversible small molecule inhibitor that targets the kinase activity of EGFR, HER2 and HER4. As one of these targets, EGFR, is expressed at high levels in a subset of TNBC, we hypothesised that neratinib is a potential treatment for at least some patients with TNBC. **Methods:** The antiproliferative effects of neratinib were investigated in a panel of 35 breast cancer cells lines including 9 luminal, 12 HER2-positive and 14 triple-negative (TN). Baseline levels of total HER proteins were determined using flow cytometry. **Results:** IC_{50} values for neratinib across the panel of breast cancer cell lines ranged from < 0.001 - 1.9 μM. HER2-positive cell lines were significantly more sensitive to neratinib than HER2-negative cells ($p = 0.008$, Student's t-test). For the 14 TN cell lines, IC_{50} values ranged from $0.03 – 1.9$ μM. TN cell lines defined as basal-type A were significantly more sensitive to neratinib than those designated basal-type B ($p = 0.02$, Student's t-test). Treatment with neratinib resulted in a reduction in HER-family signalling as detected by decreased Akt and ERK phosphorylation. Consistent with the finding that basal type A TN cells were more sensitive to neratinib than type B, significantly higher levels of EGFR expression were found in the A subtype compared to the B subtype ($p = 0.02$, Student's t-test). To determine a possible predictive marker of response for neratinib, levels of all 4 HER proteins were related to response in the basal A subgroup. Baseline levels of HER3 expression were found to correlate significantly with response to neratinib ($p = 0.02$, $r = -0.875$, $n = 7$, Spearman), i.e., cell lines with the highest levels of HER3 expression had the lowest IC_{50} values within this cohort. **Conclusions:** Our results suggest that neratinib is a potential novel therapeutic option for patients with basal A type triple negative breast cancer. HER3 may act as a predictive marker of response for this subgroup of patients. Acknowledgements**:** The authors thank SFI for funding MTCI (SRC award, 08/SRC/B1410 to MTCI) and an SFI Short Term Travel Fellowship to MM, for funding this work.

1055^   **General Poster Session (Board #20F), Sat, 1:15 PM-5:00 PM**

Quality of life (QoL) and content validity in objective tumor response.

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Background: Key properties of QoL instruments in a clinical trial setting are reliability, the ability to detect a change, and content validity. Using data from the Study 301 phase III breast cancer trial, we report here content validity and ability to detect a change for the EORTC QLQ-C30 and breast cancer-specific QLQ-BR23 questionnaires. **Methods:** Patients with locally advanced or metastatic breast cancer were randomized to 21-day cycles of either eribulin mesylate 1.4 mg/m^2 given on Days 1 and 8, or capecitabine 1.25 g/m^{2}BID orally on Days 1-14. QoL questionnaires were completed at baseline and at 6 weeks, 3, 6, 12, 18, and 24 months. Objective tumor response was evaluated (complete response [CR]; partial response [PR]; stable disease [SD]; progressive disease [PD]). Univariate and multivariate longitudinal analyses using weighted generalized estimating equations were employed to assess the responsiveness of the QoL scales to objective tumor response. **Results:** 1,102 patients were randomized (554 eribulin, 548 capecitabine). Global health status (GHS)/QoL scores were low at baseline (55). GHS/QoL scores were highest for patients with CR (70.8), followed by those patients with PR (63.5), SD (60.5), and PD (58.1). Physical functioning followed the same pattern: CR (98.3); PR (79.1); SD (72.8); PD (71.0). Role and social functioning scores were also responsive. Pain increased, while fatigue and body image worsened, with poorer tumor responses. Using the weighted generalized estimating equations, there were improvements in physical (34.78; p<0.01), cognitive (27.29; p<0.01), and social (22.04; p<0.01) functioning, and future perspective 11.47 (p<0.01), in patients who responded (CR and PR) to treatment compared with non-responders. Pain decreased significantly by 28.62 (p<0.01) on a 0-100 scale. Patients who responded also gained appetite and had fewer breast symptoms. **Conclusions:** These results suggest content validity of the EORTC QLQ-30 and QLQ-BR23 questionnaires as they correlate with changes in objective tumor assessments. Clinical trial information: NCT00337103.

1056 **General Poster Session (Board #20G), Sat, 1:15 PM-5:00 PM**

Significance of the vimentin expression in triple-negative breast cancer.

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Background: Triple-negative breast cancer (TNBC), characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). The treatment of patients with TNBC has been challenging due to the absence of these molecular targets and the heterogeneity of the disease. Therefore a better understanding of the molecular and histopathological features of TNBC and its heterogeniety is important for the development of a new therapeutic strategy and to improve the prognosis of TNBC. Recent studies suggest that there are links between TNBC and the epithelial-mesenchymal transition (EMT). To identify prognostic biomarkers and novel therapeutic targets, vimentin one of the most major factors associated with EMT was investigated in TNBC. **Methods:** Sporadic invasive ductal carcinoma specimens were obtained from 659 Japanese patients, and 90 (14%) cases were diagnosed as TNBC. The vimentin mRNA and protein expression levels were evaluated by quantitative RT-PCR and immunohistochemistry. **Results:** The mRNA expression of vimentin was significantly upregulated in the basal type breast cancer cell line. Immunohistochemically, the vimentin expression was significantly higher (p=0.0042) in TNBC compared to the other subtypes. Vimentin expression was associated with a younger age (p=0.016), high nuclear grade (p=0.023) and high Ki67 expression (p<0.0001), and a poorer prognosis in terms of both the recurrence-free survival (RFS) (p=0.0058) and overall survival (OS) (p=0.013) in TNBC patients. A multivariate analysis showed that vimentin expression was an independent prognostic factor for the RFS (p=0.043). Vimentin expression was also associated with a significantly shorter RFS (p=0.021) and OS (p=0.017) in patients with basal-like breast cancer (BLBC). **Conclusions:** The elevated expression of vimentin contributes to the aggressive phenotype and poor prognosis in TNBC. Vimentin expression might be useful as a biomarker for the prognosis of TNBC.

1057   **General Poster Session (Board #20H), Sat, 1:15 PM-5:00 PM**

Cetuximab in combination with docetaxel (T) in patients with operable, triple-negative breast cancer (TNBC): Preliminary results of a multicentre neoadjuvant pilot phase II study.

Jean Marc Nabholtz, Marie-Ange Mouret-Reynier, Isabelle Van-Praagh, Véronique Servent, Jean-Philippe Jacquin, Anne-Véronique Bourcier, Francesco Del Piano, Pascale Dubray-Longeras, Beatrice Nayl, Catherine Abrial, Fabrice Kwiatkowski, Marie-Mélanie Dauplat, Nina Radosevic-Robin, Anne Cayre, Nancy Uhrhammer, Yannick Bidet, Nassera Chalabi, Yves-Jean Bignon, Frederique Penault-Llorca, Philippe Chollet; Centre Jean Perrin/ERTICa EA 4677, Clermont-Ferrand, France; ERTICA EA 4677, Université d'Auvergne, Centre Jean Perrin, Centre d'investigation Clinique, Clinique de la Chataigneraie, Clermont-Ferrand, France; Centre Oscar Lambret, Lille, France; Department of Oncology, Institut de Cancérologie de la Loire, Saint-Priest-en-Jarez, France; Centre Hospitalier Départemental Les Oudairies, La Roche Sur Yon, France; Hopital Georges Pianta, Thonon les Bains, France; Centre Jean Perrin, Clermont-Ferrand, France; ERTICA EA 4677, Université d'Auvergne, Centre Jean Perrin, Centre d'Investigation Clinique, Clermont-Ferrand, France; Centre Jean Perrin/ERTICa EA 4677, Clermont-Ferrrand, France; Centre Jean Perrin/ERTICa 4677, Clermont-Ferrand, France; Centre Jean Perrin/INSERM UMR 990, Clermont-Ferrand, France

Background: Cetuximab is an antiboby targeting the epidermal growth factor receptor (EGFR) to which a role has been suggested in TNBC. Therefore, we evaluated the combination of docetaxel with cetuximab as neoadjuvant therapy of operable TNBC. **Methods:** 35 patients with stage II-IIIA disease were prospectively included in this multicentre pilot study. Systemic therapy (ST) consisted of 6 cycles of T (100 mg/m2) q.3 weeks, in combination with weekly cetuximab (first dose : 400mg/m², then : 250 mg/m²/week) for 6 cycles. All patients underwent surgery at completion of ST. Complete pathologic response (pCR) was the primary endpoint (Sataloff : J Am Coll Surg 1995 ; Chevallier : Am J Clin Oncol 1993), with toxicity and biologic ancillary studies as secondary endpoints. **Results:** Patients characsctics are as follows : mean age 48 [28-67] ; T1 : 3%, T2 : 73%, T3 : 24% (mean tumor size : 40 mm [15-100]) ; N0 : 61% and N1-N2 : 39%; invasive ductal carcinoma : 100%; Scarff-Bloom-Richardson Grade III : 73%, grade II : 27%. The median number of cycles was : T : 6 [1-6], cetuximab : 15 [1-18]. Pathological complete response was 24% according to Chevallier and Sataloff's classifications and 28% if we consider response in breast. Preliminary results on 23 patients show an overall clinical response rate of 57% (22% CR). Conservative surgery was performed in 75% of cases. Skin toxicity was the main side-effect : grade II : 39%, grade III : 36%, grade IV : 3%. Neutropenia grade IV : 12.7%, febrile neutropenia : 1.3%, infection : 0%. Hand-foot syndrome grade III : 3%, grade II : 3%. Ungueal toxicity grade III : 3%, grade II : 33%. **Conclusions:** These preliminary results suggest that cetuximab in combination with Tappears to have a modest efficacy in operable TNBC. Clinical trial information: NCT00600249.

1058   **General Poster Session (Board #21A), Sat, 1:15 PM-5:00 PM**

Response to the anti-EGFR antibody panitumumab combined with standard neo-adjuvant chemotherapy in triple-negative breast cancer (TNBC): The immune and IGFR pathways.

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Background: EGFR overexpression is one of the hallmarks of the "basal-like" TNBC definition by immunohistochemistry (IHC). In a phase II neoadjuvant clinical trial targeting EGFR in TNBC, we investigated various biomarkers to better identify an EGFR-sensitive population for potential further regimen development. **Methods:** Sixty patients (pts) with stage II-IIIA TNBC were prospectively included. Systemic treatment (ST) consisted of the anti-EGFR antibody panitumumab combined with FEC 100, followed by 4 cycles of docetaxel. All pts underwent surgery after ST completion. Patient characteristics: median tumor size: 40 mm (20-120); invasive ductal carcinoma: 96.7%; SBR grade III: 71.7%; complete pathological response (pCR) rate: 55.3% and 46.8% (according to Sataloff's and Chevallier's classifications, respectively). Paraffin-embedded and frozen tumor samples were collected before and after ST for biologic studies. Germinal BRCA1 mutations, and EGFR, KRAS, BRAF and PI3KCA somatic mutations were analyzed by NGS. EGFR, IGF-1R, MET, cytokeratins 5/6 and 8/18, PTEN, P-cadherin, ALDH1, Ki-67, p53, tumoral FOXP3 expression and the number of FOXP3+ or CD8+ tumor-infiltrating lymphocytes (TILs) were evaluated by IHC. **Results:** High CD8+ TILs was response-predictive ($p=3.4.10^{-6}$). Tumor FOXP3 expression and high FOXP3 TILs tended to be predictive. High IGF-1R expressors responded better than low expressors ($p = 0.028$). Comparison of EGFR, IGF-1R and Her3 in biopsies versus surgical samples showed reduced EGFR levels in non-responders ($p = 0.037$), while Her3 ($p = 0.049$) and IGF-1R ($p = 0.08$) increased. Sequencing revealed BRCA1 mutations in 10% of pts. No difference of response (pCR) was observed between mutated patients and others. Somatic mutations of PI3K were observed in 6 pts. No mutations were observed in BRAF, KRAS, or EGFR. **Conclusions:** The CD8+ TIL count seems to predict the response to panitumumab. Tumor FOXP3 expression and high FOXP3 TILs also tended to be predictive. Tumor levels of IGF-1R seem to play a determinant role in TNBC response to anti-EGFR antibodies, in concordance with our observations in a head-and-neck cancer cohort. Clinical trial information: NCT00933517.

1059 General Poster Session (Board #21B), Sat, 1:15 PM-5:00 PM

N0937(Alliance): Final clinical results and correlative data from the phase II trial of cisplatin (C) and the novel agent brostallicin (B) in patients with metastatic triple-negative breast cancer (mTNBC).

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Background: Relapsed TNBC is characterized by its poor prognosis. B is a synthetic DNA minor groove binding non-cross resistant agent that is fully active against DNA-mismatch repair deficient tumor cells. C increases GSH/GST in which enhances the efficacy of B. **Methods:** Phase II study in pts with mTNBC. C Day 1 followed by B Day 2, repeated every 21 days. Aim: Efficacy of C + B in mTNBC. Primary endpoint: PFS at 3 mo. Secondary endpoints include ORR, duration of response (DOR), 6-mo PFS, OS and AE profile. Tertiary endpoints include assessment of baseline GSH levels, prevalence of BCRA1 mutation and pERK, and correlations with outcome. **Results:** Closed 3/2012. 48 pts accrued (1 ineligible pt). Median f/u 11.4 mo (6.6-14.8); 2 pts still on treatment. 47 pts evaluable for the PFS endpoint and AEs. 49% received therapy as 3rd-5th line. Median number of cycles = 4 (range 1-15). There are currently 9 confirmed responses (8 PR and 1 CR); DOR = 2.6-14.5 mo. The 3-mo PFS = 51%; 6-mo PFS = 28%; the median TTP is 3.2 mo. AE data: 75% G3/4 hematologic AE: febrile neutropenia 19%. Non-hematologic AEs included G3 (47%) and G4 (15%): G3 fatigue 17%; and no G5 non-heme AE. No correlation of GSH/GST levels with outcome was found. Among 35 pts with evaluable data, no association between BRCA1 expression and outcomes was found. pERK expression was negatively associated with 3-mo PFS, but not 6-mo PFS. Cytoplasmic pERK expression was negatively associated with tumor response (p=0.03). No significant effect of BRCA-1 or pERK expression was found on OS. **Conclusions:** This trial showed B + C is an active regimen, especially in heavily pretreated mTNBC pts. Correlative data demonstrated a negative association between pERK expression and outcomes. A randomized phase II trial is in development. Clinical trial information: NCT01091454.

1060　　　　　　　　　　**General Poster Session (Board #21C), Sat, 1:15 PM-5:00 PM**

Triple-negative breast cancer survival in women age 75 and older.

Judith April Malmgren, Henry G. Kaplan, Mary K. Atwood; HealthSTAT Consulting, Inc., Seattle, WA; Swedish Cancer Institute, Seattle, WA

Background: Triple-negative breast cancer (TNBC) is associated with a high recurrence rate and poor prognosis, despite high initial response to chemotherapy. It is not known if TNBC patients 75 years older, an age group less likely to be treated with adjuvant chemotherapy, have the same mortality risk as younger women. **Methods:** We conducted a prospective cohort study of all women presenting with primary TNBC, age 21-89, stage I-III from 1998-2009 identified and tracked by our registry (n=529). Clinical characteristics were chart abstracted at diagnosis and follow up. The Kaplan-Meier method and log rank test were used for disease specific survival (DSS) and overall survival (OS) by age. **Results:** Mean follow up was 6.6 years, range 1.98-13.41 years. Distribution by age was 92% <75 years (n = 485) and 8% 75+ years (n = 44). The two age groups did not differ by histologic or nuclear grade, stage, or radiation therapy receipt (age 75+ by stage: I = 46%, II = 34%, III 21%, age <75: I = 37%, II = 46%, III = 17% [not significant]). Patients 75 and older were less likely to be treated with adjuvant chemotherapy (32% vs. 91%, Pearson chi square test = 119.32, p <.001). 5 year DSS was not significantly different for patients age <75 years compared to patients age 75+ years (85% vs. 84%). However, 5 year OS was significantly worse for 75 year and older patients (65%) compared to <75 year old patients (83%) (log rank test = 13.97, p < .001). **Conclusions:** In our institutional cohort, triple-negative breast cancer in older women had similar prognostic indicators (stage and histologic grade) compared to younger women and older women had equivalent disease specific survival in spite of substantially less chemotherapy treatment. At 5 years post diagnosis, women 75 years and older were 18% more likely to die of causes other than breast cancer.

1061   **General Poster Session (Board #21D), Sat, 1:15 PM-5:00 PM**

Prognostic effect of beta blockers (BB) in triple-negative breast cancer (TNBC) patients.

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Background: BB drugs have been used for decades worldwide, typically to treat hypertension and arrhythmias. Despite its therapeutic indication, evidence from recent epidemiological studies suggested that BB intake can improve prognosis of patients (pts) with cancer. With the present study we aimed at assessing whether BB intake is associated with improved prognosis in postmenopausal pts with TNBC, which represents one of the most aggressive cancers. **Methods:** We retrospectively identified 659 postmenopausal pts operated between 1997 and 2008 at the European Institute of Oncology, Milan, for a primary TNBC. Pts with advanced disease at diagnosis, presurgical systemic treatment or history of other cancers were excluded. The effect of BB intake on the risk of breast cancer recurrence and death from breast cancer (BC) was evaluated through competing risk survival analyses and multivariable Cox regression models. **Results:** At the time of cancer diagnosis, 61 pts (9.3%) out of 659 were currently using BB, while 598 (90.7%) were not. Median age was 63 years for the BB users and 60 years for the non-users (p value 0.048). All other characteristics—such as tumor size, lymph-nodal involvement, Ki-67, tumor grade, perivascular invasion, type of surgery and adjuvant therapy—were equally distributed between BB users and non-users. Median follow-up was 6 years for both groups. The 5-year cumulative incidence of BC recurrences was 11.7% and 24.1% for BB users and non-users, respectively (p = 0.030). After adjusting for age, tumor size, lymph nodal involvement, grade, perivascular invasion and use of other antihypertensive drugs, the beneficial impact of BB use remained statistically significant, with an hazard ratio of 0.44 (95% CI 0.21-0.98; p = 0.044). The 5-year cumulative incidence of BC deaths was 8.2% and 12.5% for BB users and non-users, respectively (p = 0.185). Hypertension and antihypertensive drugs other than BB did not have any significant impact on recurrence and survival. **Conclusions:** In this series of postmenopausal pts with primary TNBC, BB intake was associated with a significantly decreased risk of BC recurrence. Additional studies evaluating the potential benefits of BB on cancer prognosis are warranted.

1062   **General Poster Session (Board #21E), Sat, 1:15 PM-5:00 PM**

Androgen receptor (AR), E-cadherin, and Ki-67 as prognostic markers in triple-negative breast cancer (TNBC).

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Background: TNBC is an aggressive subset of breast cancer (BC) with central nervous system and visceral metastatic involvement and it represents a molecular subtype without specific target therapy. **Methods:** This observational, retrospectivestudy included 45 TNBC. The aim of this study was to evaluate the expression of some molecular determinants such as the AR, E-cadherin and Ki-67 in relation to histological type, time to relapse and overall survival.Immunohistochemistry (IHC) was carried out on formalin-fixed paraffin-embedded tumor samples obtained from patients (pts) defined TNBC, since ER and PgR were 0% and HER2 negative (IHC score 0/1 or FISH not amplified). **Results:** Median age was 58.8 years (range 39-77). The main histological type was ductal in 35 pts (77.7%), lobular in 7 (15.5%), medullary in 3(6.6%). 29 pts (64.4%) had a G3 tumor. Tumor stage was: I 6/45 (13.3%), IIA 21/45 (46.6%), IIIA 11/45 (24.4%), IIIB 3/45 (6.6%) and IV 4/45 (8.8%). All patients received treatments; the most frequently used regimens were anthracycline and taxanes. The androgen receptor was positive (IHC >10%) in 12/45 (26.6%). E-cadherin expression was semi-quantitatively analyzed according to the percentage of cells showing membrane positivity: 0 (0 to 10%); 1+ (10 to 30%); 2+ (30 to 70%); 3+ (> 70%). E-cadherin expression was considered positive if the score was $\geq$ 2, and negative when score was $\leq$ 1. This expression was negative in 24/45 (53.3%) cases. The Ki-67 index was $\geq$ 25% in 17/45(37.7%). The statistical analysis showed that patients with AR negative and Ki-67 positive expression have a significant correlation with the ductal histotype and G3 tumors (p < 0.001). Multivariate analysis showed that the patients with AR and E-cadherin negative but Ki-67 positive expression showed significantly (p < 0.001) worse overall survival time than those with either AR and E-cadherin positive but Ki-67 negative expression. **Conclusions:** Our data suggest that the combination of AR and E-cadherin expression as well as Ki-67 status might be useful prognostic markers in TNBC.

1063   **General Poster Session (Board #21F), Sat, 1:15 PM-5:00 PM**

Copy number changes in triple-negative breast cancer: New molecular targets.

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Background: Triple negative breast cancer (TNBC) is associated with tumor aggressiveness and high recurrence rate. Treatment options are limited due to lack of molecular-genetic markers and targeted therapy. The aim of our research is assessment of copy number changes in TNBC patients and identification of potential markers for personalized therapy. **Methods:** Fresh-frozen tumor tissues were collected from 148 patients with TNBC stage I-III. Genomes of these samples were profiled by Affymetrix SNP6.0 arrays. Arrays were normalized using R/Bioconductor and GISTIC 2.0 was used to identify copy number changes. **Results:** TNBC showed a high level of chromosomal instability and heterogeneity. More than 200 significantly altered chromosomal regions (q value < 0.25) were identified with frequency from 7.4 to 48% cases. Amplification of cell proliferation regulators (MYC, FGFR2, cyclins E1 and E2, PIK3CA, NFIB), regulators of vascularization (VEGFA) and epithelial–mesenchymal transition (CAV1 and CAV2) were found with high significance (q value < 0.1). Deletions of CDK regulators CDKN2B and CDKN2A, and tumor suppressors PTEN, RB1, APC and POT1 were also detected with highly significant q value < 0.1. Importantly, novel copy number changes of genes influencing inflammation, expression regulation and chromatin modification, localized on 1q, 7p, 8q, 9p, 17q and 19p, were found in more than 15% of samples. **Conclusions:** Despite the fact that TNBC is a heterogeneous group, several common copy number changes were identified. Our analysis confirmed copy number changes of important known genes as well as identified novel markers involved mainly in inflammatory and regulatory processes which could be targets of future therapies. Grant: Biomedreg CZ.1.05/2.1.00/01.0030.

1065   **General Poster Session (Board #21H), Sat, 1:15 PM-5:00 PM**

Differential changes in tissue biomarkers after bevacizumab (BEV) alone in a neoadjuvant study of BEV and chemotherapy in ER+ breast cancer (BC) versus triple-negative breast cancer (TNBC) patients (pts).

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Background: The benefit of the anti-VEGF antibody BEV—despite its confirmed activity with chemotherapy—remains unclear in BC pts. This may reflect that its benefit is limited to an unknown subset of BC pts. **Methods:** We previously reported the outcome and circulating biomarker data of a phase II study of neoadjuvant BEV with chemotherapy in ER+ BC and TNBC pts (NCT00546156; ASCO 2012 abstr 1026). In the present study we evaluated tissue biomarkers after 1 run-in cycle of BEV treatment alone. Patients then received BEV with standard dose-dense doxorubicin/cyclophosphamide/paclitaxel. We analyzed the changes in tissue biomarkers in ER+ BC versus TNBC pts after BEV alone and their correlation with outcome at surgery. The primary endpoint was pathologic response, measured by the Miller-Payne (MP) score (MP5=pCR). **Results:** Mean MP score was 3.1 for ER+ BC pts versus 4 for TNBC pts (area under ROC=0.60, $P<0.001$). This supports the hypothesis that the activity of BEV with chemotherapy may depend on BC subtype. In TNBCs, BEV significantly decreased mean microvascular density (MVD) by 33% ($p<0.05$). MVD was inversely correlated with the fraction of tissue positive for the hypoxia marker CAIX post-BEV ($p<0.01$). Moreover, a high pre-treatment MVD correlated with an increase in CAIX+ fraction post-BEV ($p<0.05$). In addition, a drop in MVD associated with increased CAIX+ fraction post-BEV ($p=0.05$). Finally, high ($>60\%$) pericyte coverage post-BEV—ie, more mature vessels—was inversely correlated with CAIX+ fraction ($p<0.05$). MP score was more favorable for TNBC pts with lower CAIX+ fraction at baseline ($p=0.058$) and post-BEV ($p<0.05$), and higher MVD at baseline ($p<0.05$) and post-BEV ($p<0.05$). In contrast, BEV reduced MVD non-significantly by 15% in ER+ BC ($p=0.25$). There was no correlation between MVD and CAIX+ fraction in ER+ BCs. In contradistinction to TNBC, in ER+ BCs the fraction of CAIX+ tumor was directly correlated with MP score ($p<0.01$). **Conclusions:** Our exploratory study suggests that vascular pruning post-BEV may reduce vascular function and increase hypoxia, and reduce the effectiveness of chemotherapy in TNBC. Clinical trial information: NCT00546156.

1066 **General Poster Session (Board #22A), Sat, 1:15 PM-5:00 PM**

Met and HGF inhibition in triple-negative breast cancer cell lines.

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Background: Basal-like breast cancer (BLBC) is associated with high expression of c-Met. c-Met and its ligand HGF may be rational therapeutic targets for BLBC. We evaluated expression of c-Met and response to c-Met/HGF inhibition alone/in combination with other targeted therapies in triple-negative breast cancer (TNBC) cell lines. **Methods:** Expression and phosphorylation of c-Met was measured by immunoblotting. qRT-PCR was used to measure HGF mRNA. Cell proliferation was measured by acid phosphatase assay after 5 day treatment with a c-Met inhibitor (CpdA), HGF monoclonal antibody, rilotumamab, a panHER inhibitor (neratinib) and a SRC kinase inhibitor, (saracatinib). Invasion through 0.4 μm Matrigel coated membranes was measured for two cell lines. **Results:** c-Met and p-Met were detected in 7 and 4 of the 7 TNBC cell lines tested, respectively. HGF mRNA was not detectable in any of the TN cell lines. CpdA inhibited growth in 4 TN cell lines with IC_{50} values ranging from 2.1-7.6 μM. Rilotumumab did not inhibit growth, however combined treatment with CpdA and rilotumumab resulted in significantly increased growth inhibition in 3 of 5 cell lines (Table). CpdA in combination with neratinib significantly improved growth inhibition in MDA-MB-468 cells, and in combination with saracatinib significantly improved growth inhibition in 3 of 5 cell lines (Table). CpdA also inhibited invasion of CAL-85-1 cells by 21.4% ($\pm$ 10.4%) but not HDQ-P1cells. **Conclusions:** c-Met may represent a viable molecular target in TNBC. Dual targeting of Met and HGF and/or with EGFR or SRC may increase the efficacy of c-Met inhibition in TNBC.

Percent cell growth in response to CpdA (1 μM), rilotumumab (1 μg/ml), neratinib, and saracatinib (approx IC_{50} conc).

	CpdA	Rilotumumab	CpdA + rilotumumab	Neratinib	CpdA + neratinib	Saracatinib	CpdA + saracatinib
HCC1937	85.7 ± 8.3	97.9 ± 2.5	62.9 ± 6.7*	59.2 ± 7.1	51.1 ± 12.6	63.7 ± 2.6	53.1 ± 6.8*
BT20	98.1 ± 3.03	101.4 ±1.6	98.04 ± 2.3	58.5 ± 6.02	56.8 ± 6.9	56.4 ± 2.2	61.3 ± 4.8
HCC1143	96.2 ± 13.9	114.2 ± 7.4	105.7 ± 8.5	69.6 ± 6.5	49.3 ± 10.7	95.9 ± 6.3	70.2 ± 7.9
MDA-MB-231	83.6 ± 6.7	97.5 ± 4.9	69.8 ± 10.4*	60.4 ± 6.7	53.8 ± 1.4	62.2 ± 6.7	26.2 ± 0.7*
MDA-MB-468	61.8 ± 7.5	113.1 ± 0.3	36.4 ± 1.3*	43.2 ± 1.1	14.8 ± 0.8*	52.4 ± 1.1	30.3 ± 2.1*

* Indicates a p value of <0.05 for combinations.

1067   General Poster Session (Board #22B), Sat, 1:15 PM-5:00 PM

Anaplastic lymphoma kinase (ALK): A potential oncogenic driver in triple-negative breast cancer?

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Background: TNBC, a molecularly heterogeneous subset of breast cancer, has an aggressive clinical course and no established targets for therapy. Wild-type ALK gene amplification by fluorescence in situ hybridization (FISH) was noted in 6/9 inflammatory TNBC specimens (Robertson et al. SABCS, P3-01-18). The status of ALK, full-length or fused, in non-inflammatory TNBC has not been described. Identification of a biomarker such as ALK in TNBC would be clinically significant, given the ongoing development of multiple ALK inhibitors. We screened for ALK expression in TNBC specimens with a novel patented qRT-PCR assay (Insight ALK Screen). **Methods:** We tested archived formalin-fixed, paraffin-embedded blocks of TNBC tissue. Evaluable specimens had sufficient tumor material for 10 slides with 5-micron sections. Insight ALK Screen was performed using previously described methodology (Hout, et al. AACR 2011, Abstract 2220). We subjected ALK Screen positive specimens to ALK break-apart FISH (Vysis) and direct sequencing analysis. **Results:** See clinical characteristics (Table). Insufficient RNA: 8/40 (20%). Insight ALK Screen-positive: 8/32 (25%). Break-apart FISH performed on these 8 specimens suggested 3/8 to be positive for ALK translocation and 2/8 to contain amplification of ALK without a translocation. The ALK-amplified specimens were subsequently confirmed with sequencing of RNA-PCR products to express full-length ALK. One additional ALK Screen-positive, FISH-negative specimen had full-length ALK expression confirmed on sequencing. Further analysis of the other 2 ALK Screen-positive cases is pending. **Conclusions:** ALK expression was seen in ~25% of TNBC specimens screened by Insight ALK Screen. We observed both ALK translocations and amplification/overexpression of full-length ALK. We are testing additional specimens by FISH and immunohistochemistry to evaluate the full spectrum of ALK alterations in TNBC. Updated data will be presented.

Age: median (range)	59 (33-89)
Race: N(%)	
African American	23 (58%)
Caucasian	16 (40%)
Other	1 (2%)
Stage: N(%)	
I	15 (38%)
II	17 (42%)
III	3 (8%)
IV	1 (2%)
Missing	4 (10%)

1068   **General Poster Session (Board #22C), Sat, 1:15 PM-5:00 PM**

Pathologic complete response (pCR) with weekly nanoparticle albumin bound (nab-P) plus carboplatin (C) followed by doxorubicin plus cyclophosphamide (AC) with concurrent bevacizumab (B) for triple-negative breast cancer (TNBC).

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Background: TNBC are mostly "basal-like" tumors, that have been shown to overexpress Secreted Protein Acidic and Rich in Cysteine (SPARC). Endothelial transcytosis of nab-P via albumin- gp60 -cav1 and binding of albumin to SPARC results in high intratumoral levels of nab-P. Exploiting this and the dysfunctional DNA repair in basal tumors, we hypothesized that nab-P + C would produce high rates of pCR in TNBC, further enhanced by antiangiogenesis properties of B. **Methods:** Eligible women had operable TNBC $\geq$ 2 cm. pCR in the breast and pCR in the breast + nodes were primary & secondary end points respectively. We needed 57 evaluable patients to demonstrate 40% pCR vs. 25% (P0) in a single stage phase II design (α: 0.05, β: 0.2).Schema: C AUC 6 d1 + nab-P 100mg/m^{2}d 1, 8 & 15 Q 28 d x 4 cycles followed by AC d1, Q14d x 4 cycles preoperatively with B 10mg/kg Q 14d for the first 6 cycles of preoperative chemotherapy, resuming postoperatively to complete 1 year of treatment.Baseline tumor biopsies & serial serum/blood samples were collected. **Results:** Due to slow accrual, study was closed after 42 patients. They were women between 35 and 68 years of age (median 52); 51% were African American and 46% were node positive. Safety population: N=41. Four patients came off study prior to surgery while 7 are still on pre-op treatment. Grade ¾ hematologic AEs: neutropenia (Gr3: 56%; Gr4:24%) febrile neutropenia (4%), thrombocytopenia (32%), anemia (22%). 7 patients had SAEs, with 1 grade 5 event. To date, thirty of 31 patients who had surgery (efficacy population) are considered evaluable per protocol. In-breast pCR rates are 55% (17/31) and 56% (17/30) and the rates of pCR breast + nodes are 52% (16/31) and 53% (16/30), for the efficacy and evaluable populations respectively. **Conclusions:** Majority of the patients in our study achieved a pCR, which is among the highest rates reported compared to anthracyclines+ taxanes without B in TNBC. Correlative analyses are planned. An ongoing randomized intergroup study is evaluating the individual contributions of carboplatin & bevacizumab to pCR in TNBC. Clinical trial information: NCT00777673.

1069   **General Poster Session (Board #22D), Sat, 1:15 PM-5:00 PM**

Insurance status as a strong predictor of outcome in triple-negative breast cancer (TNBC): A multi-institutional retrospective study.

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Background: TNBC accounts for about 15-20% of all breast cancer. TNBC has particularly aggressive clinical course and accounts for a disproportionate number of breast cancer relapses and deaths in early stage disease. TNBC also have worse prognosis especially in African American (AA) women compared with white women. This retrospective study aims to investigate various clinical and demographic prognostic factors in TNBC. **Methods:** 476 TNBC patients who were treated at Eastern Carolina University and University of North Carolina, CH between 4/96 and 9/11 were included in this analysis. We collected data on age, race, grade, lymphovascular invasion (LVI), stage, treatments including surgery, chemotherapy, radiation, chemotherapy drugs, insurance type and year of treatment. Overall Survival (OS) was computed from the date of diagnosis to the date of death or last FU. For disease free survival (DFS), patients were scored if they failed either locally or distally. The Cox proportional-hazards regression model was used to compute hazard ratios. **Results:** The median age was 52 years (21-88 years) with median FU of 3.7 years. 49% women were white race followed by AA 223 (47%) and Hispanic or other race (5%). Stage (p<0.001), grade (p=0.02), surgery (p<0.0001), adjuvant chemotherapy (p=0.025), LVI (p=0.05) and type of insurance were significant predictor of OS. Similarly, stage (p<0.0001), surgery (p<0.0001), LVI (p=0.03) and insurance were significant predictors for DFS. On multivariate analysis, stage, surgery and adjuvant chemotherapy remained statistically significant predictors. Medicaid vs. Private Insurance also remained a significant detriment of survival (OS: HR=3.6, p<0.0001; DFS: HR=2.8, p<0.0001) as did having No Insurance for OS (HR=2.0, p=0.0074). **Conclusions:** To our knowledge, this is a largest retrospective study showing type of insurance to be a strong predictor of outcome in this very specific breast cancer subtype which remained significant after adjusting all other variables. Further insight is needed to determine the cause of this finding.

1070   **General Poster Session (Board #22E), Sat, 1:15 PM-5:00 PM**

Claudin 1, 3, 4, and 7 expression in triple-negative breast cancer.

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Background: Triple negative breast cancer (TNBC) often grows rapidly and has poor prognosis, with a high recurrence rate. Because conventional endocrine treatment and HER2 targeted therapy for TNBC is invalid, chemotherapy is the only systemic treatment for TNBC. It is known that several subtypes within the TNBC show different responses to chemotherapy, depending on the subtypes. Recently, a claudin (CLDN) low breast cancer has been identified, exhibiting low expressions of CLDNs 1, 3, 4 and 7. CLDNs are transmembrane proteins that seal tight junctions and are critical for maintaining cell-to-cell adhesion in epithelial cell sheets. However, their role in cancer progression remains largely unexplored. **Methods:** Surgically removed, formalin-fixed, paraffin-embedded breast cancers from 341 TNBC patients were analyzed to identify CLDN expression.They underwent wide local excision or mastectomy between March, 2004 and December, 2007 at the breast surgery unit of Asan Medical Central Hospital. **Results:** In our tumor series, we found 45.0% (153/339) of high expressing cases for CLDN1, 57.0% (192/337) for CLDN3, 57.6% (194/337) for CLDN4 and 44.0% (149/339) for CLDN7. Overall, we found 20.5% (70/341) of cases were within the low CLDN expression group and 79.5% (271/341) of tumors were within the high expression group of CLDN1, 3, 4 ,7. Although the high CLDN expression group was significantly associated with positive lymph node status and higher stage, there were no significant differences between CLDN low and high groups in disease free survival (p=0.477) or overall survival (p=0.253). **Conclusions:** CLDN high tumors are associated with poor prognosis features, but they are not an independent prognostic factor in TNBC patients. However, the mechanisms underlying the different roles of CLDNs in tumorigenesis are largely unclear. Studying the associations of these CLDNs with the TNBC subgroup of breast cancers might provide us with potential diagnostic biomarkers or therapeutic targets for cancer cells.

1071   **General Poster Session (Board #22F), Sat, 1:15 PM-5:00 PM**

Efficacy and safety of metronomic capecitabine and gefitinib in heavily pretreated metastatic triple-negative breast cancer.

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Background: Metronomic chemotherapy regimens have shown efficacy in patients with metastatic breast cancer by antiangiogenic mechanisms. When used metronomically the toxicity profile of capecitabine is low. Triple negative breast cancer is a common problem in India and developing countries. Approximately 30% of triple negative breast cancer express EGFR and its mutation. **Methods:** Since October 2003 to December 2011 we objectively tested response rates, clinical benefit, and safety of gefitinib and capecitabine administered with a metronomic schedule of 500 mg thrice daily in heavily pretreated metastatic breast cancer patients with gefitinib 250 mg once daily. 300 patients were screened for EGFR expression. Among 85 enrolled patients with EGFR positivity, 76 were evaluable. ECOG performance status (PS) was 0-2, median age 52 years (range 36-65), bone plus visceral metastasis in 40% of patients. Rest had only visceral metastasis. All the patients were pretreated with anthracyclines and taxanes. The combination was administered for a median duration of 32 weeks (range 12-166). **Results:** We observed 18 partial responses (PR: 24%), 42 (55%) stable disease (SD). Median time to progression was 53 weeks, (95% CI, range 12-166 weeks). Safety of metronomic capecitabine with gefitinib was excellent. Neither grade 2-4 haematological or clinical side effects were recorded. Only 12 patients experienced grade I (WHO) hand-foot syndrome. **Conclusions:** Treatment with metronomic capecitabine and gefitinib was effective and minimally toxic in heavily pretreated breast cancer patients.

1072   **General Poster Session (Board #22G), Sat, 1:15 PM-5:00 PM**

Plasma VEGF-a, angiopoietin-2 (ANG2) and soluble(s)TIE2 in patients (pts) with HER2-negative locally recurrent or metastatic breast cancer (LR/MBC) treated with first-line bevacizumab (A) and paclitaxel (T) without or with capecitabine (X).

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Background: In the randomized phase II ATX trial, pts with HER2-negative LR/MBC were treated with first-line AT or ATX. We determined the prognostic value for outcome of VEGF-A, ANG2 and sTIE2 measured at baseline on cycle 1 day 1 (C1D1) and after cycle 1 (C2D1). **Methods**: 312 pts were randomized in 1:1 ratio to AT (T 90 mg/m^2 on d1, 8, 15 and A 10 mg/kg on d1, 15 q4w x 6 cycles, followed by A 15 mg/kg on d1 q3w for next cycles) or ATX (T 90 mg/m^2 on d1, 8, A 15 mg/kg on d1 and X 825 mg/m^{2}bid on d1–14 q3w x 8 cycles, followed by the same dose of A and X q3w for next cycles). The primary endpoint was progression-free survival (PFS). Secondary endpoints were objective response rate (ORR), response duration (RD), overall survival (OS) and safety. Plasma proteins on C1D1 (N = 173) and on C2D1 (N = 142) were measured by ELISA. The association of protein levels (continuous variable) with PFS and OS was evaluated by Cox proportional hazards model and Martingale residual plot. **Results:** At a median follow-up of 39 months (mo), there were 292 PFS events and 242 deaths. ATX significantly improved PFS as compared to AT (median 11 vs. 8.4 mo, stratified HR = 0.52; 95% CI, 0.41 – 0.67; $P < .001$). The confirmed ORR in measurable disease (N = 268) was 67% in ATX vs. 50% in AT. Median RD was 6.4 mo (95% CI, 6.1 – 8.3) in ATX v 5.4 mo (95% CI, 5.1 – 6.0) in AT. Median OS was 24.1 mo in ATX vs. 23.1 mo in AT ($P = .44$). The aselected 'biomarker' cohort (N = 173) and overall trial cohort had similar baseline characteristics. ANG2 on C1D1 moderately correlated with sTIE2 on C1D1 (Pearson's r = .44, $P < .001$). High ANG2 on C1D1 was significantly associated with poor OS (HR = 1.6; 95% CI, 1.1 – 2.3; $P = .01$), but not with poor PFS (HR = 1.3; 95% CI, 1.0 – 1.3; $P = .07$). ANG2 on C2D1 was not significantly associated with OS (HR = 1.55; 95% CI, 0.99 – 2.4; $P = .057$) or with PFS ($P = .6$). sTIE2 and VEGF-A were not associated with outcome. All pts had very low levels of free VEGF-A on C2D1 (median 8 pg/ml). **Conclusions:** In HER2-negative LR/MBC, ATX is more effective (PFS, ORR and RD) than AT. A very high plasma level of ANG2 at baseline indicates a high risk for poor survival. Clinical trial information: NTR1348.

1073 General Poster Session (Board #22H), Sat, 1:15 PM-5:00 PM

Sixteen years follow-up results of a randomized phase II trial of neoadjuvant FAC compared with CMF in stage III breast cancer.

Ariel Osvaldo Zwenger, Julieta Leone, Carlos Teodoro Vallejo, Juan Eduardo Perez, Alberto Omar Romero, Mario Raul Machiavelli, Luis Romero Acuna, Maria Ester Dominguez, Mario Langui, Hebe Margot Fasce, Bernardo Amadeo Leone, Eduardo Ortiz, Jose Pablo Leone, Julian Iturbe; Grupo Oncologico Cooperativo del Sur, Neuquen, Argentina; Hospital Provincial Neuquen, Neuquen, Argentina; Grupo Onc Cooperativo del Sur, Bahia Blanca, Argentina; Grupo Oncologico Cooperativo Del Sur, Santa Fe, Argentina; Grupo Oncologico Cooperativo Del Sur, Tres Arroyos, Argentina; Grupo Oncologico Cooperativo Del Sur, La Plata, Argentina; Grupo Oncologico Cooperativo Del Sur, La Pampa, Argentina; University of Pittsburgh Cancer Institute, Pittsburgh, PA

Background: Neoadjuvant chemotherapy allows direct evaluation of the tumor's sensitivity to therapy, eradication of micrometastatic disease and the possibility of performing breast conserving surgery. The aim of this study was to describe long-term results of neoadjuvant chemotherapy in stage III breast cancer patients (pts). **Methods:** We evaluated 126 pts with stage III breast cancer that participated in a phase-II randomized trial of neoadjuvant 5-fluorouracil, doxorubicin and cyclophosphamide (FAC every 21 days) compared with cyclophosphamide, methotrexate and 5-fluorouracil (CMF days 1 and 8 every 28). Chemotherapy was administered for three cycles prior to definitive surgery and radiotherapy, and then for six cycles as adjuvant. Response was assessed by WHO criteria. **Results:** Pts characteristics were well balanced in both groups (FAC: 64pts, CMF: 62pts). Median follow-up was 4.5 years (range 0.2-16.4). No significant difference was found regarding acute and long-term toxicity; however, alopecia was more frequent in FAC group. Breast conserving surgery was performed in 13.5% of pts with no difference between groups. Objective response rate (OR) was similar in both groups but pathological complete response was achieved by 4 pts who received FAC. Although both groups had similar locoregional and distant recurrences, contralateral breast cancer was higher in the CMF group (6.5% vs 1.6%, P=NS). Disease free survival (DFS) and overall survival (OS) data are shown in the table. After 16 years of follow-up, 42.1% (n=53) of pts are still alive. Disease progression was the principal cause of death in both groups (78.9% vs 84.2%). **Conclusions:** To the best of our knowledge, this is the first study to report long-term outcomes of FAC and CMF in the neoadjuvant setting. Within the sensitivity of our study, both regimens showed similar OR, long-term toxicity, DFS and OS rate at 16 years. Around 40% of pts are currently alive. Clinical trial information: NCT00002696.

	FAC	CMF	P value
OR (CR+PR)	60.9%	65.6%	NS
Median DFS	5.1 years	3.3 years	NS
Median OS	6.7 years	6.3 years	NS
OS at 16 years	13.7% (95%CI= 3.8-38.8)	31% (95%CI= 17.8-48.2)	NS

1074 General Poster Session (Board #23A), Sat, 1:15 PM-5:00 PM

Assessing the impact of CMF/FEC/FEC-DOC/ETC (dose-dense) adjuvant chemotherapy in dependency of positive axillary lymph nodes on survival: A retrospective multicenter cohort study of 4,526 breast cancer patients receiving adjuvant chemotherapy.

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Background: Adjuvant chemotherapy has changed dramatically in the last decades. Anthracycline-/taxane-based and dose-dense chemotherapy regimens improved survival in node positive breast cancer. This study tries to answer the following questions: (1) Are there differences in survival dependent on chemotherapy regimens in 0/0-3/4-10/<10 positive lymph nodes? (2) Is it possible to define a cut-off of positive lymph nodes for the use of Taxane-based and dose dense chemotherapy? **Methods:** This German is a multi-center [17 participating hospitals all are certified as breast cancer centers] retrospective cohort study. We included CMF (1.385), FEC (1.170), FEC-DOC (1.723), and dose-dense ETC (248) into the analysis. **Results:** In case of 0 LN CMF/FEC/FEC-DOC did not show significant differences in DFS, but OAS was significantly impaired by the use of FEC-DOC in 0 LN [p=0.024; HR=2.02 (95% CI: 1.10-3.73)] (no ETC use in 0 LN). In case of 1-3 positive LN CMF/FEC/FEC-DOC/ETC did not differ significantly in survival parameters. But in 4-10 LN FEC-DOC [p=0.049; HR=0.67 (95% CI: 0.44-0.99)] and ETC [p=0.024; HR=0.56 (95% CI: 0.34-0.93)] demonstrated a significant benefit in DFS and a strong trend in OAS. Dose-dense ETC showed a significant improvement in DFS [p=0.003; HR=0.35 (95% CI: 0.17-0.69)] and OAS [p=0.009; HR=0.35 (95% CI: 0.16-0.77)] in patients with >10 positive LN. **Conclusions:** Our data confirms that Taxane-based chemotherapy does not improve DFS in LN negative breast cancer, but rather demonstrated an inferior OAS. But in LN positive breast cancer we can demonstrate a benefit by the use of Taxane-based chemotherapy regimens. Furthermore, dose-dense ETC demonstrated a significant benefit in survival in >10 positive LN.

1075   **General Poster Session (Board #23B), Sat, 1:15 PM-5:00 PM**

The effect of HCV serological status on doxorubicin-based chemotherapy-induced toxicity and disease-free survival in breast cancer patients.

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Background: Breast cancer and HCV are two frequent diseases in Egypt. There is a considerable probability of concurrent affection. This concurrence creates a subpopulation which needs special evaluation and care. **Methods:** To evaluate a subset of Egyptian breast cancer patients receiving doxorubicin based adjuvant chemotherapy, with HCV seropositivity (Group 2) compared to HCV seronegative patients (Group 1). 102 breast cancer patients, planned to receive Doxorubicin based adjuvant chemotherapy, at the Oncology Department, Alexandria Faculty of Medicine, were recruited since June 2009. Pretreatment evaluation included serological testing for HCV. FAC adjuvant chemotherapy was given. **Results:** HCV seropositivity was detected in 52 cases. Two cases in Group 2 developed toxic hepatitis and discontinued treatment and follow up. The remaining 100 patients suffered comparable toxicities, except for more frequent SGOT and SGPT elevations in Group 2. Diarrhea was more frequent in Group 2. Treatment delays and dose reductions were more frequently observed in Group 2. The 24 month disease-free survival and relapse pattern were not significantly different between the two groups. **Conclusions:** Patients receiving chemotherapy should undergo screening for the virus. Most patients with HCV were able to tolerate chemotherapy and continue the initial chemotherapy plan, without significant change in the toxicity profile or the natural course of their malignancy. Dose or regimen adjustments may be of help to less tolerant patients. A preemptive 10% initial Doxorubicin dose reduction might reduce the frequency of severe toxicity. The assistance of a gastroenterologist in HCV positive breast cancer patients, planned for chemotherapy is important.

1076   **General Poster Session (Board #23C), Sat, 1:15 PM-5:00 PM**

Clinical impact of febrile neutropenia (FN) increase among patients receiving adjuvant docetaxel/cyclophosphamide (TC) chemotherapy compared to TC plus pegfilgrastim for breast cancer.

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Background: The FN rate for the approved regimen of TC is 5% in pivotal studies. Other small retrospective reports have reported FN rates as high as 20-35%. We report the incidence of FN from a large retrospective series of breast cancer patients receiving TC with or without pegfilgrastim (PF) for adjuvant therapy. **Methods:** We reviewed records of 240 sequential patients who had received adjuvant TC (75 and 600 mg/m^2) between Mar '07 and Nov '12 for FN, upfront PF use, and adverse events by treatment cohort. FN was defined as T> 100.4°F and ANC <500, while upfront PF was defined as PF given at physician discretion 24-48h after 1st cycle of TC administration. Comparisons between two proportions used exact binomial methods; effect of PF on FN after adjusting for baseline characteristics was tested using multivariate logistic regression. **Results**: 153 (63.7%) patients received upfront PF, while 87 (36.3%) did not (Table). Patients receiving upfront PF were older (57 vs. 52 yrs, p=0.02). Other baseline characteristics (size of primary tumor, hormone receptor status, and nodal status) were no different between groups. FN, fever, antibiotic use, hospitalization, and dose delay were significantly higher when upfront PF was not used (Table). The average length of hospital stay was 2.9 days for TC + PF, and 3.8 days for TC pts. 31/87 (35.6%) of patients without upfront PF went on to receive PF after the 1st cycle. **Conclusions**: FN for adjuvant TC meets clinical practice threshold and ASCO guidelines for upfront use of PF. FN-related outcomes such as fever, antibiotic use, dose delays, and number of hospitalizations, and were significantly increased without upfront PF. The cost-effectiveness of these findings will be presented and have major clinical implications for routine care.

Outcome	TC + upfront PF (n=153)	TC (n=87)	Adjusted odds ratio	P value
Febrile neutropenia	6 (4%)	26 (30.0%)	0.10	<0.0001
Hospitalization	17 (11.1%)	33 (38.0%)	0.19	<0.0001
Fever	28 (18.3%)	35 (40.2%)	0.32	0.0004
Antibiotic use	43 (28.1%)	40 (46.0%)	0.43	0.004
Dose delay	7 (4.6%)	10 (11.5%)	0.33	0.046
Dose reduction	13 (8.5%)	8 (9.2%)	0.83	0.71

1077   **General Poster Session (Board #23D), Sat, 1:15 PM-5:00 PM**

Development and validation of a model and web application to predict 5-year distant relapse-free survival in women receiving neoadjuvant chemotherapy.

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Background: Response to neoadjuvant chemotherapy (NAC) is an increasingly recognized intermediate marker for prognosis, but we still lack validated prognostic tools that incorporate tumor factors and response. This study aimed to create a prognostic model and nomogram for 5-year distant relapse-free survival (DRFS) and to develop a web application for providers and patients to predict the probability of distant relapse within 5 years. **Methods:** The prognostic model was developed using data from patients treated with NAC in the UNC Neoadjuvant Database and the Cox proportional hazards method. Patients who received NA trastuzumab were included in model data, but patients who received NA endocrine therapy were not included. The model was internally validated with bootstrap resampling, and externally validated with an independent, public data set (n=411) (Cancer Res 2011;71(24 Suppl):Abs S5-2). A web tool was developed to calculate probability of 5-year DRFS. **Results:** Four-hundred and seven stage I-III patients, including 106 relapse events, were used for model development. The following factors were ultimately included in the model: RCB class, age, overall grade, HER2 status, hormone receptor (HR) status, and an interaction term between age and HR status. Validation showed agreement between predicted and observed outcomes in all patients and more specifically HR+/HER2- and HR-/HER2- patients (Table). There were an insufficient number of HER2+ patient in the validation data to reliably analyze that subgroup. **Conclusions:** An externally validated predictive modelincorporating patient, tumor, and response variables is accurate in predicting 5-year distant relapse risk for patients undergoing NAC. The model can be conveniently accessed as an online application at www.NeoadjuvantRelapse.info for precise risk prediction.

Predicted and observed outcomes in external validation cohort.			
Subgroups	**Predicted 5-yr DRFS (95% CI)**	**Observed 5-yr DRFS (95% CI)**	**C-index**
All patients (n=411)	0.74 [0.72, 0.76]	0.73 [0.68, 0.78]	0.75
HR+/HER2- (n=258)	0.76 [0.74, 0.78]	0.80 [0.74, 0.86]	0.72
HR-/HER2- (n=146)	0.69 [0.66, 0.73]	0.61 [0.52, 0.71]	0.75

1078 **General Poster Session (Board #23E), Sat, 1:15 PM-5:00 PM**

The impact of patient-related factors on the occurrence of febrile neutropenia in breast cancer patients receiving (neo-)adjuvant chemotherapy with 5-fluorouracil, epirubicin, and cyclofosfamide (FEC) x6 or FEC x3 followed by docetaxel (D) x3.

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Background: Recently we described the impact of genetic variability on severe toxicity in breast cancer patients receiving (neo-) adjuvant FEC chemotherapy (Annals of Oncology 2013, In Press). We now further assessed the impact of a wide range of patient-related factors on FEC toxicity in routine clinical setting. **Methods:** Patients with early breast cancer receiving (neo-)adjuvant 6 cycles FEC or sequential 3 cycles of FEC and 3 cycles D were retrospectively evaluated through electronic chart review for febrile neutropenia (primary endpoint; CTC 3.0). Age at diagnosis, body mass index, body surface area, number of cycles received, germline genetic polymorphisms, and baseline biochemical variables (white blood cell count, absolute neutrophil count, platelets, aspartate aminotransferase, alanine aminotransferase, total bilirubin and creatinine) were available for most patients (missing data <10%). All patients had follow up for progression free survival (PFS) and overall survival (OS). Multivariate logistic regression analysis was performed including univariate associates of outcome with a p-value <0.25. **Results:** We identified 1,031 patients treated between 2000-2010 with 6x FEC (n=488) or 3x FEC followed by 3x D (n=543). 174 (16.9%) patients developed febrile neutropenia during FEC. After logistic regression analysis febrile neutropenia was found to be significantly associated with carriers of the rs45511401 variant T-allele in the MRP1 gene found in 12% of patients (p= 0.03, OR1.99, CI 1.07-3.71) and with increasing serum creatinine values (p=0.05 OR 4.58/CI 0.99-20.98); all other investigated patient-related parameters were not retained by the model. At a mean follow up of 5.2 years, the occurrence of febrile neutropenia was not correlated with PFS and OS. **Conclusions:** In this study, only the baseline level of serum creatinine and germline genetic polymorphisms in the MRP-1 gene were predictive for the occurrence of febrile neutropenia in patients receiving FEC chemotherapy. The occurrence of febrile neutropenia did not seem to impact on outcome.

1079   **General Poster Session (Board #23F), Sat, 1:15 PM-5:00 PM**

A multicenter audit of the incidence of febrile neutropenia and neutropenia associated with docetaxel and cyclophosphamide (TC) chemotherapy for early breast cancer.

Roopa Lakhanpal, Robin Stuart-Harris, Arlene Chan, Dusan Kotasek, Jane McNeil Beith, Katharine Cuff, Patricia A. Bastick, Clara Inkyung Lee; Department of Medical Oncology, The Canberra Hospital, Canberra, Australia; Department of Medical Oncology,The Canberra Hospital, Canberra, Australia; Mount Hospital, Curtin University, Perth, Australia; Adelaide Cancer Centre, Adelaide, Australia; Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, Australia; Cancer Trials Unit, Woolloong- abba, Australia; St George Public Hospital, Sydney, Australia; Westmead Hospital, Sydney, Australia

Background: A 2006 US Oncology trial reported that four cycles of docetaxel and cyclophosphamide (TC) resulted in better disease free and overall survival than four cycles of doxorubicin and cyclophosphamide (AC) in women with early breast cancer (EBC) and TC is now a frequently used adjuvant chemotherapy regimen for EBC. The 2006 trial reported that TC was associated with a 5% incidence of febrile neutropenia (FN), but others have noted a higher incidence of FN. **Methods:** We have conducted a multicentre retrospective audit of women with EBC treated with TC between January 2010 and July 2011, recruited from seven Australian centres. The primary endpoints of the study were the incidence of FN associated with the use of TC and also the incidence of grade 3 or 4 neutropenia during cycle one of TC. Patients receiving prophylactic granulocyte colony stimulating factor (G–CSF) or prophylactic antibiotics were excluded. **Results:** Of a total of 368 previously untreated women with EBC who received TC, 300 were evaluable for FN. The median age of the patients was 57 years. Overall, 73 (24.3%) patients developed FN. The highest incidence of FN was seen after cycle one (91.8%) of TC and the incidence of FN appeared higher in women under the age of 65 years. Of 304 patients evaluable for neutropenia during cycle one, eight (2.6%) developed grade 3 neutropenia and 191 (62.8%) developed grade 4 neutropenia. **Conclusions:** This is the largest study to date which reveals that TC is associated with a high incidence of grade 4 neutropenia and a high incidence of FN. The incidence of FN is above the 20% threshold for the use of G-CSF as primary prophylaxis as recommended by The EORTC and The National Comprehensive Cancer Network. Therefore, we recommend that G-CSF be considered as primary prophylaxis when TC is used as adjuvant chemotherapy for EBC.

1080   **General Poster Session (Board #23G), Sat, 1:15 PM-5:00 PM**

Community use of anthracyclines in metastatic breast cancer (MBC).

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Background: For decades, anthracyclines have been among the most useful treatments for women with MBC. Though recent publications have confirmed an overall decline in the use of anthracyclines in BC, most of that decline was felt to be due to its diminished utilization in the adjuvant management of BC. Current community anthracycline usage pattern in MBC is not known. We investigate and report, herein, how community oncologists in the southeast USA are currently utilizing anthracyclines for MBC. **Methods:** All chemotherapy treatment requests for HER2+ and HER2- Stage 4 BC were examined, from 2009 through 2012. Chi-Square test was performed for interaction between age and anthracycline utilization, with p-value less than 0.05 considered significant. The proportion of women who had been treated previously in the adjuvant setting with low cumulative doses of anthracyclines, which would have some effect upon subsequent use, was not retrievable. **Results:** During this span, 420 unique chemotherapy requests were initiated for 247 patients. These included 54 anthracycline requests for 50 MBC patients. The use of anthracyclines for metastatic HER2+ BC was virtually absent (one in 63 requests among 42 patients). The remaining 357 chemotherapy requests were for treatment of 205 HER2- MBC patients. Anthracyclines were employed in 22% of women under 65 years of age and in 25% of those older than 65 (p = 0.77). Approximately 83% (45/54) of anthracycline-requests were for conventional doxorubicin, either alone or in combination with other agents. The rest were for liposomal doxorubicin (6/54) or epirubicin (3/54). **Conclusions:** Data from the southeast USA identifies that anthracyclines are virtually never used in HER2+ MBC. Even in HER2- MBC, anthracyclines are used in only one out of 4 patients suffering from this disease. The effect of this unheralded alteration in oncology practice must be carefully considered when trends in metastatic breast cancer control are examined.

Age at first chemotherapy request	At least one line of therapy with anthracyclines in HER2- MBC	Therapy included only non-anthracycline chemotherapy in HER2- MBC
Age < 50 (n = 18)	4 (22%)	14 (78%)
Age 50-<65 (n = 49)	11 (22%)	38 (78%)
Age ≥ 65 (n = 138)	34 (25%)	104 (75%)

1081   **General Poster Session (Board #23H), Sat, 1:15 PM-5:00 PM**

Effect of capping chemotherapy dose on chemotherapy effect in morbidly obese women with breast cancer.

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Background: Obesity adversely affects outcomes from adjuvant (adj) chemotherapy for breast cancer. Capping of chemotherapy dose has been implicated as one factor that may contribute to this. We postulated that if capping resulted in underdosing, this would be reflected in the incidence of dose dependent toxicities (DDT) such as mucositis and haematological toxicity. **Methods:** We retrospectively reviewed records of breast cancer patients (pts) commencing adj chemotherapy from 1 Jan 2010-31 Dec 2010 at the Auckland Regional Blood and Cancer Service identified using a prospective pharmacy database. Baseline characteristics, BSA, body mass index (BMI), neutrophil (ANC) nadir, relative dose intensity (RDI) and dose limiting complications (DLC) were recorded. **Results:** 174 pts were identified. Median age was 49 yrs (24-73). 17.8% had a BSA >2. 3.2% pts with BSA>2 had BMI <30. 42% had a BMI ≥30 (17.9-61.0), of whom 59% had a BSA ≤2. All patients with BSA >2 had dose capping. 71 pts had a DLC. Neutropenic fever/infection or treatment delays from neutropenia were more common if BSA ≤2 vs. >2 (p=0.08) but not with other DDT. Treatment deferrals (18.8 vs. 16.1%) dose reductions (25.2 vs. 32.3%) and mucositis were similar in both groups. Mean baseline ANC was 4.4 in pts with BSA ≤2 and >2. Mean ANC nadir was 0.8 and 1.3 respectively (p<0.01). r^2BSA vs nadir ANC was 0.012. G3/4 neutropenia was seen 76.5% of pts with BSA ≤2 vs. 44.8% if BSA >2 (RR 1.3 p<0.01). No pt had > G1 thrombocytopenia. Mean RDI was 93.2 and 94.8 respectively (p=0.4) **Conclusions:** Previous studies show ANC nadirs correlate well with drug exposure (area under plasma concentration vs. time curve) but poorly with BSA. Therefore we used hematological and DDT as surrogate measures for drug exposure in pts with and without capped doses. There was more G3/4 neutropenia (p<0.01) in uncapped pts but rates of other DDT were similar. Since BSA based dosing has little impact on inter-pt variability in systemic drug exposure and trials where capping was not used still show a poorer outcome in obese pts, these results suggest dose capping is a minor contributor to the worse outcomes in morbidly obese breast cancer pts having adj chemotherapy. Addressing obesity itself may be more important.

1082   **General Poster Session (Board #24A), Sat, 1:15 PM-5:00 PM**

A randomized phase III study to determine the efficacy of capecitabine in addition to a taxane and bevacizumab as first-line therapy in patients with metastatic breast cancer.

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Background: Conventional chemotherapy combined with novel molecular targeted agents has been proven effective and tolerable in metastatic breast cancer (MBC). Taxanes (T) plus bevacizumab (B) and T plus capecitabine (X) showed a benefit in progression free survival (PFS) compared to T alone. Life-threatening or highly symptomatic situations require poly-chemotherapies in MBC patients; therefore a combination of all 3 drugs appears reasonable. **Methods:** TABEA (NCT01200212) is a prospective, randomized, open label, phase III trial comparing T plus B +/- X as 1st-line therapy in MBC. Patients with histologically confirmed HER2- locally advanced or MBC were included. All patients received T (paclitaxel 80 mg/m2 i.v. d1,8,15 q22 or docetaxel 75 mg/m2 i.v. d1 q22) and B (15 mg/kg i.v. d1 q22) (TB) and were randomized to X (1800 mg/m² daily d1-14 q22) in addition and concurrently to TB (TBX) or TB alone. Randomization was stratified by receptor status, planned taxane, and disease free interval ($\leq$ or $>$12 months). Primary objective was PFS. Secondary objectives were response rate and duration, clinical benefit rate (CR, PR, stable disease $\geq$ 24 weeks), 3yr overall survival, PFS in patients $\geq$ 65 years, toxicity, and compliance. Sample size calculation assumed a PFS of 10 and 13.3 months for TB and TBX, respectively (HR=0.75) requiring 432 patients and 386 events with 2-sided α=0.05 and β=0.2. Interim analysis was planned after 25% of required events (n=96). **Results:** Planned interim futility and safety analyses after 100 documented events in 202 patients have shown no efficacy benefit and higher toxicity in the TBX arm. For PFS, HR=1.061, 95% CI (0.715, 1.576) was observed, futility boundary was crossed. Overall grade 3-4 adverse events (e.g., thrombopenia, diarrhea, hand-foot-syndrome) (72.3 vs. 57.4%, p=0.039)and serious adverse events (40.6 vs. 24.8%, p=0.016) rates were higher for TBX after 16.3 months median follow up. There were 6 deaths in the TBX vs. 1 in the TB arm. Recruitment and therapy were stopped on 5th Oct 2012 following the advice from the IDMC. **Conclusions:** TABEA failed to show an improvement using the 3 drug regimen TBX in high-risk MBC patients. Clinical trial information: NCT 01200212.

1083 General Poster Session (Board #24B), Sat, 1:15 PM-5:00 PM

Chemotherapy (CTX) treatment patterns for early-stage breast cancer (ESBC): Changing use of anthracyclines (A).

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Background: Anthracyclines (A), given in sequence or combination, have been the mainstay of adjuvant CTX for ESBC. Recent molecular studies have questioned the value of A for ESBC. Trials for ESBC, presented primarily in 2005, have demonstrated similar or improved efficacy with non-anthracycline (NA) CTX. We sought to understand changing use of A for ESBC from 2000-2010 as reported in the population-based 9-county Greater Bay Area Cancer Registry (GBACR). **Methods:** Using the GBACR database, we recorded use of A or NA based CTX regimens in women with ESBC and no prior CTX from 2000-2010, and correlated type of CTX with tumor stage, receptor status, and age. We evaluated the use of A vs. NA (80% taxane-based) CTX from 2000-2005 and 2006-2010. **Results:** 16,476 patients (pts) met criteria for inclusion; 2,032 (12%) were excluded (missing information, or CTX not given). Pt characteristics were: median age 52 (range 21-94), stage I (25%), II (56%), and III (19%), 69% HR+. From 2000-2010, 83% received A; overall use of A decreased (87% to 57%), and use of NA increased (13% to 43%). The Table compares use of NA CTX during the two time periods by clinical variables. With short follow-up there was no difference in survival based on use of A vs. NACTX. **Conclusions:** Use of NA CTX significantly increased during 2006-2010; this trend was independent of age or receptor status and was more pronounced in earlier stage disease. The timing of this change correlated with the presentation of two phase III trials, emphasizing the impact of early data from phase III trials on treatment practice, and confirming results from a large claims database (Giordano). Potential outcome differences will be evaluated in NSABP-B49 and with longer follow-up of this cohort. This study was supported by the UCSF Cancer Registry and CPIC.

	2000-2005		2006-2010		
	Total	NA (%)	Total	NA (%)	p
Stage					
Total	7,804	597 (7.6)	6637	1,931 (29.1)	<0.0001
I	1,953	186 (9.5)	1612	797 (49.4)	<0.0001
II	4,666	346 (7.4)	3466	886 (25.6)	<0.0001
III	1,185	65 (5.5)	1559	248 (15.9)	<0.0001
Subtype					
HR+	5,261	400 (7.6)	4,700	1,390 (29.6)	<0.0001
HR-/Unk.	2,543	197 (7.7)	1,937	541 (27.9)	<0.0001
Age					
< 39	886	35 (4.0)	679	130 (19.1)	<0.0001
40-59	4,958	299 (6.0)	3,999	1065 (26.6)	<0.0001
≥ 60	1,960	263 (13.4)	1,959	736 (37.6)	<0.0001

1084   **General Poster Session (Board #24C), Sat, 1:15 PM-5:00 PM**

Neoadjuvant versus adjuvant chemotherapy with taxanes and anthracycline-based regimen: Which leads to better outcome in patients with different subtype breast cancer?

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Background: Neoadjuvant chemotherapy was reported to lead to equal outcome with adjuvant therapy in operable breast cancer. However, different molecular subtypes show variant response to chemotherapy, which is associated with different long-term prognosis. This study was to clarify whether molecular subtypes lead to different outcome between neoadjuvant and adjuvant chemotherapy. **Methods:** We identified 406 patients with stage II-III breast cancer who were treated with neoadjuvant or adjuvant chemotherapy between 2000 and 2008. To minimize the confounding bias, only patients received taxanes and anthracycline based regimen (TA) were included. Cases were divided according to receipt of neoadjuvant and adjuvant therapy. Data were compared using χ^2 test and analysis of variance. Kaplan-Meier Curves were generated. **Results:** Of the 406 patients, 201(49.5%) received neoadjuvant chemotherapy and 205(50.5%) received adjuvant TA regimen. The pCR rate was 12.9%(26/201) in total, and 7%, 14%, 33.3%, 19.4% for Luminal A, Luminal B, HER2+ and Triple negative breast cancer(TNBC), respectively. The HER2+ and TNBC have significantly higher rates of pCR than Luminal type ($p<0.05$). In general the two groups showed little survival variance ($p=0.073$ for DFS and $p=0.601$ for OS). In Luminal B, neoadjuvant settings led to worse disease free survival (DFS) and overall survival (OS) than adjuvant settings after controlling for the covariates associated with survival in unadjusted tests (HR=0.41, $p=0.028$ for DFS; HR=0.32, $p=0.020$ for OS). In HER2+ subtype, neoadjuvant group corresponded to better DFS and OS (HR=5.65, $p=0.024$ for DFS; HR=10.52, $p=0.010$ for OS). On the contrary, patients with TNBC and Luminal A undergoing neoadjuvant chemotherapy had equal DFS and OS compared with patients receiving adjuvant therapy ($p>0.05$). **Conclusions:** The results demonstrate survival difference between patients receiving neoadjuvant and adjuvant cytotoxic therapy in variant subtypes. Prospective studies are necessary to determine if the finding is durable and optimize the timing of chemotherapy for breast cancer with different molecular background.

1085 General Poster Session (Board #24D), Sat, 1:15 PM-5:00 PM

Quantitative Ki-67 score as predictive of response to neoadjuvant chemotherapy in breast cancer.

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Background: Neoadjuvant chemotherapy is administered prior to surgery for locally advanced tumors but does not confer any additional survival benefit. Measurement of Ki-67, a marker of cell proliferation, has been associated with response to therapy, but methods of measurement are controversial. There is no universal cut-point for association due to subjectivity in threshold for positivity and selection of the field of view. Here we propose that quantitative objective measurement for Ki-67 will provide a reproducible assay for likelihood of response to chemotherapy. **Methods:** A cohort of 115 consecutive (between 2002 and 2010) invasive breast cancer patients that received neoadjuvant therapy were included if pre-surgical biopsies were obtainable. Ki-67 expression was measured using quantitative immunofluorescence (AQUA) technology using the MIB-1 antibody. Images for each specimen were collected in 5 to 100 fields of view (FOV), and summary scores were obtained corresponding to the average and maximum of all the FOVs. **Results:** AQUA scoring was comparable to automated calculation of percent positive nuclei for prediction of response to chemotherapy (OR: 2.832 vs. 2.712). Both average and maximum AQUA scores showed Ki-67 expression was directly correlated to pathological complete response (pCR) (Ave p = 0.0002; Max p = 0.0011). Although examining the maximum field of view was more predictive of response to therapy (OR: 3.546 vs. 2.832), averaging all fields provided more sensitivity and specificity (AUC 0.769 vs. 0.732). Ki-67 average (p = 0.0025) and maximum (p = 0.0239) AQUA scores were also significant predictors of pCR in multivariable analysis with tumor size, nuclear grade, nodal status, ER status, and HER2 status considered. **Conclusions:** Measurement of Ki-67 expression by objective quantitative methods shows increased Ki-67 levels are an independent predictor of response to neoadjuvant chemotherapy. This assay is most sensitive and specific when the average Ki-67 expression from all fields of view is used.

1086   **General Poster Session (Board #24E), Sat, 1:15 PM-5:00 PM**

Polymorphisms interaction to predict bevacizumab (BV) efficacy in metastatic breast cancer (MBC) patients (pts): An exploratory retrospective analysis.

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Background: Previous retrospective studies have attempted to identify a possible role of VEGF single nucleotide polymorphisms (SNPs) to predict BV efficacy in terms of OS and PFS in MBC pts with conflicting results (Schneider 2008, Grimaldi 2011, Lambrechts 2011). **Methods:** On the basis of these preliminary data, we decided to assess in a MBC population if different VEGF, VEGFR-2, IL-8, IL-6, HIF-1alfa, EPAS-1 and TSP-1 genotypes could predict first line BV + paclitaxel (P) response in terms both of OS and PFS. Analyses were performed on germline DNA obtained from blood samples. Fourteen polymorphisms were investigated by real-time PCR technique. Both single and combinations of SNPs were investigated. The multifactor dimensionality reduction (MDR) methodology was applied to identify a genetic interaction profile for PFS (http://sourgeforge.net/projects/mdr/). **Results:** 102 pts have been enrolled from 8 Oncology Units. Main pts characteristics are: median age 59 years (range 32-81), ECOG-PS 0/1 in 78%/22%, hormone receptor positive 83%, previous adjuvant chemotherapy 68%, disease free interval (DFI) < 12 months 27%. After a median follow up of 17.4 months (1.9-54.7), mPFS was 11.6 months (95% CI: 10.6-12.6) and mOS was 32.4 months (95% CI: 25.9-38.9). None of SNPs were individually associated with PFS. Conversely, a genetic interaction profile consisting of VEGFR-2 rs11133360 and IL-8 rs4073 was significantly associated with PFS. mPFS was 14 months (95% CI: 11.7-16.3) and 10.9 months (95% CI: 9.3-12.4) for the favorable and unfavorable genetic profile, respectively (HR=0.63, 95% CI: 0.4-0-99, p= 0.046). Furthermore, at the multivariate analysis hormone receptor positive (HR=0.22, 95% CI: 0.12-0-41, p<0.0001), DFI >12 months (HR= 0.4, 95% CI: 0.2-0.82, p= 0.011) and BV maintenance (HR=0.63, 95% CI: 0.25.0.71, p=0.001) were significantly associated with a better PFS. **Conclusions:** Genetic interaction between VEGFR-2 rs11133360 and IL-8 rs4073 polymorphisms could predict BV response in terms of PFS. With a longer follow-up correlations with OS will be investigated. Prospective study is planned. Study supported by the non-profit foundation F.A.R.O.

1087   **General Poster Session (Board #24F), Sat, 1:15 PM-5:00 PM**

Etirinotecan pegol (EP) target-specific pharmacodynamic (PD) biomarkers measured in circulating tumor cells (CTCs) from patients in the phase III BEACON study in patients with metastatic breast cancer (mBC).

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Background: EP is a unique topoisomerase 1 inhibitor that provides continuous exposure to SN38. EP demonstrated a 29% overall response rate in patients with mBC, leading to a phase III global BEACON study in patients with mBC. CTCs in patient blood samples provide a minimally invasive approach to detect PD markers of drug activity. We developed quantitative multiplex immunofluorescent assays to measure target-specific PD biomarkers for EP in CTCs isolated pre- and post-treatment. **Methods:** Assays for Top1, Top2, g-H2Ax, Rad51, ABCG2, and Ki-67 were developed using control (0.1% DMSO) and drug-treated (SN38, 10 uM) tumor cell lines (HCT116, MCF7, A549, SKBr3) and PBMCs from healthy donors. The optimal antibody for each biomarker was then multiplexed in a panel with antibodies against cytokeratin, CD45 and DAPI for phenotypic identification of CTCs. For analysis of BEACON pts, serial 7.5 mL whole blood samples were drawn and shipped ambient to Apocell (Houston, TX) for further processing. PBMCs were separated and CTCs were isolated using ApoStream technology. CTCs were stained for PD markers and analyzed using an iCys laser scanning cytometer equipped with image analysis software. **Results:** Antibodies bound to tumor cells showed staining confined to the nucleus (Top1, Top2, g-H2AX, Ki-67) or membrane (ABCG2), exhibited defined peak separation from their isotype controls, and signal strength correlated with cellular expression of high and low levels of markers. To date, ~ 80% of BEACON pts consent to participate in the CTC sub-study. As of 30 Oct 2012, data from 167 pre-dose blood samples from BEACON pts were available. 99% of blood samples were successfully processed. 93% had detectable CTCs, yielding a median of 216 CTCs (range: 7.5-14816). Staining was positive for Top1, Top2, g-H2Ax, Rad51, ABCG2, and Ki-67 in 82%, 89%, 16%, 53%, 31%, 52% of samples, respectively. **Conclusions:** EP target-specific pharmacodynamic biomarkers can be reliably measured in CTCs isolated from patients participating in BEACON. Sample collection and analysis of pre- and post-treatment samples is ongoing. Clinical trial information: NCT01492101.

1088   **General Poster Session (Board #24G), Sat, 1:15 PM-5:00 PM**

Association between single nucleotide polymorphism (SNPs) of CYP3A4 and SLC28A3 and clinical outcome in metastatic breast cancer (MBC) patients receiving paclitaxel plus gemcitabine (PG) chemotherapy as first-line treatment.

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Background: Paclitaxel and gemcitabine (PG) combination chemotherapy is an effective regimen in metastatic breast cancer (MBC) patients as first-line chemotherapy. The primary purpose of our study was to investigate the association of the single nucleotide polymorphisms (SNPs) and clinical outcome in MBC patients treated with PG chemotherapy. **Methods:** A total of 324 MBC patients were enrolled in this prospective multicenter trial as the first-line chemotherapy. Eighty five of 324 patients were available for SNP analysis. Germline DNA from peripheral blood (PB) mononuclear cells was extracted. SNPs in 15 genes (27 SNPs) from pathways that may influence cellular sensitivity to paclitaxel and gemcitabine were genotyped from PB sample. **Results:** Median progression free survival (PFS) and overall survival (OS) of all 324 patients was 8.7 months (95% CI: 7.5-9.6 mo.) and 26.9 months (95% CI: 23.6-30.1 mo.), respectively. Among clinical parameters, young age (p = 0.047, HR 1.03 [95% CI, 1-1.07]), positive hormonal receptor status (p = 0.0004, HR 0.26 [95% CI, 0.12-0.54]), and hepatic metastasis (p = 0.046, HR 2.30 [95% CI, 1.02-5.18]) were identified predictive factors for OS in Cox-regression analysis. SLC28A3 SNP which participates in transcription showed correlation with OS. OS of the patients with CC and CT genotypes in SLC28A3 was significantly longer than the OS of the patients with TT genotype (median OS: 31 vs. 37 vs. 21 months, p = 0.027, HR 2.6 [95% CI, 1.1-6.3]). OS of the patients with TT genotype in CYP3A4 was significantly longer than the OS of the patients with TC genotype (median OS: 37 vs. 19 months, p = 0.021, HR 5.8 [95% CI, 1.3-25.7]). After adjusting hormonal receptor status, age, and hepatic metastasis, prognostic value of SLC28A3 remained significant (HR 2.9, p = 0.047). Other SNPs were not significantly associated with PFS, OS, or toxicities. **Conclusions:** SLC28A3 SNP can predict with the clinical outcome of MBC patients treated with PG chemotherapy. Further studies for functional mechanism of germline polymorphisms in SLC28A are warranted.

1089   **General Poster Session (Board #24H), Sat, 1:15 PM-5:00 PM**

Circulating biomarkers in patients receiving neoadjuvant chemotherapy combined with sunitinib for locally advanced breast cancer.

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Background: Biomarkers to guide the use of antiangiogenic therapy are lacking. Circulating endothelial cells (CECs) and their progenitor cells (CEPs) are increased in cancer patients. VCAM is an endothelial protein increased in response to VEGF stimulation, while CAIX is elevated in states of hypoxia; both correlate with tumor aggressiveness. **Methods:** We examined these circulating biomarkers in a phase II neoadjuvant trial in 63 patients (pts) with locally advanced HER2 negative breast cancer treated with 12 weeks (wks) of paclitaxel (T) plus sunitinib (S) followed by 15 wks of daily oral cyclophosphamide and weekly doxorubicin plus daily G-CSF (AC+G-CSF). Toxicity and clinical outcomes are reported as a separate abstract. Blood was collected at baseline, wk 12 and pre-surgery. For this analysis, responders were defined as patients with a pathologic complete response (pCR) and/or MDACC CPS+EG score $\leq$ 2 (a validated score combining clinical and pathologic results for predicting survival in the neoadjuvant setting). Plasma VCAM and CAIX levels were measured by ELISA using commercially available validated kits and CEC/CEPs by flow cytometry in our laboratory as previously published. **Results:** 28 (44%) pts were responders. CECs decreased significantly in response to T+S (p = 0.04) but not further with AC+G-CSF. No significant changes were seen in CEPs. VCAM and CAIX levels increased in pts with baseline levels below the median in response to T+S (VCAM p = 0.0003, CAIX p = 0.009). ER negative tumors had higher levels of plasma VCAM and CAIX at baseline compared to ER positive tumors (VCAM p = 0.01, CAIX p = 0.1). Lower baseline levels of VCAM and CAIX were associated with both response and pCR. VCAM and CAIX levels were correlated at baseline (r = 0.4, p = 0.01). **Conclusions:** CEC, VCAM, and CAIX levels significantly changed after treatment with T + S. Higher baseline levels of VCAM and CAIX were associated with ER negative tumors and lower response rates. Our results suggest that elevated baseline VCAM and CAIX levels are associated with more aggressive biology, and may correspond to less (not more) favorable outcome with the addition of a targeted antiangiogenic agent. Clinical trial information: NCT00513695.

1090   **General Poster Session (Board #25A), Sat, 1:15 PM-5:00 PM**

A phase II study evaluating the safety and efficacy of sunitinib with weekly paclitaxel followed by doxorubicin and daily oral cyclophosphamide plus G-CSF as neoadjuvant chemotherapy (NC) for locally advanced (LABC) or inflammatory breast cancer (IBC).

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Background: Sunitinib (S) is an oral tyrosine kinase inhibitor with anti-tumor and anti-angiogenic activity. The primary objective of this trial was to assess the pathologic complete response rate (pCR) in patients (pts) treated with NC consisting of S with weekly paclitaxel (T) followed by doxorubicin and daily oral cyclophosphamide plus G-CSF (AC+G-CSF). Correlative studies including circulating biomarkers are reported separately. **Methods:** Pts with HER2 negative LABC or IBC were eligible for this multicenter, phase II trial. Pts received S 25 mg po daily with T 80 mg/m^2 IV Qweek (wk) x 12 wks, then AC+G-CSF (doxorubicin 24 mg/m^2 IV Qwk + oral cyclophosphamide 60 mg/m^{2}po daily + G-CSF 5 mcg/kg SC days 2-7) x 15 wks. pCR in the breast and axilla was assessed at surgery, and the MDACC CPS+EG score (validated score combining clinical and pathologic results for predicting survival in the neoadjuvant setting) was calculated. **Results:** 70 pts (ages 33-79) were enrolled; 68 received protocol therapy. 37 (53%) had ER and/or PR positive tumors. 2 patients were unevaluable (hypersensitivity to T, toxicity possibly related to S) and 3 withdrew consent prior to surgery. 61 pts reported any grade AE in S+P period. Among grade 3 or 4 AEs, neutropenia was most common in S+P period occurring in 31/68 (46%). pCR in the breast was observed in 27% (17/63, 95% CI 17%-40%) and breast and axilla in 15/63 (24%). In pts with ER positive tumors, pCR rate in breast was 8/34 (24%) and 9/29 (31%) for pts with ER negative tumors. 18 evaluable pts (29%) had CPS+EG scores ≤2, 40 (63%) had CPS+EG scores of ≥3, and 5 had insufficient information to calculate the CPS+EG score. When response was defined as pCR and/or CPS+EG score ≤ 2, 28 pts (44%) were responders. **Conclusions:** NC with T+S followed by AC+G-CSF was well tolerated. Using a combined definition of response of pCR and/or CPS+EG score ≤2, 28/63 (44%) pts had response; 19/34 (56%) for ER positive and 9/29 (31%) for ER negative disease. The addition of S to NC may result in promising incremental benefit for pts with ER positive breast cancer. Clinical trial information: NCT00513695.

1091 **General Poster Session (Board #25B), Sat, 1:15 PM-5:00 PM**

Randomized phase II trial of gemcitabine versus gemcitabine and imatinib mesylate in patients with previously treated metastatic breast cancer.

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Background: Gemcitabine (GEM) as a standard 30-min infusion has activity as a single-agent in metastatic breast cancer (mbc). Prolonged infusion of GEM at a fixed dose rate (FDR) of 10 mg/m^2/min is associated with greater formation of active metabolite and may result in improved antitumor activity. Imatinib mesylate (IM)-mediated inhibition of PDGFR reduces tumor interstitial fluid pressure allowing for improved chemotherapy penetration into tumors. We evaluated the addition of IM to FDR GEM in patients (pts) with previously treated mbc. **Methods:** This was a randomized phase II trial in mbc pts who progressed after 1 but no more than 2 prior cytotoxic regimens. Eligibility included measurable disease; no prior GEM or IM exposure. Group 1 received FDR GEM IV 1250 mg/m^2 at 10 mg/m^2/min (over 120 min) on days 3 and 10 every 21 days; Group 2 received the same FDR GEM dose and schedule plus IM 400 mg orally daily on days 1-5 and 8-12 every 21 days. Primary endpoint was time to progression (TTP). Sample size of 40 pts per group was needed to detect an 8 mo increase in TTP with the combination (80% power, $\alpha = .05$, 2-sided). Secondary endpoints included ORR and safety. **Results:** Between 5/2006-4/2011, 44 pts were randomized (22 per group). Study closed early due to slow accrual. Median age 54 (31-75); median ECOG PS 1 (0-2); 52% were hormone receptor-positive and HER2-negative; 27% triple-negative, and 20% HER2-positive. Median number of cycles was 2 in Group 1 (range 1-12) and 3.5 in Group 2 (range 1-13). Most common adverse events (%) of any grade, Group 1 vs Group 2 were neutropenia (68 vs. 78), anemia (48 vs. 65), thrombocytopenia (24 vs. 47), nausea (40 vs. 52) and vomiting (24 vs. 21). One gr 4 thrombotic thrombocytopenic purpura occurred in Group 2. Median TTP were 2 mo (95% CI: 1-5 mo) in Group 1 and 2.5 mo (95% CI: 1-5 mo) in Group 2 (p = 0.3 log rank test). ORR was 9.1% in each group (95% CI: 1.6-30.6%), with 2 PRs in each group. Stable disease ($\geq$ 3 mo) was 32% in Group 1 and 41% in Group 2. **Conclusions:** This study was underpowered to draw any conclusion regarding a difference in TTP between the two groups at the time it was prematurely closed. Combination of IM and FDR GEM showed a trend to increased toxicity compared to FDR GEM alone. Clinical trial information: NCT00323063.

1092   **General Poster Session (Board #25C), Sat, 1:15 PM-5:00 PM**

The prognostic and predictive impact of genomic grade index (GGI) versus central grade or molecular class in intermediate-risk breast cancer (BC): Results from the EC-Doc trial.

Oleg Gluz, Cornelia Liedtke, Helene P. Peyro Saint Paul, Ulrike Nitz, Ronald E. Kates, Jens Bodo Huober, Arndt Hartmann, Hans Heinrich Kreipe, Enrico Pelz, Ramona Erber, Walther Kuhn, Nadia Harbeck; West German Study Group; Evangelic Hospital Bethesda, Moenchengladbach, Germany; University Clinics Luebeck, Lübeck, Germany; Ipsogen, Marseille, France; West German Study Group, Moenchengladbach, Germany; University Clinics Tuebingen, Tuebingen, Germany; Institute of Pathology, University Erlangen, Erlangen, Germany; Hannover Medical School, Hannover, Germany; Institute for Pathology, Viersen, Germany; University Clinics Regensburg, Regensburg, Germany; Department of Obstetrics and Gynecology, University Hospital Bonn, Bonn, Germany; Breast Center, Department of Obstetrics and Gynecology, Ludwig-Maximilians-University and West German Study Group, Munich, Germany

Background: Potential markers for adjuvant taxane-based chemotherapy (CTx) in early, intermediate-risk BC include histologic grade (HG), Ki-67, Genomic Grade (GG) or molecular classification. The randomized EC-Doc trial demonstrated improvements in DFS and OS for EC-Doc vs. FEC in patients with 1-3 positive LN. **Methods**: Centrally assessed protein expression data by IHC, histology/HG (n=772) and GG (n=476) were obtained. Luminal A/B classes were defined as: ER/PR+/KI-67<20/>20% and/or HER2+. Correlations/concordance of these factors were estimated; impact on DFS and value for predicting taxane-based CTx benefit was assessed. **Results**: Low, equivocal and high GG (GG-1/-EQ/-3) categories were observed among 54 (11%); 60 (13%); 358 patients (76%) and associated with decreasing 5-yr-DFS rates of 100%, 92% and 82% (p < 0.001).There is only 60% concordance between local (L)/central(C) HG assessments and 63% between GG and C-HG. 37.7% of GG-3 tumors were L- HG3 vs. 72% C-HG3; 79% of C-HG2 and 83% of L-HG2 tumors were re-classified (56-71% to GGI3). Only 5.6-6% of GG1 were HG1 by L/C-HG respectively.GG was prognostic only in L-HG subgroups.In univariate subgroup analyses, EC-Doc was significantly superior to FEC: C-G3 (HR=0.58, 0.39-0.93), high Ki-67 (HR=0.55, 0.32E0.92) and GG-3 (HR=0.58, 0.34-0.99) subgroups. In multivariate analyses of HR+ disease (including age, therapy, GGI category, tumor size, LN status, central/local HG, Ki-67, HER2), either C-HG3 / high Ki-67 (as dichotomous variables) or C-HG3 / GGI (as continuous variable) were identified as independent prognostic factors.In interaction analysis, only C-HG, luminal A subtype and interaction of luminal-B/therapy were significant. If local HG was included instead of C-HG, only GG was as independent prognostic factor. **Conclusions**: These data support GGI as independent prognostic factor in early HR+ BC and as predictive marker regarding taxane benefit by univariate analysis. There is heterogeneity between L/C-HG and GGI. C-HG and Ki-67 assessment appear similarly informative. A predictive effect regarding benefit of taxane-containing CTx was seen in the IHC-luminal B subtype.

1093　　　　　　　　　**General Poster Session (Board #26A), Sat, 1:15 PM-5:00 PM**

Safety and tolerability of adjuvant dose dense chemotherapy in elderly patients with node-positive early breast cancer.

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Background: Intensive chemotherapy confers benefit to older and younger patients with early breast cancer (BC). We aim to characterize the feasibility and toxicity profile of adjuvant dose-dense chemotherapy (ADDC) in older women with early node positive (BC). **Methods:** Available data from women who received ADDC for BC within three randomized trials between 1997 and 2008 were retrieved from our electronic database. These trials included HE 10/97: epirubicin and cyclophosphamide, methotrexate and fluorouracil (CMF) with or without paclitaxel, HE 10/00: epirubicin and concurrent or sequential paclitaxel and CMF and HE 10/05: a sequential three arm study of epirubicin, paclitaxel and CMF compared with epirubin, CMF and either weekly paclitaxel or docetaxel. We identified women aged >65 years and we looked at differences in tolerability and delivery of chemotherapy, toxicity, and treatment outcome. **Results:** From a total of 2,640 patients with a median age of 52 years, who received ADDC, we identified 453 patients (17%) > 65 years, hormonal positive in 76%, all node negative. At least 90% of the planned doses were delivered in 37% of the elderly, compared to 49% of the younger patients (p < 0.0001). Grade 3 and 4 hematological toxicity was observed in 32% of elderly patients compared to 21% of younger (p < 0.0001). Febrile neutropenia occurred in 4.5% of elderly patients as opposed to 2% of younger (p < 0.002). Elderly patients experienced more frequently grade 3 and 4 fatigue, mucositis and sensory neuropathy, though the incidence of these toxicities was relatively low (all p < 0.0001). Relative dose intensities were significantly lower in elderly patients, mainly affected docetaxel and paclitaxel administration. Treatment discontinuation, regardless causality, was not different in both groups. At a median follow-up of 120 months, there was no significant difference in disease free survival. **Conclusions:** Elderly node positive BC patients treated with ADDC derive comparable clinical benefit as younger patients, mainly in the cost of increased risk of hematological toxicity. This should be taken into account in decision making and treatment individualization in high risk BC patients.

1094   **General Poster Session (Board #26B), Sat, 1:15 PM-5:00 PM**

Guidelines for the definitions of time-to-event endpoints in randomized clinical trials: Results of the DATECAN Project for Breast Group.

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Background: With the necessity of reducing randomized clinical trial (RCT) duration, cost and number of patients, surrogate endpoints of overall survival (OS) are increasingly being used in cancer RCTs. However, most of these endpoints currently lack of standardized definition enabling a comparison of RCT results. Some recommendations have been proposed for specific cancer sites but they do not rely on a formal consensus methodology. The objective of the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project is to provide guidelines to standardize definitions of time-to-event endpoints in RCTs for different cancer sites. Here, we present results for BREAST cancer. **Methods:** We relied on the modified Delphi consensus method, a validated formalized consensus process for the development of practice guidelines. International experts with various backgrounds and expertises were involved. First, the coordinating committee, a group of statisticians and epidemiologists involved in the design and conduct of RCTs, led a comprehensive literature review to identify time-to-event endpoints, events of interest and the existence of guidelines in adjuvant and metastatic settings. The steering committee, which included additional medical experts, validated the list and prepared the questionnaire sent for rating to an independent expert committee. **Results:** The consensus process involved 2 rounds of scoring (31 experts) and 1 in-person meeting (in parallel to ASCO'12). Each expert had to rate on a 1-9 scale if s/he agreed or not for including events (e.g. death from breast cancer) in the definition of time-to-event endpoints (e.g. progression-free survival). 150 events had to be scored for the 11 selected endpoints. Consensus was reached for 57% of the events after the 2 rounds of scoring. After the in-person meeting, consensus was reached for all the remaining events except one. **Conclusions:** The DATECAN guidelines should help standardizing definitions of commonly used endpoints. This process should (i) facilitate the comparison of RCTs and (ii) improve the quality of future RCTs by providing better estimation of sample size and treatment effect.

1095   **General Poster Session (Board #26C), Sat, 1:15 PM-5:00 PM**

Phase Ib study of eribulin (ERB) and cyclophosphamide (CTX) in metastatic breast cancer (MBC).

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Background: ERB is a non-taxane microtubule inhibitor approved for the treatment (Tx) of taxane (TAX) and anthracycline-treated MBC based on improved OS compared to treatment of physician choice. In the adjuvant setting, docetaxel/CTX (TC) was superior to doxorubicin/CTX for DFS and OS. ERB is active in TAX-resistant disease with a low rate of peripheral neuropathy (PN); its primary dose-limiting toxicity (DLT) is bone marrow suppression. We hypothesized that the combination of ERB and CTX would be well tolerated and active in patients with TAX-resistant disease, with potential applicability to the adjuvant setting. **Methods:** We designed a 3+3 phase Ib study of ERB, administered in 2 escalating doses on day 1 and 8, with CTX 600 mg/m^{2}day 1 every 21 days. Eligibility included PN $\leq$ grade 1. Correlative studies to identify predictors of response and toxicity included whole blood for SNPs, GWAS, circulating tumor cells (CTC), and archived tumor RNA/protein expression analysis. Toxicity assessment included QoL and evaluation of PN. **Results:** 6 patients (pts) with MBC, median age 50 (47-63), were enrolled. All pts had prior TAX exposure and 4 pts had baseline grade 1 PN. Tumor characteristics included hormone receptor + (5 pts), HER2+ (2 pts), and triple-negative (1 pt). Median number of prior Tx for MBC was 5 (1-8). No DLTs were observed; the RP2D is eribulin 1.4 mg/m2 on D1 and D8 with CTX D1 600mg/m2. Neutropenia was the only G3/G4 non-DLT observed at this dose, requiring GCSF support in cycle1 in 2 of 3 pts. All grade toxicities included neutropenia (50%), thrombocytopenia, fatigue, nausea, PN, rash, mucositis, alopecia (33% each), and elevated liver enzymes (17%). Pts received a median of 5.5 cycles (range 3-13), with 3 pts still on Tx. Responses included 2PRs (33%) and 4 SD (67%). 2 pts stopped study Tx for QoL and continued ERB alone. Only 2 pts met threshold of >5CTC/7.5ml at baseline; these had a mean decrease of 90.5% at the start of cycle 2. **Conclusions:** ERB and CTX is a well-tolerated regimen with promising activity in MBC, with the primary toxicity being neutropenia requiring growth factor support. A phase II study in MBC is underway. Additional correlative studies are ongoing including molecular analyses of CTC. Clinical trial information: NCT01554371.

1096   **General Poster Session (Board #27A), Sat, 1:15 PM-5:00 PM**

Effect of very small tumor size on recurrence-free survival and breast cancer-specific mortality stratified by guideline adherence: An analysis of the BRENDA Study Group.

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Background: Small tumor size ($<$5mm, T1a) carry an excellent prognosis, despite a variety of treatment approaches. Controversy exists over the extent of treatment, as to whether less than conventional treatment can be done. We therefore sought to explore the effect of very small tumor size on RFS and BCSM stratified by guideline adherence. **Methods:** The multicenter study population included 8935 early breast cancer patients diagnosed between 1992-2008, where 614 patients (6.9%) were T1a. T1a-patients were categorized according to guideline adherence and the influence on survival was calculated by Cox proportional hazard analyses (adjusted for age, grading, nodal status, hormonal status and co-existing morbidity). **Results:** The median age was 61 years and the median follow-up was 55 months. 449 [73.1%] patients were postmenopausal. 13.1% had G1, 61.9% G2 and 25% G3. 81.9% were HR positive and 18.4% HER2/neu-positive. 77.1% were N0, 11.9% had 1-3 and 11% more than 3 affected lymph nodes. Only 262 (42.7%) pts. were guideline adherent. Compared to guideline adherent patients RFS and BCSM were significantly (p$<$ 0.001) worse for guideline-non-adherent patients (RFS: HR$=$3.88; 95% C.I.: 1.91-7.87) and (BCSM: HR$=$ 4.28; 95% C.I.:2.04-9.00). After adjusting for age, grading, nodal status, hormone receptor status and comorbidity guideline adherence was still the most important variable for RFS and BCSM (RFS: p$<$0.001; HR$=$3.71; 95%C.I.: 1.80-7.67) and (BCSM: p$<$0.001; HR$=$3.82; 95% C.I.:1.80-8.11).The most important impact on RFS and BCSM had guideline violations of radiation (RFS: p$=$0.001; HR$=$3.19;95%C.I.:1.66-6.13) and (BCSM: p$=$0.009;HR$=$2.42;95%C.I.:124-4.72) respectively of chemotherapy (RFS: p$=$0.001; HR$=$1.43; 95%C.I.:1.43-4.39) and (BCSM: p$<$0.001;HR$=$3.17;95%C.I.:1.84-5.46). **Conclusions:** There is a strong association between guideline adherence and improved recurrence free survival and reduced breast cancer-specific mortality for breast cancer patients with very small tumor size. Violation of treatment guidelines for postoperative irradiation or chemotherapy is clearly associated with a deterioration of prognosis.

1097   **General Poster Session (Board #27B), Sat, 1:15 PM-5:00 PM**

ALDH1-positive cells in primary tumor and axillary lymph node metastases after chemotherapy as a prognostic factor in breast cancer patients.

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Background: The cancer stem cell theory that was established for hematopoietic neoplasms has significantly changed the concept of cancer therapy. Aldehyde dehydrogenase 1 (ALDH1)-positive cells show stem-like or progenitor ability, and have been considered as a clinically important diagnostic and therapeutic target in breast cancer patients. However, responsiveness of ALDH1-positive cells to chemotherapy in primary and metastatic lesions remains unclear, along with relationships to prognosis in patients with breast cancer. This study evaluated responsiveness to chemotherapy in the ALDH1-positive cells for primary and metastatic lesions and relationships to prognosis in patients with node-positive breast cancer. **Methods:** We evaluated 115 breast cancer patients with cytologically confirmed lymph node metastases who had undergone surgery after neoadjuvant chemotherapy (NAC). Using ALDH1 immuno-histochemistry of core needle biopsy for the primary tumor and cytology samples for axillary lymph nodes before NAC and pathological samples of each after NAC, we evaluated the clinical significance of ALDH1-positive cell status in primary and metastatic lesions before and after NAC. **Results:** Presence of ALDH1-positive cancer cells, not ALDH1-negative cancer cells, in primary and metastatic lesions after NAC was associated with worse prognosis. In multivariate analysis, only ALDH1-positive cells in metastatic lesions after NAC correlated with overall survival. Responsiveness of ALDH1-positive cells to chemotherapy differed between primary and metastatic lesions, and ALDH1-positive cells in metastatic lesions after NAC might clinically precede those in the primary lesion. **Conclusions:** Responsiveness of the ALDH1-positive cells to chemotherapy in primary and metastatic lesions, and the prognostic significance, were clarified in breast cancer patients. ALDH1-positive status might offer a surrogate marker as a new concept in patients with node-positive breast cancer.

1098   **General Poster Session (Board #27C), Sat, 1:15 PM-5:00 PM**

Improved outcome and selection bias in primary breast surgery for patients with metastatic breast cancer.

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Background: Retrospective studies showing improved survival in patients with metastatic breast cancer (MBC) who undergo surgical treatment of the primary tumor have been criticized for bias in favor of younger, healthier women with lower disease burden. We attempted to identify these biases in our population. **Methods:** Our institutional cancer registry was queried for patients with MBC from 1994-2010. Demographics, clinical, radiologic and pathologic staging, as well as treatments and outcomes were recorded. Surgical and non-surgical groups were compared for differences in overall survival (OS) and clinicopathologic variables, including comorbidities, using uni- and multivariate analysis. **Results:** Ninety-one patients with metastatic disease identified within 3 months of initial diagnosis were eligible. 53% (48 pts) had primary breast surgery and 47% (43 pts) did not undergo surgery. Patients in the surgery group were younger on univariate analysis (mean age 53 vs. 62, p<0.01). Neither BMI (mean 30 vs. 29 kg/m²) nor Charlson comorbidity score (mean 6 in both groups) were significantly different, p=NS. Bone metastases were more common in the surgery group (48 vs. 26%) and multiple metastases in the non-surgery group (35 vs. 17%), p<0.05. Patients in the non-surgery group had ≥ 1 visceral metastasis when compared to the surgery group (62 vs. 35%), p<0.05. Higher OS was demonstrated in the surgery group both with Kaplan Meier curves (p<0.05) and univariate analysis (mean 3 vs. 2 yrs, 95% CI 2.6, 3.7), p<0.05. Survival was higher in the surgery group (p<0.01), at 1 year, but this difference did not persist at 3 and 5 years. On multivariate analysis, only difference in age remained significant (p<0.01). **Conclusions:** Our study supports existing data that women with MBC who have surgical treatment of the primary tumor have an improved survivorship. However, it also suggests a bias towards increased use of surgery in patients who are younger with smaller burden of metastatic disease. We did not find a bias in favor of healthier patients. Further study to determine the mechanism and magnitude of benefit of primary tumor extirpation is still needed.

1099   **General Poster Session (Board #28A), Sat, 1:15 PM-5:00 PM**

Axillary lymph node ratio (LNR) versus pathologic nodal stage (pN) as a prognostic factor in breast cancer: Validation of Vinh-Hung's model in an Indian population.

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Background: The axillary lymph node ratio (LNR), i.e., the ratio of positive over excised lymph nodes offers potentially improved prognostication, selection for adjuvant therapy and inter-institutional comparability compared to conventional pathological nodal staging (pN). A consensus on appropriate cut-offs however, remains to be achieved. Values of 0.20 and 0.65 to classify patients into low, intermediate and high-risk groups were proposed by Vinh-Hung et al, in the largest study on the subject till date. We perform a validation of the LNR concept for the first time in an independent patient population from the Indian subcontinent. **Methods:** 225 patients with a median follow-up of 42 months (range: 2 – 246 months) who underwent upfront surgery for breast cancer at a tertiary care hospital in Delhi, India, were retrospectively analysed, using Cox multivariate regression. **Results:** Using the above cut-off points, 10-year disease-free survival (DFS) rates of 83%, 74% and 28% and adjusted hazard ratios (HR) of 1.19 (95% CI 0.33 to 4.37), 2.21 (95% CI 0.75 to 6.51) and 6.88 (95% CI 1.58 – 29.92; P = 0.01) were obtained for the low-, intermediate- and high-risk groups respectively. The corresponding risks for the pN1, pN2 and pN3 categories were 1.74, 1.74, and 1.35, representing inadequate, even reversed prognostic separation. When both the LNR and pN were included as continuous variables, the nodal ratio remained prognostically significant with an adjusted HR of 12.33 (95% CI 1.1 – 142.5, P = 0.04) in contrast to the number of positive nodes which were not found to be significantly associated with DFS (HR = 0.97, 95% CI 0.9 – 1.1, P = 0.41). **Conclusions:** The LNR outperformed the pN staging in predicting DFS in our cohort of patients, irrespective of whether it was modeled as a categorical or a continuous variable. Simultaneous analysis with pN only increased its prognostic weight and resulted in exclusion of pN from the multivariate model. Our study thus provides independent external validation of Vinh-Hung's proposed cut-offs and contributes to the growing body of literature supporting the incorporation of a ratio-based system into breast cancer staging.

1100   **General Poster Session (Board #28B), Sat, 1:15 PM-5:00 PM**

Neoadjuvant bevacizumab: Surgical complications of mastectomy with and without reconstruction.

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Background: Neoadjuvant therapy is commonly used in operable breast cancer. We prospectively evaluated the surgical complications in a cohort of patients who underwent mastectomy following neoadjuvant doxorubicin hydrochloride/cyclophosphamide/paclitaxel (AC/T) plus bevacizumab and compared the rate of complications to a matched cohort of neoadjuvant AC/T without bevacizumab. **Methods:** One hundred patients with HER2-negative breast cancer enrolled in a single-arm trial of neoadjuvant AC/T plus bevacizumab (cohort 1), 60 of these patients underwent mastectomy and were matched with 59 patients who received standard neoadjuvant AC/T (cohort 2) over a similar time period in the same healthcare system. All patients underwent mastectomy with or without reconstruction. Fisher's exact tests were used to compare complication rates, with a p<0.05 was considered significant. **Results:** Patients were matched well in terms of demographics. The overall complication rate was 33% in cohort 1 and 31% in cohort 2 (P-value=0.84; Table). In cohort 1, 7 of 23 (30%) patients who underwent immediate expander/implant reconstruction had complications, including 2 patients who had explantation of their reconstructions. In cohort 2, 0 of 8 (0%) had complications (p value=0.15). **Conclusions:** Nearly a third of patients undergoing neoadjuvant therapy with AC/T with or without bevacizumab developed a postoperative complication after mastectomy. The use of bevacizumab was not associated with a significant increase in surgical complications, although this is a non-randomized data with a small sample size. As larger data sets become available with the use of neoadjuvant bevacizumab with mastectomy, further refinement may be necessary.

	AC/T plus B cohort 1 (n=60)	AC/T cohort 2 (n=59)
Overall complications	20 (33%)	18 (31%)
Seroma	9	9
Hematoma	1	2
Infection	4	3
Skin necrosis	4	4
Expander/Implant loss	2	0
Patients who underwent reconstruction	35 (58%)	26 (44%)
Complications in patients with reconstruction	12 (34%)	8 (31%)
Expander/implant	7 of 23 (30%)	0 of 8 (0%)
Complications in patients without reconstruction	8 (32%)	10 (30%)

1101   **General Poster Session (Board #28C), Sat, 1:15 PM-5:00 PM**

Acute and late side effects after intraoperative electron radiotherapy during breast conserving surgery of breast cancer.

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Background: Intraoperative boost irradiation as part of breast-conserving therapy is a perfect method to adequately capture the high risk tumor relapse area. The most homogeneous dose distribution is achieved with electrons. Intraoperative electron radiotherapy (IOERT) as a boost for breast cancer releases a high single dose of radiation to the breast tissue; therefore acute toxicity is of particular attention. To date there is only inadequate information available on breast cancer patients treated with IORT using electrons applied as a boost. We therefore analyzed the acute toxicity and late side effects after radiotherapy with 10 Gy as a boost with a minimum follow-up of 3 months. **Methods:** A total of 385 patients treated with IOERT (10 Gy with 5, 7 and 9 MeV electrons) with a dedicated robotic linac (NOVAC 7, New Radiant Technology, Aprilia, Italy) to the tumor bed during breast-conserving surgery as a boost followed by whole-breast radiotherapy (WBRT,50- 50.4 Gy; 1.8-2 Gy per fraction) were included in this study. All patients underwent a retrospective follow-up regarding acute and late side effects. Toxicities were documented using the common toxicity criteria (CTC 4.0 of the European Organization for Research and Treatment of Cancer) and normal tissues subjective, objective, management and analytic scales (LENT-SOMA). **Results:** The IOERT was well tolerated and the cosmetic results were good. As a side effect there were five patients with seroma. Two patients developed a secondary wound healing. Two patients developed chronic pain in the irradiated breast. Ten patients developed a grade 2 fibrosis. The remaining patients did not develop any grade 3 or 4 side effects. The observed toxicity rates were not influenced by age, tubus size, electron energy or systemic therapy. 80 patients had a follow up longer than 5 years. Three of them developed distant metastasis and one patient died. **Conclusions:** After IOERT of the breast using electrons we did not find any unexpected acute and late toxicity rates.

1102   **General Poster Session (Board #29A), Sat, 1:15 PM-5:00 PM**

Study to explore the willingness of patients (pts) to undergo biopsy at the time of breast cancer (BC) recurrence.

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Background: Physicians (MDs) may not request a biopsy (BX) when metastatic (M1) diagnosis is certain, however, there is increasing awareness of the value of tissue for cancer discovery. In addition, biomarkers can change from initial BC to M1 in 20%, affecting treatment. With ethics approval we investigated under what conditions BC pts would agree to a BX of recurrent cancer, to guide MD practice. **Methods:** Consenting English speaking pts with M1, or at least 3 months post adjuvant therapy, were asked to complete a survey (at home or with research assistant) about willingness to undergo BX at M1. Demographic and disease information was collected. The BX scenarios increased in inconvenience/discomfort and decreased in direct benefit to pt. **Results:** Among 204 participants, mean age was 60 (29-92), 71% were caucasian, 73% completed more than high school, 84% lived within 1 hour of the cancer centre. 87 (43%) pts had no relapse (M0) and 116 (57%) had M1 (including 20 [17%] with local relapse only, 21 [18%] de novo M1). 82 (71%) of M1 pts reported having had a BX for M1. When it required only image guidance and minimal discomfort (eg ultrasound guided liver BX), 86% of M1 pts would have a BX to join a trial and 81% would for pure research; 69% and 76% of M0 pts would have a BX to join a trial, or for research only, respectively. The Table shows the responses for the most invasive BX. **Conclusions:** Two thirds of BC pts would undergo the most invasive/inconvenient BX to join a trial, and half would for pure research. This demonstrates a large degree of altruism in this BC population. Willingness increased as direct benefit increased and the pain/inconvenience decreased. This data suggests MDs should not be hesitant to ask BC pts for a BX at M1. This study was limited to English speaking pts and most were well educated, thus it may not reflect all cultural attitudes toward BX.

Pt willingness to undergo BX at M1.

Would have BX under general anaesthetic if:	M1 n=116	M0 n=87
1. The diagnosis was in doubt, n (%)	87 (75)	74 (85)
2. The diagnosis was not in doubt, but treatment options might change, n (%)	86 (74)	72 (83)
3. It was required to join a clinical trial, n (%)	73 (63)	53 (61)
4. It was purely for research (no direct pt benefit), n (%)	63 (54)	40 (46)

1103   **General Poster Session (Board #29B), Sat, 1:15 PM-5:00 PM**

Applicability of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial results in invasive lobular carcinoma.

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Background: The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that, for patients with clinical T1-T2, N0 breast cancer and one or two positive sentinel lymph nodes undergoing breast conserving therapy, there was no difference in local-regional recurrence (LRR), disease-free survival or overall survival (OS) between patients who underwent sentinel lymph node dissection (SLND) alone or completion axillary lymph node dissection (ALND). However, there were a limited number of invasive lobular carcinoma (ILC) participants (7%) in the study. In addition, it is known that ILC has a different pattern of metastases, frequently presenting as small foci requiring immunohisto-chemistry for detection. Together, these considerations raise concern regarding the applicability of the ACOSOG Z0011 data to patients with ILC. **Methods:** Patients with ILC who met the ACOSOG Z0011 eligibility criteria were identified from the Surveillance, Epidemiology, and End Results database (1998-2009). Patients were evaluated based on the extent of axillary surgery: SLND alone or ALND. Clinicaloutcomes of the two groups were compared. **Results:** At a median follow-up of 71 months, there were no LRRs in the SLND arm, and only 4 (0.45%) in the ALND arm. There were no differences in OS or disease-specific survival between the two groups. **Conclusions:** Omission of completion ALND is appropriate in patients with ILC who fulfill the ACOSOG Z0011 eligibility criteria.

1104   **General Poster Session (Board #29C), Sat, 1:15 PM-5:00 PM**

Reliability of prognostic and predictive factors evaluated by needle core biopsy for breast cancer in large tumors.

Camille Petrau, Florian Clatot, Anca Berghian, Liana Veresezan, Marie Cornic, Marc Baron, Francoise Callonnec, Corinne Veyret, Sophie Laberge, jean-Michel Picquenot; Centre Henri Becquerel, Rouen, France; Department of Medical Oncology, Henri Becquerel Center, Rouen, France

Background: Preoperative needle core biopsy (NCB) in breast cancer allows both invasive carcinoma diagnosis and the assessment of the main prognostic/predictive markers. However, large tumors, which may be candidates for preoperative chemotherapy, are potentially more heterogeneous than small ones, and the reliability of these factors measurements by NCB in these cases has been less documented than in whole surgical specimens (SS). The aim of this study was to evaluate the correlation for the main histological and immunohistochemical (IHC) features between NCB and SS in large tumors ($>$2cm), and to assess major discordances that may impact the therapeutic decisions. **Methods:** All patients treated in our center for newly diagnosed early breast cancer between January 2008 and December 2011 were retrospectively screened. Large tumors for which both NCB and SS were available were included. Patients treated by preoperative chemotherapy were excluded. The assessed histological and IHC parameters were histological type, SBR grade, estrogen (ER) and progesterone receptors (PR) expression, HER2 status (completed by CISH if needed), intrinsic subtype, and proliferation markers (mitotic activity index (MAI), Ki67). All samples were independently read twice. Comparisons were performed using Kappa test. **Results:** 163 pairs of NCB-SS were analyzed. Average pathological tumor size was 3.2cm. Correlation was excellent for ER and HER2 (k=0.98 and 0.91 respectively), good for histological type (k=0.74), PR (k=0.79) and intrinsic subtype (k=0.73), but poor for Ki67 (k=0,60), SBR grade (k=0.29) and MAI (k=0.24). Among major discordances, 6 tumors were graded SBR I on NCB but SBR III on SS; 1 tumor was negative for ER on NCB but positive on SS. Importantly, 3 of the 21 HER2 positive cases (14%) were negative after CISH on NCB but positive on SS. **Conclusions:** Diagnostic NCB in large early breast tumors allows reliable determination of hormonal receptors expression, histological type and intrinsic subtype. SBR grade may however be deeply underestimated by this method, and false negative evaluation of the HER2 status in 14% of HER2 positive patients would have led to a detrimental lack of trastuzumab administration.

1105 General Poster Session (Board #29D), Sat, 1:15 PM-5:00 PM

Metabolic characterization of inflammatory breast cancer (IBC) with baseline FDG-PET/CT: Relationship with histopathology, hormone receptor status, and pathologic response after neoadjuvant chemotherapy.

Trisha Youn, Heather A. Jacene, Pamela Dipiro, Yoko Tanaka, Jennifer Ruth Bellon, Faina Nakhlis, Judith Hirshfield-Bartek, Eren Yeh, Beth Overmoyer; Dana-Farber Cancer Institute, Boston, MA; Department of Radiology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA; Brigham and Women's Hospital, Boston, MA

Background: Higher metabolic activity on FDG-PET is associated with triple negative (TN) hormone receptor status and invasive ductal histopathology in non-IBC breast cancer. Pts with IBC and a complete pathologic response (pCR) in mastectomy tissue after neoadjuvant chemotherapy (NAC) have a better prognosis compared to pts with residual disease. The objectives were to characterize IBC on baseline FDG-PET with respect to hormone receptor status, tumor grade and to determine if baseline metabolic activity in primary or metastatic lymph nodes (LN) predicts pCR. **Methods:** This is an IRB-approved retrospective study of 28 pts. SUVmax of primary IBC tumor and local LN metastases were compared between (b/w) pts with pCR versus residual disease, b/w pts with different receptor status (ER, PR, HER2), and b/w pts with different grade tumors (1-3). **Results:** Baseline SUVmax was higher in 6 pts with TN tumors (median 12.4, range 5.4-29.3) compared with 22 pts with ER+ or PR+ or HER2+ tumors (5.0, 2.0-16.3, p=0.04). SUVmax in local LN metastases tended to be higher in TN tumors vs. others (11.2, 2.7-27.9 vs. 5.4, 2.0-15.5, p=0.06). SUVmax in primary IBC was not different based on tumor grade (p=0.26), but higher SUVmax was seen in metastatic LN in pts with grade 3 vs. 2 tumors (10.5, 2.0-27.9 vs. 4.7, 2.0-10.2, p=0.02). SUVmax of primary IBC tumor was not significantly different b/w pts with pCR (median 10.6, range 2-29.3) vs. residual disease (6.4, 2.5-13.6, p=0.36). No significant difference was seen b/w baseline SUVmax of locally metastatic LN between pts with pCR (9.0, 3.3-27.9) vs. residual disease (6.1, 2.0-16.2, p=0.13). **Conclusions:** Baseline metabolic activity of primary IBC tumor and locally metastatic LN did not predict pCR at mastectomy. Triple-negative receptor status is associated with higher SUVmax in primary tumor and marginally in metastatic LN suggesting a more aggressive nature. These findings are consistent with data in non-IBC breast cancer.

1106   **General Poster Session (Board #29E), Sat, 1:15 PM-5:00 PM**

The prognostic impact from the difference of surgical procedure after ipsilateral breast cancer recurrence.

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Background: Mastectomy is the current standard of surgical procedure for ipsilateral breast cancer recurrence (IBTR). However, there is little evidence about a prognostic impact of surgical procedure after IBTR, due to small number of incidence of IBTR. **Methods:** A total of 271 consecutive patients who had histologically confirmed IBTR without distant metastases and underwent definitive surgery for the IBTR between 1989 and 2008 were included from eight institutions as a scientific research from the Japanese Breast Cancer Society. Distant Disease free survival (DDFS) rates were calculated by the Kaplan-Meier method. Univariate analysis was performed using the log rank test and multivariate analysis by Cox's proportional hazard model. **Results:** Of the 271 patients, 149 patients (55%) underwent lumpectomy and 122 patients (45%) underwent mastectomy after IBTR. One hundred thirty four patients (49%) did not receive radiation therapy after initial lumpectomy (52% in lumpectomy patients and 47% in mastectomy patients). The median follow-up period from definitive surgery for IBTR was 55 months. Seventy-six patients (28.2%) relapsed after IBTR (23.7% of lumpectomy patients, 33.6% of mastectomy patients). In comparing groups by type of surgery, patient and tumor demographics in each group were significantly less positive HER2 status and smaller tumor size of IBTR, and more receiving adjuvant endocrine therapy and less adjuvant chemotherapy for IBTR in lumpectomy patients compared with mastectomy patients. On univariate analysis, lumpectomy group was significantly longer DDFS than mastectomy group (p=0.012), but this difference was not appeared on multivariate analysis (p=0.35). Furthermore, only using small IBTR (<2cm) population, this difference was not appeared (p=0.71). On multivariate analysis, the time intervals from initial surgery to IBTR (<5years) (HR, 1.93; 95%CI, 1.01-3.67; p=0.047) and lymphovascular invasion of the IBTR (HR, 2.31; 95%CI, 1.18-4.52; p=0.015) were independent predictive factor for poor DDFS. **Conclusions:** Our study suggests that the type of surgical procedure after IBTR does not affect DDFS. Further analyses are needed. (UMIN-CTR number UMIN000008136).

1107   **General Poster Session (Board #29F), Sat, 1:15 PM-5:00 PM**

SPIO-enhanced MR imaging at 3T for the detection of metastases in sentinel nodes in patients with breast cancer.

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Background: We previously demonstrated the usefulness of SPIO-enhanced MR imaging at 1.5T for the detection of metastases in sentinel nodes localized by computed tomography lymphography (CT-LG) in patients with breast cancer (Ann Surg Oncol 2011, ASCO 2012). The aim of this study was to evaluate the accuracy of MR imaging at 3T with SPIO enhancement for the detection of metastases in sentinel nodes. **Methods:** This study included 60 patients with breast cancer and clinically negative nodes. Sentinel nodes identified by CT-LG were evaluated prospectively using SPIO-enhanced MR imaging at 3T. 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 54.2 years (range, 33-78). Sentinel nodes were identified by CT-LG successfully in 59 (98.3%) of 60 patients. The mean number of sentinel nodes identified by CT-LG was 1.43 (range, 1-3). All 16 patients with positive sentinel nodes definitively diagnosed by pathology demonstrated metastases on SPIO-enhanced MR imaging. Five (31.3%) of them had micrometastases. Forty-one of 43 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 100%, 95.3%, and 96.6%, respectively. No adverse events were associated with either CT or MR imaging. **Conclusions:** SPIO-enhanced MR imaging at 3T is useful for accurate diagnosis of sentinel node metastases, and therefore sentinel node biopsy may be avoided for most patients with breast cancer.

1108 **General Poster Session (Board #29G), Sat, 1:15 PM-5:00 PM**

Intraoperative radiotherapy in early breast cancer: 400 consecutive patients in one institution.

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Background: From 2006 we offer intraoperative radiotherapy as the only post lumpectomy breast irradiation as an alternative to the standard post-operative WBRT in low risk early breast cancer patients (age > 60, invasive ductal carcinoma < 2 cm and clinically negative axilla). Younger patients (>50) or patients with tumors up to 3.5 cm or other histologies are treated too if they are not candidate for standard local therapy. In patients found to have high risk tumor characteristics at final pathology, additional local breast therapy is considered. **Methods:** Intrabeam System is used administering 20 Gy at the surface of surgical cavity. **Results:** 400 patients were treated. Their median age was 70 years (55-90). Median clinical tumor size was 12 mm (5-30). 14.5% had mild to moderate local complications: 6.5% wound infection, 5.8% complicated seromas, 1.7% bleeding or hematoma and 0.5% small skin necrosis. 6.2% experienced major complications: 2.5% required surgical intervention, 2% had late healing (> 90 days), 1% required IV antibiotics and 0.7% had grade III RTOG fibrosis. Median pathologic size was 14 mm (1-40). Pathologic free margins > 1mm were obtained in 98.8% of patients. 15.5 % were found to have axillary l-nodes involved (11% one node only), 12% of patients had adverse unexpected breast pathologic findings (7.5% EDCIS or LVI) and 11% had additional local therapy, most of them WBRT. Median follow up is 30 months (1-76) in the whole group and 43 months (3-76) in the first 200 patients treated. Seven ipsilateral breast failures (1.7%) and one axillary recurrence were observed, all had radical local therapy. Four patients developed systemic disease (1%), one of them with simultaneous breast recurrence and one had contralateral breast cancer. **Conclusions:** We conclude that intraoperative radiotherapy using the Intrabeam system is feasible and may offer an alternative to whole breast RT in low risk breast cancer patients. Clinically significant local morbidity rate is low and self limiting. Longer follow up is needed to evaluate final results and late toxicity.

1110 **General Poster Session (Board #30A), Sat, 1:15 PM-5:00 PM**

Cosmetic outcome after intraoperative radiotherapy or external beam radiotherapy for early breast cancer: An objective assessment of patients from a randomized controlled trial.

Mohammed R. Keshtgar, Norman R. Williams, Tammy Corica, Max Bulsara, Christobel Saunders, Henrik Flyger, Neils Bentzon, Jaime S. Cardoso, Nikolaus Michalopoulos, David John Joseph; Royal Free Hospital, London, United Kingdom; Clinical Trials Group, UCL Division of Surgery and Interventional Science, London, United Kingdom; Sir Charles Gairdner Hospital, Perth, Australia; University of Notre Dame, Fremantle, Australia; Department of Breast Surgery F118, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; INESC TEC and Faculty of Engineering, University of Porto, Porto, Portugal; Royal Free Hospital NHS Foundation Trust, London, United Kingdom

Background: The international randomised contolled TARGeted Intraoperative radioTherapy (TARGIT) trial has demonstrated non-inferiority between the novel technique of TARGIT (intra-operative radiotherapy with Intrabeam) and conventional whole-breast external beam radiotherapy (EBRT) in women with early breast cancer, in terms of the primary outcome measure of risk of local relapse within the treated breast. With very low recurrence rates, cosmesis becomes an increasingly important outcome of breast conserving treatment with both surgery and radiotherapy. This study was performed to determine if the single high dose of TARGIT leads to impaired cosmesis. **Methods:** A validated, objective assessment tool for evaluation of cosmetic outcome was used. Frontal digital photographs were taken at baseline (before TARGIT or EBRT) and yearly thereafter for up to five years. The photographs were analysed by BCCT.core software which produces a composite score based on symmetry, colour and scar. **Results:** 342 patients were assessed, all over 50 years old with a median age at baseline of 64 years (IQR 59 to 68). The scores were dichotomised into Excellent and Good (EG), and Fair and Poor (FP). There were statistically significant increases in the odds of having an outcome of EG for patients in the TARGIT group relative to the EBRT group at year 1 (OR = 2.07, 95%CI 1.12 to 3.85, p = 0.021) and year 2 (OR = 2.11, 95%CI 1.0 to 4.45, p = 0.05). **Conclusions:** Following an objective assessment of aesthetic outcome in patients from a randomised setting, this study demonstrates that those treated with targeted intraoperative radiotherapy have a superior cosmetic result compared with those patients who received conventional whole-breast external beam radiotherapy.

1111   **General Poster Session (Board #30B), Sat, 1:15 PM-5:00 PM**

Randomized study of capecitabine versus S-1 in women with metastatic or recurrent breast cancer: Japan Breast Cancer Research Network (JBCRN) 05 trial.

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Background: Capecitabine and S-1 are orally administered fluorinated pyrimidines with high-level activity against metastatic breast carcinoma (MBC). **Methods:** This randomized multicenter phase II study was conducted to investigate the activity and safety of two oral fluoropyrimidines, capecitabine and S-1, in breast cancer patients. Patients with MBC were randomly assigned to receive capecitabine at 1,657 mg/m^{2}two times daily on days 1–21 every 4 weeks, or S-1 at 40–60 mg two times daily according to the body surface area on days 1–28 every 6 weeks. **Results:** One hundred and forty-two patients were enrolled, and 136 patients were randomized to capecitabine (N=71) or S-1 (N=65). The median progression-free survival, the primary end-point, was 1.4 years for capecitabine and 1.3 years for S-1, with a hazard ratio (S-1/capecitabine) of 0.85 (95%CI: 0.52-1.38) (log-rank p = 0.5). The confirmed ORR for both populations was 24.0% for capecitabine and 23.1% for S-1(p = 0.938). The median OS was 3.5 years for capecitabine and 2.7 years for S-1; the hazard ratio (S-1/ capecitabine) was 1.32 (95% CI: 0.7–2.48) (p = 0.39). Further, the most common treatment-related adverse events were grade 1/2 in intensity. However, there were more adverse events, thrombocytopenia (p = 0.040, S-1: 9.2%, capecitabine: 1.4%), and nausea (p = 0.079, S-1: 26.2%, capecitabine: 14.1%) in the S-1 group. Hand–foot syndrome occurred in the S-1 and capecitabine groups (p = 0.029, S-1: 10.8%, capecitabine: 25.4%). **Conclusions:** The results of the current study demonstrate that S-1 or capecitabine is an effective and well-tolerated treatment in patients with MBC. In addition, they are convenient and orally administered drugs, which makes them attractive agents for use in outpatient treatment. Clinical trial information: NCT 00438100.

1112   **General Poster Session (Board #30C), Sat, 1:15 PM-5:00 PM**

Meta-analysis to determine the clinical effectiveness of axillary lymph node dissection in the treatment of operable primary breast cancer.

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Background: The optimum surgical management of the axilla is controversial. Guidelines mandate axillary surgery in the setting of positive sentinel nodes. However, recent studies have questioned the oncological benefits of this potentially morbid procedure. Therefore a meta-analysis of relevant randomised trials was performed to clarify this issue. **Methods:** A comprehensive search of published randomized trials that compared patients with primary operable breast cancer with/without axillary lymph node dissection (ALND) was performed using MEDLINE and available data was cross referenced. Reviews of each study were conducted, and data were extracted. Primary outcomes were overall survival and recurrent axillary disease. **Results:** A total of 4,759 patients with operable primary breast cancer were identified from 13 randomised controlled trials comparing patients with/without ALND. Overall survival favours patients not having ALND (OR = 1.38 (95% CI = 1.12 TO 1.69, p=0.002)) however patients undergoing ALND had similar disease free survival (OR=1.04 (95% CI= 083-1.31, p=0.7). However, though axillary recurrence was uncommon it was significantly less so following ALND (1% vs. 5 %, p<0.05, ALND vs. No ALND). **Conclusions:** Based on this meta-analysis, ALND does not appear to positively impact on breast cancer survival. Enhanced and targeted adjuvant treatment strategies may facilitate less aggressive axillary surgery. The management and implications of a positive sentinel node need to be re-evaluated in this regard.

1113   **General Poster Session (Board #30D), Sat, 1:15 PM-5:00 PM**

Prognostic significance of reduction rate of Ki-67 after neoadjuvant chemotherapy in breast cancer patients with non-pCR.

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Background: A pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is well established predictive marker for long-term prognosis in patients (pts) with HER2 or triple negative (TN) breast cancer. However, predictive marker has not been established in pts with non-pCR after NAC yet. Reduction of Ki-67 value after NAC has been reported to be associated with a favorable prognosis. However, the association between the reduction rate of Ki-67 and prognosis has not been investigated in detail. This study investigates whether reduction rate of the Ki-67 could indicate a survival advantage in pts with non-pCR. **Methods:** A total of 450 pts who had received neoadjuvant anthracycline with or without taxane chemotherapy and surgery were analyzed retrospectively. Ki-67, hormone receptor and HER2 status were examined by immunohistochemistry (IHC) in pre-NAC biopsy samples and post-NAC surgical specimens. Pts with non-pCR were subdivided into threesubgroups according to Ki-67 change after NAC: High-reduction (absolute value of Ki-67 was reduced by $> 80\%$ compared with that prior to NAC), low-reduction (absolute value of Ki-67 was reduced by from 0% to 80% compared with that prior to NAC), and increase groups (absolute value of Ki-67 was increased compared with that prior to NAC). The relapse-free survival (RFS) rates were compared among subgroups. **Results:** pCR was observed in 19.5% of pts. In pts with non-pCR, a reduction in Ki-67 was observed in 64% (232/362 pts) and the median reduction rate was 60%. A total of 15% of pts were in the high-reduction, 63% in the low-reduction and 22% in theincrease group. The median follow-up was 64.5 months. The 5-year RFS rates among three groups were significantly different ($p < 0.0001$). Similar positive results were observed in the HER2($p = 0.033$), TN ($p = 0.034$) and luminal subtype ($p = 0.001$). Pts in the high-reduction group showed comparable RFS to pts with pCR (hazard ratio 1.12 $p = 0.792$). **Conclusions:** In pts with non-pCR, the reduction rate of Ki-67 after NAC significantly predicted RFS regardless of their tumor subtypes. Pts who are non-pCR but achieve a high reduction of the Ki-67 can be expected to have a favorable prognosis similar to that of pts with pCR.

1114   **General Poster Session (Board #30E), Sat, 1:15 PM-5:00 PM**

Long-term quality of life in patients with breast cancer according to sentinel lymph node biopsy or axillary lymph node dissection: A multicenter cohort study with 6 years follow-up.

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Background: the aim of this study was to assess long term quality of life (QoL) over a period of 6 years in women with a breast cancer (BC) who underwent sentinel lymph node biopsy (SLNB), axillary lymph node dissection (ALND), or SLNB followed by ALND. **Methods:** The EORTC-QLQ-C30 and the EORTC-QLQ-BR-23 questionnaires were used to assess QoL before surgery, just after surgery, 6, 12 and 72 months later. The Kruskal Wallis test with the Bonferroni correction was used to compare scores. A mixed model analysis of variance for repeated measurements was then applied to assess the longitudinal effect of surgical modalities on QoL. **Results:** Five hundred and eighteen BC patients were initially included. The median follow-up was 6 years. During the follow-up, 61 patients died. None of the patients of the SLNB group has developed lymphedema during follow-up and the relapse rate was not different between the different groups (p=0.62). Before surgery, global health (GHS) (P = 0.5226) and arm symptoms (BRAS) (P = 0.9902) QoL scores were similar whatever the surgical procedure. BRAS score (p=0.0001) was better in the SNLB group 72 months after surgery. Moreover, compared to ALND patients, patients treated with SLNB had fewer arm symptoms with the follow-up. In addition, body image (P = 0.0005), upset by hair loss (P = 0.0045), systemic therapy side effects (P = 0.0097) and future perspective (P = 0.0375) QoL dimensions remained better 5 to 6 years after diagnosis in patients treated by SLNB. **Conclusions:** Long term follow-up showed that, SLNB is a safe and acceptable accurate method associated with less morbidity than ALND.

1115   **General Poster Session (Board #30F), Sat, 1:15 PM-5:00 PM**

Impact of lymph node ratio (LNR) on prognosis of early breast cancer.

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Background: Breast cancer is currently staged according to the TNM (tumors, nodes, metastases) classification of the American Joint Committee on Cancer (AJCC) Staging System. Lymph node ratio (LNR, the ratio of positive axillary lymph nodes to the total number of nodes examined) may provide additional prognostic information to that provided by TNM scores. Furthermore, LNR may potentially identify subpopulations within the traditional AJCC stages that are at increased risk of adverse outcomes. **Methods:** We performed a single institution retrospective study of all patients diagnosed with early breast cancer between January 2000 and January 2011. Patients were divided into low- ($\leq$0.14), intermediate- (0.15-0.39) and high-risk ($\geq$0.4) LNR groups. We assessed the impact of LNR and conventional AJCC staging parameters on overall survival (OS) and disease-free survival (DFS). **Results:** 786 patients were included in the analsyis, 238 of whom were node positive. As expected nodal status according to pathologic nodal (pN) stage was prognostic for OS and DFS with OS decreasing from 88.3% in pN1 patients to 40.8% in those with pN3 disease (p<0.001). LNR was also significantly associated with prognosis. OS decreased from 94% in the low-risk LNR group to 64% in the high-risk group, while DFS decreased from 92% in the low-risk LNR group to 50% in the high-risk (p<0.001). When Stage III patients were divided into low- and high-risk LNR groups, OS decreased from 100% in the low LNR group to 63% in the high LNR group (p<0.05). Similarly, DFS decreased from 96% in the low LNR group to 56% in the high LNR group (p<0.05). A similar trend was not observed when Stage III patients were stratified according to pN status. LNR was also found to be prognostic when pN1 patients were divided into low- and high-risk LNR groups. Although both LNR and nodal status were significantly associated with OS and DFS on univariate analysis, LNR retained its significance on multivariate analysis, while nodal status did not. **Conclusions:** LNR can identify subpopulations within the traditional AJCC staging that are at higher risk of adverse outcomes. These findings should be examined in larger retrospective studies and, if validated, be considered as a stratification factor in future adjuvant trials.

1116   **General Poster Session (Board #30G), Sat, 1:15 PM-5:00 PM**

Changes in the biologic markers between primary tumor and ipsilateral breast tumor recurrence after breast conserving surgery: Discordance and prognosis.

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Background: Changes in biological markers due to recurrence are clinically experienced in breast cancer. However, the clinical significance is still uncertain, especially after breast conserving surgery. The changes in biological markers between primary tumor and ipsilateral breast tumor recurrence (IBTR) and their correlations with prognosis were investigated, retrospectively. **Methods:** A total of 117 consecutive patients with IBTR without distant metastases were enrolled in this study. All patients were examined for ER, PgR, HER2 and Ki-67 in both the primary and recurrent tumors. The cases were categorized into 3 groups: patients with Ki-67 values $<20\%$, $<50\%$ and $\geq50\%$, and divided into 2 groups according to the IBTR site, same quadrant(SQ)and different quadrant(DQ) from the initial sites. The distant disease-free survival (DDFS) was calculated using the Kaplan-Meier method and evaluated by the log-rank test and multivariate analyses using Cox proportional hazards model. The median follow-up period was 4.8 years after IBTR. **Results:** The PgR positive rate from the primary tumor to IBTR decreased from 57% to 39% and the Ki-67 values increased significantly from a mean of 17% to 23%. The concordance rate of the subtype was 62%. In the SQ group, the PgR positive rate significantly decreased and the mean Ki-67 values significantly increased, whereas there was no significant difference in the DQ group. In terms of changes by category due to relapse, the discordance rate in Ki-67 was high in the SQ group, and HER2 was high in the DQ group. Regarding DDFS by a change in the categorization, the cases with discordance in Ki-67 values had significantly lower DDFS in the SQ group(5-year DDFS: 75% vs 52%, p=0.04). However, a clear difference was not found in the DQ group. **Conclusions:** The PgR positive rate decreased while the mean Ki-67 values increased due to IBTR in the SQ group. The categorical discordance in the Ki-67 values was significantly associated with lower DDFS, especially in the SQ group. These findings suggest that the recurrent site and change in the biological markers were clinical significant in the evaluation of the characteristics and treatment in cases with IBTR.

1117   **General Poster Session (Board #30H), Sat, 1:15 PM-5:00 PM**

Sentinel lymph node biopsy (SNB) in pregnancy-associated breast cancer (PABC).

Adrienne Gropper, Katherina Zabicki Calvillo, Susan Troyan, Laura Stewart Dominici, Esther Rhei, Katherine E. Economy, Lidia Schapira, Nadine M. Tung, Jane L. Meisel, Ann H. Partridge, Erica L. Mayer; Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; Massachusetts General Hospital, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA

Background: SNB in PABC is not often pursued due to concerns for potential fetal harm. There are only limited data available regarding the safety and efficacy of SNB in patients (pts) with PABC. **Methods:** Pts with PABC who underwent SNB were identified from within an existing multi-institutional PABC cohort diagnosed 1996-2013. Factors evaluated included method and result of SNB evaluation, maternal disease outcome, and fetal outcomes. **Results:** Within a cohort of 78 PABC pts, 53 had breast surgery while pregnant; 23 (43%) underwent SNB, 27 (51%) underwent initial axillary node (AN) dissection, 18 of whom were clinically node negative, and 3 had no nodal evaluation. Of SNB pts, 21 (91%) had stage 1-2 disease; 14 (61%) had ER/PR+ disease and 7 (30%) HER2+. Eight (35%), 9 (39%), and 6 (26%) women had SNB in the first, second, and third trimesters, respectively. 99-Technetium-labelled sulfur colloid (99-Tc) alone was used for SNB in 14 pts; methylene blue (MB) dye alone was used in 7. SN was identified in 100% of pts; see Table. There were no SNB-associated complications. At a median of 2.4 years from diagnosis, there were no locoregional recurrences, 3 (13%) distant recurrences, and 1 (4%) death from breast cancer. Among pts who underwent SNB, there were 20 liveborn infants and 3 pregnancies ongoing. Of the 20 infants born, 18 were healthy, 1 unknown, and 1 had cleft palate (in setting of maternal risk factors including smoking and methadone). **Conclusions:** SNB in PABC appears to be a safe and accurate procedure using either 99-Tc or MB techniques. This is one of the largest experiences reported to date of SNB during PABC; however, numbers remain limited and rates of SNB in our cohort were lower than current rates in non-PABC patients. Additional research and monitoring for safety of this procedure is warranted in women with PABC.

SNB characteristic (N=23)	Number (%)
Weeks gestation at SNB: median 16 (range 4 – 32)	
Method of SNB: 99-Tc alone	14 (61)
MB alone	7 (30)
Unknown	2 (9)
Number of SN identified: median 2 (range 1-10)	
> 1 SN positive for metastases	6 (26)
Underwent subsequent axillary lymph node (ALN) dissection	6 (26)
Number of ALN retrieved: median 18 (range 10-28)	
> 1 ALN positive for metastasis	3 (13)

1118 **General Poster Session (Board #31A), Sat, 1:15 PM-5:00 PM**

A phase I-II study of tipifarnib plus weekly paclitaxel (P) followed by dose-dense doxorubicin/cyclophosphamide (AC) in stage IIb-IIIc breast cancer (BC).

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Background: Tipifarnib (T) is an orally bioavailable farnesyl transferase inhibitor (FTI) that has activity in metastatic BC (J Clin Oncol 2003; 21:2492-9). We previously showed that adding T (200 mg PO BID days 2-7) to preoperative AC was associated with a higher pathologic complete response (pCR) than expected compared with historical data (Clin Cancer Res. 2009;15;2942-8), and preclinical data suggest that FTIs enhance the antineoplastic effects of P (Cancer Res 2005; 65:3883-93). **Methods:** Eligible pts with HER2-negative clinical stage IIB-IIIC BC received 12 weekly doses of P (80 mg/m2) followed by AC (60/600 mg/m2 every 2 weeks and pegfilgrastim), plus T 100 mg or 200 mg on days 1-3 of each P dose in cohorts of 3-6 pts in the phase I (and T 200 mg PO BID on days 2-7 each AC cycle in both the phase I and II). Simon two-stage design used for the phase II in two strata generally resistant to neoadjuvant chemotherapy. The trial was powered to detect an improvement in breast pathologic complete response (pCR) from 15% to 35% in each stratum (alpha 0.10, beta 0.10), which required breast pCR in at least 4/19 eligible pts in stage I to proceed to stage II, and at least 8/33 pts in stage I and II to be considered promising. **Results:** Sixty patients accrued in both the phase I and II. Two patients were non evaluable. There were no DLTs in the first 6 evaluable patients treated at dose level 1 and 2.The recommended phase II dose of T identified in the phase I trial was 200 mg BID.All protocol therapy was completed in 43/55 pts (78%) in the phase II, and one pt died of pneumonitis during therapy of uncertain cause. The prespecified efficacy endpoint was not met for either stratum. **Conclusions:** The addition of the FTI tipifarnib to neoadjuvant sequential weekly paclitaxel followed by dose-dense AC did not result in a higher breast pCR rate compared with historical data. Clinical trial information: NCT00049114.

	Stratum A	Stratum B
Definition	ER and/or PR-positive Non-inflammatory	Inflammatory Any ER/PR status
Breast pCR/treated	18% (N=6/33)	4% (N=1/22)
95% confidence intervals	7%, 36%	0%, 8%
Residual Cancer Burden Class (RCB)		
0	5	1
I	1	2
II	14	9
III	11	5
Unknown	2	2
No surgery		3

1119   **General Poster Session (Board #31B), Sat, 1:15 PM-5:00 PM**

Sentinel node biopsy in patients with microinvasive breast cancer: A systematic review and meta-analysis.

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Background: The aim of this meta-analysis is to evaluate the role of sentinel lymph node biopsy (SLNB) in patients with microinvasive breast cancer. **Methods:** We searched MEDLINE and ISI Web of Science to identify studies including patients with microinvasive breast cancer who underwent SLNB and reported the rate of sentinel-node positivity. We performed proportion meta-analysis using either fixed or random-effects model based on the between-study heterogeneity. **Results:** A total of 23 studies including 952 patients met the eligibility criteria. The summary estimate for the sentinel-node (SN) positivity rate was 3.1% (95% Confidence Interval (CI): 2.0%-4.4%), 4.1 % (95% CI 2.8%-5.6%), and 2.8% (95% CI : 1.6%-4.5%) for macrometastasis, micrometastasis and isolated tumor cells (ITC) respectively. Significant between-study heterogeneity was observed only in the meta-analysis of ITC positivity rate. **Conclusions:** The amount of positive sentinel node in patients with proven microinvasive breast cancer is relatively low. As a result, the indications for SLNB in these patients should be probably individualized.

1120   **General Poster Session (Board #31C), Sat, 1:15 PM-5:00 PM**

Intraoperative versus external beam boost for breast cancer: A matched-pair analysis.

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Background: After breast conserving surgery, radiotherapy leads to a better overall survival. In addition to whole breast radiotherapy (WBRT) a boost to the tumor bed leads to a better local control. The tumor bed boost is usually added after WBRT or can be done intraoperative (IORT). Belletti et al. (Clin Cancer Res., 2008) described positive effects, an antitumoral effect and modulation of microenvironment after IORT with 50kV x-rays. A matched pair analysis was performed to investigate the impact of IORT boost on overall survival compared to standard external beam boost. **Methods:** Between 2002 – 2009, 370 patients were treated for breast cancer with WBRT + boost (external beam (EBRT) boost n = 146, IORT boost n =224). A matched pair analysis (1:1 propensity score matching for age, TNM, grading, hormonal treatment and chemotherapy) for overall survival and local recurrence free survival could be done for 53 pairs. All patients underwent breast conserving surgery and WBRT with 46-50Gy. 53 patients received an EBRT boost with 16Gy (2Gy/fraction, dedicated linear accelerator) and 53 patients received an IORT boost with 20Gy (INTRABEAM system, 50kV x-rays). Median follow-up was 6 months (range, 1-77 months) for the EBRT boost patients and 56 months (range, 2-97 months) for IORT boost patients. Kaplan Meier estimates were performed for overall survival and local recurrence free survival. **Results:** IORT boost patients had a longer follow-up than EBRT boost patients. Despite the difference in follow-up times, there was a strong trend towards better overall survival after IORT boost (90.2% vs. 62.3%, p = 0.375). One local recurrence was present in each group (EBRT boost after 15 months, local recurrence free survival 95%; IORT boost after 12 months, local recurrence free survival 98.1%). **Conclusions:** IORT given as a boost seems to have a positive impact on overall survival in breast cancer patients after breast conserving surgery. To identify such an effect a prospective randomized trial should be conducted.

1121 General Poster Session (Board #31D), Sat, 1:15 PM-5:00 PM

TARGIT-A trial: Updated results for local recurrence and survival for the German centers.

Frederik K. Wenz, Jayant S. Vaidya, Max Bulsara, Marc Suetterlin, Elena Sperk, Beyhan Ataseven, Steffi Pigorsch, Petra C. Feyer, Jens U. Blohmer, Manfred Kaufmann, Claus Roedel, Klaus Friese, Claus Belka, Erich Solomayer, Jochen Fleckenstein, Tjoung-Won Park-Simon, Michael Bremer, David John Joseph, Jeffrey S. Tobias, Michael Baum; Department of Radiation Oncology, Mannheim Medical Center, University of Heidelberg, Mannheim, Germany; University College London, London, United Kingdom; University of Notre Dame, Fremantle, Australia; Department of Gynecology, Mannheim, Germany; Department of Gynecology, Rotkreuzkliniken Munich, Munich, Germany; Deptartment of Radiation Oncology, Technical University Munich, Munich, Germany; Clinic of Radiooncology and Nuclear Medicine, Vivantes Klinikum Neukölln, Berlin, Germany; Brustzentrum Sankt-Gertrauden-Krankenhaus, Berlin, Germany; University Hospital, Frankfurt, Germany; University of Frankfurt, Frankfurt, Germany; Department of Gynecology and Obstetrics, Klinikum der Ludwig-Maximilians-Universität, Munich, Germany; Department of Radiation Oncology, Ludwig Maximilians University Munich, Munich, Germany; Department of Obstetrics and Gynecology, University Medical Center, Homburg/Saar, Germany; Saarland University Medical School, Homburg/Saar, Germany; Hannover Medical School, Hannover, Germany; Department of Radiation Oncology, Hannover, Germany; Sir Charles Gairdner Hospital, Perth, Australia

Background: In 2010, we reported data on local control and early toxicity for the TARGIT-A trial of intraoperative radiotherapy after lumpectomy for early breast cancer. The updated results and first analysis of survival of the whole cohort (n = 3,451) were presented at San Antonio Breast Cancer Symposium in December 2012. We analysed the German cohort of patients, which was supposed to be more homogeneous (prepathology IORT only, homogeneous treatment in EBRT arm) and lower risk (older, smaller tumors, larger margin) than the international cohort of patients due to legal restrictions for radiotherapy studies in Germany. **Methods:** TARGIT-A was a randomised trial in patients $>=50$ years with invasive ductal carcinoma ($<= 2$cm) undergoing breast conserving surgery comparing standard fractionated whole breast EBRT (56 Gy) with single dose TARGIT (20 Gy) immediately after tumor excision / at the time of the primary operation. The experimental arm mandated additional EBRT (46 Gy, excluding a boost, n = 126) if adverse features were detected on final pathology (EIC, N+, margin < 1 cm) making this a "risk-adapted policy". Median follow-up was 2 years and 5 months. **Results:** 734 patients recruited from 7 centres in Germany. Patient's ages were $<=50$y 3%, 51-60y 33%, 61-70y 51%, >70y 12%. Tumour sizes were 0-1cm 35%, 1.1-2cm 55% and >2cm 11%. Grade I 29%, II 59%, III 12% and nodes negative 81%, 1-3 nodes 16%, >3 nodes 3%. At 5-years, the absolute number of events in TARGIT vs. EBRT were as follows: Primary outcome: IBR 4 vs. 1, Exploratory outcome: All recurrences (breast +axilla+contralateral+distant recurrence) 11 vs. 7, Secondary outcome: All deaths 6 vs. 12, Breast Cancer deaths 3 vs. 5, Non-Breast Cancer deaths 3 vs. 7. **Conclusions:** Patients in the TARGIT-A trial have excellent 5 year outcomes (local control > 97%, overall survival $>= 94$%) in both arms of the trial. Clinical trial information: protocol 99PRT/47.

1122   **General Poster Session (Board #31E), Sat, 1:15 PM-5:00 PM**

Sentinel lymph nodes before chemotherapy: The Besançon experience.

Loic Chaigneau, Elsa gannard Pechin, Hamidi Almotlac, Guillaume Mouillet, Fernando Bazan, Cristian Villanueva, Laurent Cals, Philippe Montcuquet, Nathalie Meneveau, Thierry Nguyen, Elsa Curtit, Jean-Loup Sautiere, Yolande Maisonnette, Marie-Paule Algros, Xavier B. Pivot; Institut Regional Du Cancer En Franche-Comté - University Hospital, Besançon, France; Centre Hospitalier Universitaire Jean Minjoz, Besançon, France; Institut Regional du Cancer en Franche-Comté - University Hospital, Besançon, France; Centre Hospitalier Universitaire, Besançon, Besançon, France

Background: It is debatable whether sentinal lymph node (SLN), before chemotherapy in locally breast cancer (LBC) is feasible. Impact on survival and locoregionally recurrence are unknown. **Methods:** 256 consecutive patients with LBC treated in Franche Comté (France) between 2004 and 2010 by standard neoadjuvant chemotherapy were retrospectively studied. 177 patients underwent axillary lymph node (ALN) dissection after chemotherapy (cohort A) and 79 patients underwent SLN before chemotherapy (cohort B). The aim of this study was designed to confirm the feasible of SLN before neoadjuvant chemotherapy without negative impact of recurrence and survival. Disease-free survival (DFS) and overall survival (OS) were calculated using Kaplan-Meier method. Differences in OS and DFS according ALN exploration were tested for significance using the Log-Rank test. **Results:** No statistically significant differences were observed in terms of median age (respectively 59 and 48 years in cohort A and B), tumor size, histological type, grading score, estrogen receptor, progesteron receptor and human epidermal receptor-2 status. No difference of breast conserving surgery was observed between cohort A and B (56.25 vs. 64.56%, p = 0.21). In cohort B, 38 patients (48.10%) of patients underwent SLN alone. For others patients (n = 41, 51.90%), secondary complete axillary lymphadenectomy was performed in the same time of breast surgery. After a median follow up of 57 months (range: 38-105), there was no significant difference in termsof local and axillary recurrences (1.13 vs. 1.27%), metastatic recurrence (11.30 vs. 11.40%). Five-year DFS (76 *vs* 81%, p = 0.55) and 5-year OS (91 vs. 97%, p = 0.76) did not differ between patients in cohort A and B. **Conclusions:** SLN before neoadjuvant chemotherapy is feasible and allows to avoid ALN dissection in nearly 50% of patients without impact on recurrence and survival.

1123 General Poster Session (Board #31F), Sat, 1:15 PM-5:00 PM

Propensity-score matched pair comparison of accelerated partial breast irradiation (APBI) and whole breast irradiation (WBI) for ductal carcinoma in situ (DCIS).

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Background: DCIS remains a cautionary criterion for APBI by the ASTRO APBI consensus statement. We performed a matched analysis to compare the efficacy of WBI and APBI for patients with DCIS. **Methods:** Women with DCIS treated with APBI or WBI were reviewed. APBI (n=102) patients with ≥2 y follow-up were matched 1:3 to WBI (n=546) patients with ≥5 y follow-up by age, tumor size, nuclear grade, ER status, margin status, and laterality. Ipsilateral breast tumor recurrence (IBTR), distant metastasis (DM), contralateral breast cancer (CLBC) and cause-specific survival (CSS) were compared by cumulative incidence (Gray's) and competing risks regression (Fine and Gray's), and overall survival (OS) and disease-free survival (DFS) by Kaplan-Meier (log-rank test). **Results:** Median follow-up was 4.6 y (2.0-14.7) for APBI and 9.0 y (5.4-27.0) for WBI. Median (range) or percentages are shown (Table). Patients did not differ by match criteria. There were 17 LR, 1 DM, 19 CLBC, 2 CSS, 22 OS, and 19 DFS events during follow-up. The patient groups had similar rates of cancer-related events including ipsilateral and contralateral breast recurrences at both five and eight years. Treatment type, age, tumor size, nuclear grade, ER status, and hormone therapy (HT) were not prognostic of LR or CLBC on uni- and multi-variate analyses. **Conclusions:** APBI provides equivalent and exemplary outcomes compared to WBI following breast-conserving surgery for DCIS. These findings support previous reports on the efficacy of APBI in the treatment of noninvasive breast carcinoma. Prospective randomized comparison of APBI to WBI for DCIS is needed.

	APBI (n=102)	WBI (n=306)	P
Age (y)	62 (43-84)	62 (29-88)	0.83
Tumor size (mm)	6 (0-28)	5 (1-30)	0.85
Nuclear grade			0.24
1	28%	31%	
2	54%	45%	
3	17%	24%	
ER status			0.76
Positive	88%	86%	
Margin status			0.09
Clear (≥2mm)	88%	93%	
Adjuvant HT	54%	55%	0.91
Detection by			0.63
Mammogram	93%	91%	
Patient	6%	5%	
Other	1%	4%	
Laterality			0.82
Left-sided	60%	61%	
Race			0.02
Caucasian	78%	90%	
African American	14%	6%	
Other	8%	4%	
Outcomes 5y / 8y			
IBTR	2% / 2%	2% / 3%	0.96
DM	0% / 0%	0% / 0%	0.93
CLBC	1% / 5%	3% / 4%	0.63
DFS	98% / 98%	98% / 97%	0.98
CSS	100% / 100%	100% / 100%	0.93
OS	96% / 96%	100% / 98%	0.04

1124   **General Poster Session (Board #31G), Sat, 1:15 PM-5:00 PM**

Volume-based parameters on FDG-PET/CT as early predictors of disease recurrence in postmastectomy breast cancer patients with one to three positive axillary lymph nodes without adjuvant radiotherapy.

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Background: The indication for postmastectomy radiotherapy (PMRT) in patients with 1-3 lymph node metastases in the axilla have been controversial, despite the recommendation that PMRT should be applied. In the current study, we focused our study on volume-based parameters of pretreatment FDG-PET/CT, with the aim of investigating a measurement that could help identify high-risk populations for recurrence. **Methods:** We retrospectively analyzed 88 patients of breast cancer treated with modified radical mastectomy and were found to have 1-3 metastatic axillary lymph nodes between 2006 and 2010. All of them were studied with FDG-PET/CT for initial staging. We evaluated the relationship between clinicopathologic factors or PET parameters including the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) and recurrence. MTV and TLG of the primary tumor and metastatic lymph node were measured by using semi-automatically delineated volume of interest (VOI) with an isocontour threshold of 40 % of the SUVmax. The optimal cutoffs of PET parameters were determined by ROC curve analysis. **Results:** The median follow up duration was 39 months. Median MTV was 21.1and median TLG was 42.7. Recurrence was observed in 10 patients. The area under the ROC curve of MTV and TLG for DFS was 0.82 and 0.85, respectively. In Cox univariate analysis, estrogen receptor status (HR = 6.8, p = 0.003), triple negativity (HR = 10.4, p = 0.0008), SUVmax (HR = 71.1, p = 0.001), MTV (HR = 130.3, p < 0.0001), and TLG (HR = 234.1, p = 0.0001) were significantly related to disease free survival (DFS). The estimated 3-year DFS rates were 96.4 % for the lower MTV group (< 31.8) and 71.4% for the higher MTV group (≥ 31.8, p = 0.0005). The estimated 3-year DFS rates were 95.8 % for the lower TLG group (< 109.6) and 50.0 % for the higher TLG group (≥ 109.6, p < 0.0001). On multivariate analysis, TLG was an independent prognostic factor of DFS (HR = 8.5, p = 0.005). **Conclusions:** Volume-based parameters on FDG-PET/CT were significant predictors of DFS in postmastectomy breast cancer patients with 1-3 metastatic axillary lymph nodes.

1125   **General Poster Session (Board #31H), Sat, 1:15 PM-5:00 PM**

PTEN-deficient breast cancer in neoadjuvant treatment.

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Background: Loss of function mutations in the tumour suppressor gene PTEN or lack of PTEN expression have both been observed in a wide range of human tumours. PTEN encodes a phosphatase, whose activity antagonizes PI3 kinase signal pathway by dephosphorylation the plasma membrane lipid, phosphoinositide-3,4,5-trisphosphate (PIP3). Loss of PTEN phosphatase activity is thought to foster tumorigenesis, at least in part, by causing downstream constitutive activation of AKT. In addition to this role, PTEN has been suggested to have a nuclear function in maintaining genomic stability[2]. Our proposal is to identify those tumours without expression of PTEN, their characteristics and response to treatment. **Methods:** We have studied PTEN expression by immunohistochemistry in tumours samples from 86 patients treated with neoadjuvant treatment. Normal breast epithelium or vascular endothelium were used as positive control. PTEN was evaluated by inmunoreactive stain score, taking into account staining intensity and percentage of positive cells, PTEN deficiency (PTEN -) has been stablished by a IRS=0[1]. We analyzed the PTEN localization (nuclear vs citoplasmatic). **Results:** In our serie, 38 (44.2%) of the tumours samples were PTEN deficient. Taking into account as reference PTEN + tumours, we have found that PTEN deficient tumours are more frequently; ductal carcinoma (94.2% vs 81.8%), G3 (72% vs 48.7%), ER negative (47% vs 30.4%), Triple negative (24.2% vs 15%) and higher Ki67 expression (>20%) in the 100% of PTEN deficient tumours. The pathological rate response was PTEN -:18.4% vs PTEN +:19.1% p:ns, and the recurrence rate was higher in PTEN- (26,3% vs 8,3%) p:0.025. **Conclusions:** The PTEN deficient breast tumours is associated to more histological aggressive profile, and we have not found relations with the pathological rate response to neoadjuvant treatment.

1126   **General Poster Session (Board #32A), Sat, 1:15 PM-5:00 PM**

Clinicopathologic features of multiple phyllodes tumors of the breast.

Fumi Yoshidaya, Naoki Hayashi, Atsushi Yoshida, Hiroshi Yagata, Hiroko Tsunoda, Koyu Suzuki, Seigo Nakamura, Hideko Yamauchi; St. Luke's International Hospital, Tokyo, Japan; St. Luke's International Hospital, Tokyo, Japan; Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, Tokyo, Japan

Background: Phyllodes tumor of the breast is one of the rare neoplasm accounting for 0.3-0.5% of all breast tumors. It is difficult to diagnose the histological type of phyllodes tumors preoperatively by radiological and even pathological findings. The aim of this study is to clarify the clinicopathological features of phyllodes tumors. **Methods:** We retrospectively reviewed records from 116 patients with phyllodes tumors who underwent surgery between 2003 and 2011. We determined the clinicopathological characteristics, including the presense of multiple lesions and the type of surgical procedure, of each histological type of phyllodes tumors which were classified as benign, borderline, and malignant. **Results:** The median follow-up time was 23.3 months. Benign phyllodes tumors were presented in 91 patients (78.4 %), borderline were in 17 patients (14.6 %), and malignant were in 8 patients (6.9 %). Ten patients (8.6 %) had multiple phyllodes tumors; 9 for ipsilateral and one for bilateral breasts. One hundred two patients underwent lumpetcomy and 14 patients underwent mastectomy. No patients received chemotherapy or radiation therapy. Noteworthy, all multiple tumors were diagnosed histologically benign. The median age at operation were 41 years (range, 12-72 years) for benign tumors, 44 years (26-67 years) for borderline, and 47 years (39-60 years) for malignant. The size of malignant tumors was significantly large (a median, 11.3 cm; range, 6-27 cm) compared to benign (a median, 4.4 cm; range 1-21 cm) and borderline (a median, 4.7cm; range 1-16 cm) (p = 0.001, and 0.03, respectively). Local recurrence developed in 14 of the 91 patients (15.4 %) with benign, 2 of the 17 patients (11.8 %) with borderline, and 2 of the 8 patients (25 %) with malignant tumors. Four patients (50 %) with malignant tumors but none with benign and borderline developed distant metastasis. Of the 4 patients, 3 had undergone mastectomy and one had lumpetcomy for initial treatment. No benign and borderline tumor had malignant change when tumors recurred. **Conclusions:** Our new findings indicated that multiple phyllodes tumors may be histologically benign. Furthermore, patients with benign or borderline phyllodes tumors had good prognosis regardless of surgical procedure.

1127 General Poster Session (Board #32B), Sat, 1:15 PM-5:00 PM

Does radiation therapy increase late cardiac death in patients with left breast cancer?

Chi Lin, Kyle A. Denniston, Mary E. Charlton; University of Nebraska Medical Center, Omaha, NE; University of Iowa College of Public Health/VA Center for Comprehensive Access and Delivery, Research and Evaluation, Iowa City, IA

Background: The objective of this study was to evaluate the effect of external beam radiation therapy (RT) on late cardiac death (CD) in patients with left breast cancer. **Methods:** A total of 529,246 patients who were diagnosed with adenocarcinoma of the breast between 1983 and 2004 and survived $\geq$ 5 years were identified from the SEER database. After excluding patients who were male, had right breast cancer, received brachytherapy or had missing data, 163,894 patients remained. Examined risk factors for CD include age ($\leq$49/50-59/60-69/70-100), race (white/non-white), stage (In situ/local/regional/distant), breast subsite (nipple and areola/inner quadrant/outer quadrant), diagnosis year (1983-1993/1994-2004), surgery status (none/less than mastectomy/mastectomy) and RT. Time to CD was evaluated using the Kaplan-Meier method. A multivariate logistic regression model was used to evaluate factors associated with the use of RT and the Cox Proportional Hazards model was used to evaluate risk factors for CD. **Results:** A multivariate logistic regression model revealed that patients who received RT tended to be younger, white, more recently diagnosed, have inner quadrant and more advanced disease and undergo less than mastectomy. Median overall survival for patients with RT was significantly longer than those without RT (263 vs. 226 months, Log-Rank p < .0001). RT group had a lower risk of CD than no-RT group (Log-Rank p < .0001). Median time to CD was not reached in either group. The probability of CD was increased with increasing age and stage, and decreased with more recent diagnosis year and after mastectomy. Cox model found RT to be associated with lower probability of CD (HR 0.66, 95% CI 0.62-0.70), after adjusting for age, stage, surgery status and diagnosis year. Race and breast subsite were not associated with CD. **Conclusions:** Patients with left breast cancer who survived $\geq$ 5 years and received RT had a lower risk of cardiac death than those who did not. The cause of this difference is unclear but suggests influence from an uninvestigated factor, potentially the increased use of cardiotoxic chemotherapy or other cardiovascular comorbidity in those patients not receiving RT. Continued study, accounting for such factors, is warranted.

1128   **General Poster Session (Board #32C), Sat, 1:15 PM-5:00 PM**

Nomogram for predicting breast-conservation surgery after neoadjuvant chemotherapy.

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Background: The indications for neoadjuvant systemic treatment (NST) have broadened to early breast cancer patients and more patients can undergo breast conservation with results in better cosmetic outcomes. However, a significant number of patients with operable breast cancer still require mastectomy after NST with a small number of patients experiencing disease progression which may hinder complete surgical resection. Therefore, accurate prediction of each patient's likelihood of achieving breast conservation after NST is important for establishing a treatment plan for patients with operable breast cancers. **Methods:** We identified 534 women from the Seoul National University Hospital Breast Care Center, who were stage II and III, and treated with neoadjuvant chemotherapy and surgery from Jan. 2001 to Dec. 2010. Breast conservation surgery (BCS) and tumor size reduction to less than 3cm were clinical outcome variables for nomograms, and we analyzed the various clinicopathologic factors best predicting these outcomes. To develop well-calibrated and exportable nomograms for BCS and for residual tumor size, we built each model in a training cohort and validated it in an independent validation cohort. **Results:** Of the 513 patients, pCR was observed in 10.5% and BCS was performed in 50.1%. The nomogram for predicting BCS and tumor size reduction to less than 3cm were constructed using logistic regressing model. Initial tumor size($p<0.001$), the distance between the lesion and the nipple ($p < 0.001$), the presence of suspicious calcifications in the mammography ($p = 0.0127$) and multicentricity ($p = 0.0146$) were independently associated with breast conservation surgery. ER status ($p = 0.001$), initial tumor size ($p < 0.001$), histologic type ($p = 0.012$) were independently associated with a residual tumor size <3cm. Mastectomy rate in the larger than 3cm tumors were 72.7%, and breast conservation surgery in smaller than 3cm tumors were 63.2%. ($p < 0.001$). **Conclusions:** In conclusion, we have established a new model to predict BCS and residual tumor size after NST. The model showed the outperformed prediction accuracy compared with previous similar models with reflecting novel factors impacting on surgical decision making.

1129	**General Poster Session (Board #32D), Sat, 1:15 PM-5:00 PM**

Clinicopathologic analysis of a large series of microinvasive breast cancer.

Joseph W. Leach, Tamera Lillemoe, Janet Krueger; Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Minneapolis, MN

Background: Microinvasive breast cancer (Tmic) is defined by the AJCC as extension of cancer cells beyond the basement membrane with no single focus larger than 1 mm. The clinical behavior of this entity is unclear. Most series suggest that prognosis is similar to non-invasive cancer although the literature is mixed. Surgical management typically reflects invasive breast cancer including lymph node sampling. Published incidence of nodal involvement is also variable with some small series reporting incidence as high as 20%. We present a clinicopathologic review of a large series from a community practice setting. **Methods:** Using the AJCC definition of Tmic, we retrospectively identified all cases treated within Allina Health System from 2001-2011. Inclusion criteria included no prior history of breast cancer and available follow-up data. Data collected included ER/PR and HER2 status (when available), margin status and surgical and adjuvant therapy. **Results:** 118 eligible cases were identified with a mean follow-up of 3.65 years and mean age of 56.8 years (34-88). 39 were triple negative and 29 were HER2+. ER/PR data was available on all cases, HER2 on 60. 72 were treated with mastectomy. All patients underwent axillary staging. Lymph node metastasis was identified in 2 cases (one triple negative, one HER2+). In one case the metastasis measured 0.25 mm, in the other 0.4 mm. Complete axillary dissection performed on both cases demonstrated no additional lymph node involvement. Isolated tumor cells were also identified in 9 cases. 2 cases developed local recurrence following lumpectomy and radiation, both in the ipsilateral breast. One recurred with microinvasive disease, the second with DCIS only. There were no cases of metastatic recurrence and no breast cancer associated deaths. **Conclusions:** The clinical behavior of microinvasive breast cancer in this series is similar to DCIS. The incidence of lymph node metastasis was low (1.7%) and there were no cases of distant metastasis. Our data supports management of microinvasive breast cancer as a subset of DCIS and suggests that the benefit of routine lymph node sampling is questionable.

1130 General Poster Session (Board #32E), Sat, 1:15 PM-5:00 PM

Influence of guideline-concordant adjuvant therapy on all-cause and disease-specific survival among breast cancer patients in rural Georgia.

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Background: This study examines whether receipt of chemo-, radiation, and hormonal therapy regimens that are jointly guideline concordant improve survival outcomes among women diagnosed with breast cancer in a rural region of the United States. **Methods:** All women identified by the state cancer registry residing in rural southwest Georgia diagnosed with early stage breast cancer during 2001-2003 were included. Medical chart abstraction and registry data were used to determine treatment concordance with the 2000 NIH consensus development conference guidelines on breast cancer treatment. Patients were Concordant versus Non-Concordant according to whether their receipt (or non-receipt) of each adjuvant therapy type was according to guidelines. To examine the effects of concordance on all-cause and breast cancer-specific survival, Cox models were developed that used both propensity score weighting and 2-stage residual inclusion instrumental variable techniques to adjust for patient selection effects. **Results:** In all-cause analyses, Concordance versus Non-Concordance was associated with significantly better survival (hazard ratios (HRs) 0.41 (95% CI: 0.24-0.72) to 0.54 (95% CI: 0.33-0.87). Similar findings emerged in breast cancer-specific survival analyses, with HRs significantly less than 1.0 in most cases. Diagnosis at older age or later disease stage strongly predicted poorer survival outcome; being not married was significant in all-cause but not breast cancer-specific models. Survival was not generally associated with surgical treatment delay, insurance status, socioeconomic status, rural/urban status, comorbidities, tumor grade, or hormonal status. HR for black women versus white was greater than 1.0 across models but never significant (p=0.05). **Conclusions:** Breast cancer patients in rural Georgia who received guideline-concordant adjuvant therapy had significantly better all-cause and breast cancer-specific survival, based on Cox model analyses that attempted to control for multiple clinical and demographic factors, as well as selection effects. These findings extend the evidence that guideline bundles of care improve outcomes.

1131   **General Poster Session (Board #32F), Sat, 1:15 PM-5:00 PM**

Incidence and characteristics of breast cancer following a diagnosis of ductal carcinoma in situ.

Xiudong Lei, Shaheenah S. Dawood, Constance T. Albarracin, Rebecca Dent, Sudeep Gupta, Javier Cortes, Elizabeth Ann Mittendorf, Thomas A. Buchholz, Ana M. Gonzalez-Angulo; The University of Texas MD Anderson Cancer Center, Houston, TX; Dubai Hospital, Dubai, United Arab Emirates; National Cancer Center Singapore, Duke-National University Singapore, Singapore, Singapore; Tata Memorial Centre, Mumbai, India; Vall d'Hebron University Hospital, Barcelona, Spain

Background: Recent data indicate that the incidence of DCIS is rising. The purpose of this retrospective population based study was to examine incidence of and factors that contribute to the development of a subsequent breast primary. **Methods:** Using the SEER registry we identified female pts with a primary DCIS diagnosed between 1990 to 2005. Pts who had an invasive or in situ malignancy diagnosed prior to a diagnosis of DCIS were excluded. Cumulative incidence of a subsequent breast primary (invasive/non invasive) was estimated and compared across groups using the Chi-square test. Multivariable logistic regression models were then fitted to determine factors that could predict for the development of a subsequent breast primary. **Results:** 96,130 pts were identified of whom 14,573 (15.2%) had subsequent primaries. 9,037 (62%) pts had a subsequent primary in the breast of which 5,915 (65.5%) pts had an invasive breast cancer. Among pts who developed an invasive breast cancer 68% had hormone receptor positive disease, 59% had grade I/II disease and 80% had stage I/II disease. 2 and 5-year cumulative incidence of developing a subsequent breast primary was 3.2% and 5.9% respectively. 2 and 5-year cumulative incidence of developing a subsequent invasive breast primary was 1.6% and 3.4% respectively. 5-year cumulative incidence of developing a subsequent breast primary among pts who were of white, black and other race was 5.8%, 6.8% and 6.1% respectively (P<0.001). In the multivariable logistic model the probability of developing a subsequent breast primary decreased with each increasing year of diagnosis of DCIS (OR 0.91, 95%CI 0.91-0.92, p<0.001). Other factors that predicted for the development of a subsequent breast primary included younger age at diagnosis, non-white race and lack of surgical or radiation therapy for DCIS. **Conclusions:** Our results indicate that a significant proportion of pts with a diagnosis of DCIS go on to develop invasive breast cancer and may warrant further investigation to determine biological risk factors, appropriate screening procedures and possible interventions to decrease incidence. Target groups that may benefit include pts who are young and of non white race at the time of diagnosis of DCIS.

1132   **General Poster Session (Board #32G), Sat, 1:15 PM-5:00 PM**

Distinctive lipid profiles of human breast cancer and adjacent normal tissues by desorption electrospray ionization mass spectrometry imaging.

Diana L. Caragacianu, Xiaohui Liu, Isaiah Norton, Jennifer Ide, Andrea Richardson, Deborah Dillon, Ferenc A. Jolesz, Mehra Golshan, Nathalie Y.R. Agar; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA

Background: Routine intra-operative distinction between normal breast tissue and tumor is currently not possible in breast conserving surgery (BCS). This limitation affects the success of surgery, resulting in up to 40% requiring more than one operative procedure. Desorption electrospray ionization mass spectrometry (DESI MS) has been successfully used to discriminate between normal and cancerous human tissues from anatomical sites such as the liver and brain. The aim of this proof of concept study was to determine the feasibility of using DESI MS imaging for tissue identification and differentiation of breast cancer versus normal tissue. **Methods:** DESI MS imaging was carried out on 14 human invasive breast cancer samples. Breast cancer and adjacent normal paired human tissue sections (margin of tumor, 2cm and 5 cm from tumor) from 14 patients undergoing mastectomy were flash frozen in liquid nitrogen, sectioned, and thaw mounted to glass slides. All samples were imaged using DESI MS at 200 μm imaging resolution. DESI MS images were overlaid and compared with hematoxylin and eosin (H&E) images of the same sections. **Results:** Discrimination between cancer and adjacent normal tissue was achieved on the basis of the spatial distribution and varying intensities of particular fatty acids and lipid species. Several fatty acids such as oleic acid (m/z 281) and arachidonic acid (m/z 303) displayed much greater signal intensities in the cancer specimen compared to low or undetectable intensities in normal tissue. The cancer margins delineated by the DESI MS images of these molecules were consistent with H and E images of the tumor edge. Cancerous tissue was distinguished from normal tissue based on the qualitative assessment of molecular signatures and the distinction was in agreement with expert histopathology evaluation in 85% of samples. **Conclusions:** Our findings offer proof of concept that examination and classification of breast normal and cancer tissue by mass spectrometry imaging is highly accurate. The results are encouraging for development of a MS-based method that could be utilized intra-operatively for rapid detection of residual cancer tissue in the lumpectomy bed in BCS.

1133 General Poster Session (Board #32H), Sat, 1:15 PM-5:00 PM

Immediate tissue expander breast reconstruction following mastectomy in pregnancy-associated breast cancer.

Katherina Zabicki Calvillo, Diana L. Caragacianu, Yoon S. Chun, Stephanie Caterson, Jennifer Ruth Bellon, Julia S. Wong, Susan Troyan, Esther Rhei, Laura Stewart Dominici, Katherine E. Economy, Nadine M. Tung, Lidia Schapira, Jane L. Meisel, Ann Partridge, Erica L. Mayer; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA

Background: Management of pregnancy-associated breast cancer (PABC) requires balancing benefits of therapy with potential risks to the developing fetus. Surgical management can be influenced by gestational age of fetus and tumor stage. Minimal data describe surgical and obstetrical outcomes after mastectomy with immediate breast reconstruction (IR) in a pregnant patient (pt). **Methods:** Pts who underwent IR after mastectomy were identified within a multi-institutional PABC cohort. Retrospective chart review was performed for outcomes including adverse intraoperative events, immediate postoperative complications, gestational age at delivery and fetal weight. Other parameters evaluated included stage at presentation, duration of surgery, and use of delayed reconstruction in pts who did not receive IR. **Results:** Within a cohort of 79 PABC pts, 25 (32%) had mastectomy while pregnant, 8 (32%) of whom had IC; 17 (68%) did not undergo IR. Mean gestational age at time of IR was 16.6 weeks (range 10-30) and all IR utilized tissue expander (TE) placement followed by permanent implant placement in 7 pts. In the IR cohort, 1 (12.5%) pt was stage 0, 3 (37.5%) stage I and 4 (50%) stage IIB. There were no intraoperative or immediate postoperative surgical complications. The mean duration of surgery was 198 min with IR (7 pts) vs. 157 min without IR (available for 12 pts). All women who underwent IR delivered at, or close to, term infants of normal birthweight. One pt had pre-term labor after surgery at 29 weeks which resolved with tocolysis. Mean gestational age at delivery was 37.3 weeks in the IR cohort vs. 36.3 weeks in the non-IR cohort. No fetal abnormalities or major obstetrical complications were seen after IR. Post-mastectomy radiation (PMRT) was provided after pregnancy in 2 pts (25%) in the IR cohort and cosmetic outcome was not adversely affected. **Conclusions:** This report represents one of the largest series describing IR after mastectomy in PABC. Results suggest immediate tissue expander placement after mastectomy may increase duration of surgery but does not lead to adverse obstetrical or fetal outcomes. IR with tissue expanders may preserve reconstructive options when PMRT is indicated.

TPS1134   **General Poster Session (Board #33A), Sat, 1:15 PM-5:00 PM**

Phase II study of ruxolitinib in patients with pStat3+ breast cancer.

Nancy U. Lin, Rebecca Sue Gelman, Jane E. Brock, Aditya Bardia, Erica L. Mayer, Beth Overmoyer, Vivian Wang, Marie Iannone, Ian E. Krop, Kornelia Polyak, Eric P. Winer; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Multiple lines of evidence implicate the IL-6/JAK2/Stat3 signaling pathway in metastatic progression and therapeutic resistance in breast cancer (Marotta et al, *JCI* 2011; Britschgi et al, Cancer Cell 2012). Ruxolitinib, an oral inhibitor of JAK1 and JAK2, is approved for the treatment of intermediate or high-risk myelofibrosis, but has not been extensively tested in solid tumors. **Methods:** Pts with triple-negative breast cancer or inflammatory breast cancer of any subtype are eligible for prescreening of archival tumor tissue for pStat3 expression by immunohistochemistry. Pts with high (Cohort A; T-score >5) or low (Cohort B; T-score 3-4) pStat3 expression, measurable disease, adequate organ function, ECOG PS 0-2, and progression through > 1 line of prior therapy may proceed to receive ruxolitinib, 25 mg orally twice daily. Staging studies are performed at baseline (BL) and every 8 weeks (wk). Baseline tumor biopsy is required for pts who have accessible disease, with an optional biopsy at progression. Blood for IL-6, CRP, and circulating tumor cells are collected at BL, Wk 4, and off-treatment. Patient reported outcomes including EORTC QLQ C-30 and the M.D. Anderson Symptom Inventory are collected at BL, Wk 4, Wk 8, and off-treatment. Statistical Considerations: The primary endpoint of this open-label phase 2 trial is objective response by RECIST 1.1. The study is designed to distinguish between a response rate of 5% versus 20% in each cohort, separately. If > 2 responses out of 21 pts are observed in the first stage of Cohort A, a further 20 pts will be entered on that cohort; the agent will be deemed worthy of further study if > 5 of the total 41 pts achieve an objective response (power 0.90, type I error 0.046). Cohort B will open to accrual if Cohort A passes the first stage. If > 2 responses out of 21 pts are observed in the first stage of Cohort B, a further 20 patients will be entered into Cohort B, and the agent will be deemed worthy of further study if > 5 of the total 41 pts achieve an objective response (power 0.90, type I error 0.046). Study Status: A total of 85 patients have consented for prescreening of tumor tissue. As of January 3, 2013, 5 of a planned 41 patients with high pStat3 IHC scores have been treated with ruxolitinib, and accrual is ongoing. Clinical trial information: NCT01562873.

TPS1135 General Poster Session (Board #33B), Sat, 1:15 PM-5:00 PM

An adaptive randomized phase II trial to determine pathologic complete response with the addition of carboplatin with and without ABT-888 to standard chemotherapy in the neoadjuvant treatment of triple-negative breast cancer.

Tiffany P. Avery, Adam C. Berger, Albert J. Kovatich, Hallgeir Rui, Terry Hyslop, Edith P. Mitchell; Thomas Jefferson University, Philadelphia, PA; Department of Surgery, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; MDG Global Systems, Windber, PA; Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; Kimmel Cancer Center of Thomas Jefferson University, Philadelphia, PA

Background: Inhibition of poly (ADP-ribose) polymerase (Parp) is a potential targeted therapy for triple-negative breast cancer (TNBC). Clinical trials of Parp inhibitors in metastatic TNBC have shown conflicting results. Issues regarding the use of Parp inhibitors in TNBC include choosing a selective Parp inhibitor and selecting an appropriate chemotherapy backbone. The current trial addresses these questions by combining a validated Parp inhbitor, ABT-888, with carboplatin and paclitaxel. Platinum agents have shown synergy with Parp inhibitors in preclinical models and efficacy in clinical trials. The combination of paclitaxel and carboplatin with Parp inhibitors has shown efficacy in phase I trials. **Methods**: This is a phase II, two-arm neoadjuvant trial of women with TNBC. Eighty patients will be enrolled. Randomization will follow a 1:1 allocation initially, then will follow a Bayesian adaptive allocation in which each prior response will be evaluated and patients assigned preferentially to the better responding arm. The primary endpoint is pathologic complete response (pCR). Secondary endpoints include correlation of pCR with biomarkers, imaging, and circulating tumor cells (CTCs). Treatment: Arm 1: Paclitaxel 80 mg/m^2 + carboplatin AUC=2 (12 weekly cycles) + filgrastim followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 (4 cycles every 3 weeks) + pegfilgrastim. Arm 2: ABT-888 (150mg PO bid) + paclitaxel 80 mg/m^2 + carboplatin AUC=2 (12 weekly cycles) + (filgrastim) followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 (4 cycles every 3 weeks) + (pegfilgrastim). Eligibility: Women $\geq$ 18 years old with clinical stage IIB or stage IIIA, IIIB, or IIIC untreated TNBC (ER <1% , PR <1% , Her-2/neu 0, 1+ on IHC or 2+ and FISH ratio < 1.8) are eligible. Correlative Studies: Correlation of pCR with tissue expression of CK5, EGFR, ERCC1, Ki-67, Parp1, and longitudinal enumeration of CTCs will be done. Exploratory tissue biomarkers with prognostic and predictive value will be correlated with pCR. Enrollment: The trial will begin accrual in February 2013.

TPS1136 **General Poster Session (Board #33C), Sat, 1:15 PM-5:00 PM**

The ENCHANT-1 trial (NCT01677455): An open label multicenter phase II proof of concept study evaluating first-line ganetespib monotherapy in women with metastatic HER2-positive or triple-negative breast cancer (TNBC).

Ahmad Awada, Angel Augusto Rodriguez, Anthony Kong, John Kalil Erban, Javier Cortes, Max S. Mano, Edith A. Perez, Iman El Hariry, Vojislav M. Vukovic, Florentina Teofilovici, Ilker Yalcin, Robert Bradley, David A. Cameron; Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium; Methodist Cancer Center, Houston, TX; Churchill Hospital, Oxford University Hospitals NHS Trust and University of Oxford, Oxford, United Kingdom; Division of Hematology Oncology, Tufts Medical Center, Boston, MA; Vall d'Hebron University Hospital, Barcelona, Spain; Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil; Mayo Clinic, Jacksonville, FL; Synta Pharmaceuticals, Inc., Lexington, MA; University of Edinburgh, Edinburgh, Scotland

Background: Hsp90 is a molecular chaperone protein required for the stabilization and activation of many proteins, referred to as Hsp90 'clients', including those commonly implicated in breast tumorigenesis such as HER2, EGFR, ER, PI3K, AKT, P53 and VEGFR. Ganetespib is a novel triazolone inhibitor of Hsp90 being studied in over 20 clinical trials, with over 700 patients treated to date. Ganetespib is ~50x more potent than 1st-generation Hsp90 inhibitors, and has been well tolerated in clinical trials with a favorable safety profile. Mild to moderate, transient diarrhea is the most common adverse event associated with ganetespib infusion and is manageable with appropriate supportive care. Ganetespib has shown activity in preclinical models of HER2+, ER+/PR+ and triple negative breast cancer (TNBC). In a phase I trial, ganetespib demonstrated single-agent clinical activity in HER2+ disease with an objective response rate (ORR) of 15% and a disease stabilization rate of 46% in heavily pretreated patients. This efficacy-screening study is designed to provide further evidence of ganetespib activity and identify potentially predictive biomarkers in metastatic breast cancer. **Methods:** The ENCHANT-1 trial is an international, first-line Phase II study in two cohorts of breast cancer patients: Cohort A, HER2 amplified (n=35), and Cohort B, TNBC (n=35). HER2+ patients must have received prior anti-HER2 therapy in the adjuvant setting. Patients are treated with ganetespib at 150 mg/m^2 twice weekly on a three out of four-week regimen. Primary endpoint: ORR assessed using RECIST1.1 criteria. Key secondary endpoints include metabolic effects as assessed by PET/CT at week 3. Tumor genetic signature and proteomic profiling are performed on patient's tumors in an effort to develop biomarkers of response. At the time of submission 6 patients have been enrolled into this study. Clinical trial information: NCT01677455.

TPS1137 **General Poster Session (Board #33D), Sat, 1:15 PM-5:00 PM**

Adjuvant phase III trial to compare intense dose-dense adjuvant treatment with EnPC to dose dense, tailored therapy with dtEC-dtD for patients with high-risk early breast cancer (GAIN-2).

Volker Moebus, Helmut Forstbauer, Grischa Wachsmann, Andreas Schneeweiss, Angelika Ober, Ekkehard von Abel, Petra Krabisch, Heinz-Gert Hoeffkes, Karin Kast, Bernd Christensen, Michael Niedermeier, Mustafa Deryal, Christoph Uleer, Yvonne Fauster, Thomas Goehler, Sibylle Loibl, Valentina Nekljudova, Gunter Von Minckwitz, German Breast Group; Klinikum Frankfurt Hoechst, Frankfurt, Germany; GOSPL Troisdorf, Troisdorf, Germany; Klinikum Sindelfingen-Böblingen, Sindelfingen-Böblingen, Germany; University Hospital Heidelberg, Heidelberg, Germany; St. Vincent Hospital Limburg, Limburg, Germany; Klinikum Schwäbisch-Gmünd, Schwäbisch-Gmünd, Germany; Klinikum Chemnitz, Chemnitz, Germany; Klinikum Fulda, Fulda, Germany; Department of Gynecology and Obstetrics, University Hospital Dresden, Dresden, Germany; Ruppiner Kliniken, Neuruppin, Germany; Onkologische Gemeinschaftspraxis, Memmingen, Germany; Caritasklinik St. Theresia Saarbrücken, Saarbrücken, Germany; Gynecology Practice, Hildesheim, Germany; Kreiskrankenhaus Freudenstadt, Freudenstadt, Germany; Onkozentrum Dresden, Dresden, Germany; German Breast Group, Neu-Isenburg, Germany

Background: Intense dose-dense (idd) chemotherapy (CT) significantly improves overall survival in breast cancer patients. Two preceding trials explored iddETC vs a dd combination of EC-TX (GAIN) and dtEC-dtD vs conventional dosed FEC-D (Panther). Nab-paclitaxel (nP) provides a better toxicity profile and higher efficacy compared to solvent based taxanes and might be preferred in an idd regimen. **Methods:** This is a multicenter, prospective, randomized, open-label phase III trial comparing iddEnPC or dtEC-dtD as adjuvant CT. Pts with uni- or bilateral primary high risk node-positive (N^+) breast cancer (BC) and centrally confirmed ER/PR/HER2 and Ki-67 status can be included. Luminal A pts are only recruited with N+ $\geq$4. Randomization to iddEnPC or dtEC-dtD will be stratified by biological subtype defined by hormone receptor, HER2 and Ki-67. The iddEnPC arm will receive epirubicin (150mg/m^2) q2w x3 followed by nP (260-330mg/m^2, dose to be determined in run-in phase) q2w x3, followed by cyclophosphamide (2g/m^2) q2w x3. The dtEC-dtD arm will receive EC (38-120/450-1200 mg/m2) q2w x4 followed after 1 wk rest by docetaxel (60-100mg/m2) q2w x4. GAIN-2 will compare toxicity and efficacy of an idd regimen (EnPC) vs a dd regimen with modification of single doses depending on individual hematological and non-hematological toxicities. Primary objective is invasive disease-free survival (IDFS). Secondary objectives are survival by other definitions, compliance, safety, side effects of taxanes and subgroup analyses (by 0-3, 4-9 or 10+ involved nodes and Ki-67). Efficacy analyses are planned 60 mths after end of accrual, safety interim analyses after 200 and 900 pts have completed CT. It was assumed that dtEC-dtD will achieve a 5-yr IDFS of 75% and ddEnPC will improve IDFS to 79% (HR 0.819) with a power of 80% (α=0.05, ß= 0.2).GAIN-2 is registered under NCT01690702 Results: 75pts were recruited since 1stOct 2012. Recruitment (in total 2886 pts) is planned for 36 mths in 80-100 sites in Germany. Run-in safety data to be presented. Conclusion: GAIN-2 will compare the efficacy of adjuvant iddEnPC and dtEC-dtD in pts with early N^+ BC. Clinical trial information: NCT01690702.

TPS1138   **General Poster Session (Board #33E), Sat, 1:15 PM-5:00 PM**

Randomized, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple-negative or luminal b/HER2 normal breast cancer (GENEVIEVE).

Stefan Paepke, Sherko Kümmel, Jens U. Blohmer, Serban Dan Costa, Holger Eidtmann, Wolfgang Eiermann, Bernd Gerber, Claus Hanusch, Joern Hilfrich, Jens Bodo Huober, Christian Jackisch, Andreas Schneeweiss, Carsten Denkert, Keyur Mehta, Sibylle Loibl, Gunter Von Minckwitz, German Breast Group; TU München, München, Germany; Department of Obstetrics and Gynecology, University of Duisburg-Essen, Essen, Germany; Brustzentrum Sankt-Gertrauden-Krankenhaus, Berlin, Germany; Universitaets-Frauenklinik, Magdeburg, Germany; Universitätsklinikum Schleswig-Holstein - Klinik für Gynäkologie und Geburtshilfe, Kiel, Germany; Interdisziplinäres Onkologisches Zentrum München, Munich, Germany; Klinikum Sued, Department of Obstetrics and Gynecology, Rostock, Germany; Rotkreuzkliniken, Muenchen, Germany; Eilenriedeklinik, Hannover, Germany; University Duesseldorf, Duessledorf, Germany; Klinikum Offenbach, Offenbach, Germany; National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany; Charité-Universitätsmedizin Berlin, Institute of Pathology, Berlin, Germany; German Breast Group, Neu-Isenburg, Germany

Background: Cabazitaxel is a new taxoid promoting the tubulin assembly in vitro and stabilizing microtubules against cold-induced depolymerization as efficiently as docetaxel. It has shown superior survival against mitoxantrone plus prednisone in docetaxel pre-treated hormone refractory metastatic prostate cancer pts leading to its registration. It showed a favorable toxicity profile with a low rate of alopecia. In the GENEVIEVE study it will be compared to weekly paclitaxel, which is currently most widely used in breast cancer (BC) pts. **Methods:** This is a prospective multicenter, randomized, open label study investigating efficacy and safety of cabazitaxel. Pts with uni- or bilateral primary BC (stage cT3/T2/T1c and cN+/T1c and pNSLN+), tumor lesion $\geq$ 2cm (palpation) or $\geq$ 1cm (sonography) and centrally confirmed TNBC or luminal B/HER2- can be included. Pts will be randomized to four q3w cabazitaxel (25mg/m² i.v.) vs. 12 q1w paclitaxel (80mg/m² i.v.). Randomization will be stratified by nodal status and subtype. Treatment will be given until surgery, disease progression, unacceptable toxicity or withdrawal of consent. The primary objective is pathologic complete response (pCR) (ypT0/is ypN0/+). Secondary objectives are pCR in stratified subgroups and by other definitions, objective response rate, pCR and local recurrence free survival in pts with clinical complete response and neg. core biopsy before surgery, breast conservation rate, toxicity, compliance, survival rates, biomarkers predicting response. Assuming 15% pCR in controls and targeting a smallest clinical improvement of 10% (i.e. pCR = 25% in experimental arm), a total of 326 pts (163/arm) are required for the one-sided proportion comparison test (α=0.1) with 80% power. The trial is registered under NCT01779479. Results: Recruitment is planned for 12 mths in 45 (+10 back-up) sites in Germany. 1st pt in is planned for Feb 2013. Conclusion: GENEVIEVE will rapidly and precisely compare efficacy and tolerability of cabazitaxel vs. paclitaxel to decide if further development in BC is reasonable. Clinical trial information: NCT01779479.

TPS1139   **General Poster Session (Board #33F), Sat, 1:15 PM-5:00 PM**

NSABP B-47: A randomized phase III trial of adjuvant therapy comparing chemotherapy alone to chemotherapy plus trastuzumab in women with node-positive or high-risk node-negative HER2-low invasive breast cancer.

Louis Fehrenbacher, Jong-Hyeon Jeong, Priya Rastogi, Charles E. Geyer, Soonmyung Paik, Patricia A. Ganz, Stephanie R. Land, Joseph P. Costantino, Sandra M. Swain, Eleftherios P. Mamounas, Norman Wolmark; National Surgical Adjuvant Breast and Bowel Project and Kaiser Permanente Northern California, Vallejo, CA; Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA; NSABP and the University of Pittsburgh Cancer Institute, Pittsburgh, PA; NSABP and the University of Texas, Southwestern Medical Center, Dallas, TX; NSABP, Pittsburgh, PA; NSABP; and the Division of Cancer Prevention and Control Research, UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, CA; NSABP Biostatistical Center, Pittsburgh, PA; National Surgical Adjuvant Breast and Bowel Project Biostatistical Center, University of Pittsburgh, Graduate School of Public Health, Department of Biostatistics, Pittsburgh, PA; NSABP and the Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC; MD Anderson Cancer Center Orlando, Orlando, FL; National Surgical Adjuvant Breast and Bowel Project; The Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA

Background: Adjuvant trastuzumab trials in HER2+ breast cancer (BC) demonstrated a large reduction in recurrence and death. Central testing showed HER2 non-amplified participants derived similar benefit. Among HER2-amplified patients (pts), multiple studies showed no effect on benefit by degree of amplification. Blinded internal and external review confirmed the non-amplified nature of the HER2 normal group. Based on these findings, NSABP B-47, sponsored by the NCI, was activated January 2011 and is actively accruing. The study is NCI central IRB approved, open via the CTSU, and endorsed by SWOG, ECOG, and RTOG. **Methods:** Study**:** Chemotherapy treatment is by physician choice: The non-anthracycline regimen is TC (docetaxel 75 mg/m2, cyclophosphamide (C) 600 mg/m2) IV q 3 wks for 6 cycles; the anthracycline regimen is AC → WP (doxorubicin 60 mg/m2 and C 600 mg/m2 IV either q 3 wks or q 2 wks [investigator discretion] for 4 cycles → paclitaxel 80 mg/m2 IV wkly for 12 doses). Pts are randomly assigned to chemotherapy with or without trastuzumab for 1 year. Pts receive adjuvant radiation therapy and endocrine therapy, as clinically indicated. Detailed menstrual history, concurrent medications, weight changes, and biomarkers (estrogen, stress, inflammation), are being collected. Eligibility: Eligibility includes: node positive or high risk node negative BC pts; HER2 IHC 1+ or 2+ scores, but non amplified by FISH; normal cardiac, renal, and liver function. Detailed eligibility will be provided. Statistical Design: The primary aim is to determine whether the addition of trastuzumab to chemotherapy improves invasive disease-free survival (IDFS). 3,260 pts 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. First pt was entered in February 2011. As of January 23, 2013, 1,416 of 3,260 (43.4 %) pts have been enrolled. Updated information on enrollment and study background will be provided. Support**:** NCI U10-12027, -37377, 69651, 69974, and Genentech, Inc. Clinical trial information: NCT01275677.

TPS1140 **General Poster Session (Board #33G), Sat, 1:15 PM-5:00 PM**

Phase II study of eribulin mesylate as first- or second-line therapy for metastatic HER2-negative breast cancer.

Mitsuhiko Iwamoto, Nayuko Sato, Risa Terasawa, Hiroya Fujioka, Yuko Takahashi, Kosei Kimura, Satoru Tanaka, Kazuhisa Uchiyama; Osaka Medical College, Osaka, Japan; Osakaq Medical College, Osaka, Japan

Background: Eribulin mesylate is a nontaxane microtubule dynamics inhibitor that is approved in patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens (including an anthracycline and a taxane) for metastatic breast cancer. In a previous phase III study, eribulin mesylate demonstrated to significant improvement in overall survival in patients with heavily pretreated, locally recurrent or metastatic breast cancer when compared to treatment of physician's choice. The majority of patients were HER2-negative and all had previously failed 2 or more regimens. Overall, the tolerability and positive phase III findings in this patient population suggest eribulin mesylate may provide a treatment advantage when given earlier in the course of therapy for HER2-negative, metastatic breast cancer. **Methods:** This study is phase II, multicenter, open-label, single-arm in patients with HER2-negative metastatic breast cancer who have been treated with chemotherapeutic regimens including an antheracycline and a taxane. Eribulin mesylate ($1.4mg/m^2$) will be given on days 1 and 8 of each 21-day cycle. The primary endpoint is objective response rate, and secondary endpoints include duration of response, progression-free survival, overall survival, the safety of the treatment, and quality of life. Eligibility Criteria: Patients must have confirmed HER2-negative metastatic breast cancer with at least 4 weeks since prior neoadjuvant or adjuvant chemotherapy, and have not received over 2 chemotherapeutic regimens for metastatic disease. Additional eligibility criteria include adequate performance status (ECOG PS:0-2) and end organ/marrow function, and ejection fraction $> 50\%$. Accrual: This study began in December 2012. The expected end of accrual of 35 patients will be the last quarter 2015.

TPS1141 **General Poster Session (Board #33H), Sat, 1:15 PM-5:00 PM**

A randomized phase III trial comparing nanoparticle-based paclitaxel with solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (GeparSepto): GBG 69.

Christian Jackisch, Frank Wiebringhaus, Bettina Conrad, Michael Weigel, Bahriye Aktas, Harald Wagner, Kunibert Latos, Andreas Kohls, Ute Bueckner, Tanja Hauzenberger, Nikola Bangemann, John Hackmann, Michael R. Clemens, Bernhard Heinrich, Oliver Tome, Sibylle Loibl, Valentina Nekljudova, Gunter Von Minckwitz, German Breast Group; Klinikum Offenbach, Offenbach, Germany; St. Barbara-Klinik Hessen, Hamm, Hamm, Germany; Elisabeth Krankenhaus Kassel, Kassel, Germany; Leopoldina-Krankenhaus der Stadt Schweinfurt, Schweinfurt, Germany; Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany; Praxis, Fuerth, Germany; Katharinen-Hospital Unna, Germany, Unna, Germany; Ev. Krankenhaus Ludwigsfelde-Teltow, Ludwigsfelde-Teltow, Germany; Praxis Dr. Bückner, Bochum, Bochum, Germany; Klinikum St. Marien, Amberg, Amberg, Germany; Charité-Universitätsmedizin Berlin, Berlin, Germany; Marienhospital Witten, Witten, Germany; Klinikum Mutter-haus, Trier, Germany; Hämatologisch-Onkologische-Praxis Augsburg, Augsburg, Germany; St. Marienklinik, Karlsruhe, Germany; German Breast Group, Neu-Isenburg, Germany

Background: Anthracyclines (A) followed by taxanes (T) are standard of care for neoadjuvant therapy in breast cancer (BC). A reverse sequence of T followed by A was suggested to achieve higher pCR rates. Previous studies have shown that dual anti-HER2 blockade is superior to trastuzumab (H) alone and thus can increase the pCR rate by 20%. Nab-paclitaxel (nP) is a solvent-free formulation of P encapsulated in albumin and might also improve the pCR rate with eventually lower toxicity. **Methods:** The GeparSepto study (NCT01583426) will randomize 1200 patients to either nP (150 mg/m²) q1w or P (80mg/m²) q1w for 12 weeks followed by 4 cycles conventionally dosed EC (E 90mg/m², C 600 mg/m²) q3w for 4 cycles. Primary objective is to compare the pCR rate (ypT0+ ypN0). Patients with untreated, histologically confirmed cT2- cT4d BC can be included. HER2+ patients receive H (loading dose 8mg/kg; 6 mg/kg) plus pertuzumab (loading dose 840 mg; 420 mg) q3w concomitantly. Biomaterial including FFPE from core biopsy, serum, plasma and full blood is collected. HER2, ER, PgR, Ki67 and SPARC status will be centrally assessed prior to randomization for stratification. P was assumed to achieve a pCR rate of 33% which will be increased to 41% when using nP, corresponding to an odds ratio of 1.41. To investigate resistance to anti-HER2 treatment, patients with HER2+ BC are randomized prior to start of chemotherapy to receive either 6 weeks H, pertuzumab or the combination as biological window with biomaterial collection prior to start of therapy and after week 6 prior to start of chemotherapy. **Results:** After been approved by ethics committees and authorities recruitment started in 7/2012 in 56 sites. 293 patients were recruited (53 HER2+; 240 HER2-) by 1st Feb 2013. A first safety interim analysis is planned after 60 patients have finished therapy. **Conclusions:** GeparSepto investigates the efficacy of neoadjuvant nP compared to solvent-based P given weekly with a dual blockade of the HER2 receptor in HER2-pos BC. Interim safety results for nP will be presented. The window-substudy is funded within the EU-FP7 project RESPONSIFY No 278659. Clinical trial information: NCT01583426.

TPS1142^   **General Poster Session (Board #34A), Sat, 1:15 PM-5:00 PM**

MERiDiAN: A phase III, randomized, double-blind study of the efficacy, safety, and associated biomarkers of bevacizumab plus paclitaxel compared with paclitaxel plus placebo, as first-line treatment of patients with HER2-negative metastatic breast cancer.

David Miles, Leonardo Faoro, Yan V. Wang, Joyce O'Shaughnessy; Mount Vernon Cancer Centre, Northwood, United Kingdom; Genentech, Inc., South San Francisco, CA; Texas Oncology–Baylor Charles A. Sammons Cancer Center, Dallas, TX

Background: Bevacizumab (BV), a humanized monoclonal antibody targeting the angiogenic VEGF, has demonstrated activity in patients with metastatic breast cancer (MBC). Plasma VEGF-A levels ($[VEGF\text{-}A]_p$) appear to positively correlate with the effect of BV on progression-free survival (PFS) in MBC, metastatic pancreatic, and advanced gastric cancers. The MERiDiAN study will prospectively investigate (1) whether baseline $[VEGF\text{-}A]_p$ predict treatment benefit with BV, (2) efficacy of BV with weekly paclitaxel (P), based on previously observed differences in the magnitude of benefit compared with BV + non-P chemotherapies. **Methods:** MERiDiAN is a global, randomized, double-blind, phase III study enrolling patients with HER2-negative MBC (first patient was enrolled in August 2012). The co-primary endpoints are PFS by investigator assessment in the intent-to-treat (ITT) population, and PFS in the subgroup with high baseline $[VEGF\text{-}A]_p$. Secondary endpoints are overall survival (OS), 1-year survival, objective response rate and duration, and safety. Exploratory objectives include assessing the predictive or prognostic potential of blood, DNA and tumor tissue markers, and genetic variants involved in angiogenesis and tumorigenesis, with regard to BV efficacy and safety. Patients will be randomized 1:1 to either P 90 mg/m^2 IV weekly (qw) for 3 weeks followed by a 1-week rest and BV 10 mg/kg every 2 weeks (q2w) until disease progression (PD); or P 90 mg/m^2 IV qw for 3 weeks followed by a 1-week rest and placebo 10 mg/kg q2w until PD. An interim analysis of OS will be performed at the time of the primary PFS analysis. Clinical Trial Registry Number NCT01663727. Clinical trial information: NCT01663727.

TPS1143   **General Poster Session (Board #34B), Sat, 1:15 PM-5:00 PM**

Randomized controlled phase II trial of simvastatin as prophylaxis against radiation-induced skin toxicity in breast cancer patients.

Shibu Joseph, Glenys Round, Michael B. Jameson, Jenny May Boyd, Rajan Ragupathy; Waikato Hospital, Hamilton, New Zealand; Waikato District Health Board, Hamilton, New Zealand

Background: Most women receiving adjuvant radiation (RT) for breast cancer (BC) have significant acute skin toxicities ranging from erythema to moist desquamation. Late skin toxicities include fibrosis and telangiectasia. The inflammatory response to RT is mediated by RT-induced endothelial cell expression of the cell adhesion molecule E-selectin, to which neutrophils and monocytes adhere and then infiltrate into tissues. Blockade of this mechanism could interrupt the inflammatory cascade at an early stage. Preclinical studies have shown that statins can inhibit RT-induced E-selectin expression and skin and intestinal inflammation in vivo without impairing DNA damage or tumour response to RT. Retrospective clinical studies have shown reduced relapse rates with statins in breast cancer patients. Thus statins have the potential to reduce the acute RT-induced inflammatory component without compromising the DNA-damaging effects essential to cancer cell death. This is the only registered trial evaluating the effects of statins on acute RT toxicity. **Methods:** Randomised open controlled phase II trial of simvastatin 40mg daily during and for 3 weeks after RT. Eligibility: women with invasive or in-situ BC receiving whole-breast +/- lymphatic RT; dose fractionation schedules include 50Gy/25 #, 45Gy/20#, 42.5Gy/16 # or 40Gy/15#, with or without a boost; may have had prior chemotherapy, and be on hormonal or Trastuzumab therapy during RT; no prior statins within 6 weeks of starting RT. Stratification by breast conserving surgery vs mastectomy, use of boost and fraction size ($<$2 Gy vs $>$2 Gy). Primary endpoint: incidence of $>$ grade 2 acute RT-related skin toxicity. Secondary endpoints: time to onset of skin toxicity, proportion requiring additional topical treatment, compliance with trial medication, statin-related toxicities and subjective RT-related toxicities (breast discomfort and fatigue). Statistical design: 130 randomised patients gives 90% power (one-sided a 0.20) to detect a reduction in $>$ grade 2 acute skin toxicity from 55% to 35%. Enrolment opened January 2013, planned to complete by April 2014. Clinical trial information: ACTRN12612000662864.

TPS1144   **General Poster Session (Board #34C), Sat, 1:15 PM-5:00 PM**

Digoxin as an inhibitor of global hypoxia inducible factor-1α (HIF1α) expression and downstream targets in breast cancer: Dig-HIF1 pharmacodynamic trial.

Aditya Bardia, Cesar Augusto Santa-Maria, Lisa K. Jacobs, Ashley Cimino-Mathews, Peng Huang, Stuart Russell, Melissa Camp, Mehran Habibi, Julie R. Lange, Stacie Jeter, Penny Powers, Shannon Slater, Edward Gabrielson, Michael Anthony Carducci, Gregg Semenza, Vered Stearns; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Unlike normal cells, tumor cells thrive in a hypoxic microenvironment, and intratumoral hypoxia correlates with increased tumor invasiveness, metastasis, and poor prognosis in cancer. The hypoxic microenvironment is primarily mediated through HIF1α, a transcription factor for over 200 genes involved in cellular metabolism, proliferation, and angiogenesis. In pre-clinical models, cardiac glycosides, including digoxin, act as potent inhibitors of HIF1α protein synthesis and expression of HIF1α target genes (Zhang et al, PNAS 09). **Methods:** Trial design: The proposed study is a randomized, controlled, two arm, pre-surgical study. Eligible patients include women with stage I-III carcinoma of the breast scheduled to undergo definitive surgery, tumor size ≥ 1cm, grade 2/3 or Ki-67 ≥ 10%, normal organ function, and no known cardiac arrhythmias. Participants will receive oral digoxin daily, or no therapy, for 14 days (±4 days) prior to scheduled surgery. Trial Objectives: 1) To evaluate whether daily oral digoxin therapy, as compared to no study drug, reduces HIF1α expression by IHC and mRNA or its target genes (*VEGF, CA-9, and GLUT1*) in breast cancer tissue. 2) To evaluate whether daily oral digoxin therapy, as compared to no study drug, reduces levels of serum VEGF & PAI-1, reduces tissue Ki-67 expression, and modulates proteomic profiles of breast cancer tissue. 3) To assess safety and tolerability of digoxin therapy in the pre-surgical setting. Statistical methods: The primary hypothesis is that 2 weeks of digoxin therapy will reduce the level of HIF1α expression in breast cancer tissue assessed by pathologists blinded to the treatment assignment. Our preliminary study shows the mean HIF1α expression level is 2.43. A 33% reduction would be considered clinically relevant. Allowing for up to 20% attrition, a total sample size of 64 will provide more than 85% power to detect 33% reduction with a two-sided significance level of 0.05. Target accrual: 64 (32 each arm). Funding and Acknowledgement: Dept. of Defense, Commonwealth Foundation, ASCO YIA. Contact Person: Dr. Vered Stearns, Email: vstearn1@jhmi.edu.ClinicalTrials.gov Identifier: NCT01763931. Clinical trial information: NCT01763931.

TPS1145   **General Poster Session (Board #34D), Sat, 1:15 PM-5:00 PM**

SHAVE: A randomized controlled trial of routine shave margins versus standard partial mastectomy.

Anees B. Chagpar, Karen Stavris, Brigid K. Killelea, Theodore Tsangaris, Nina Ruth Horowitz; Yale University, New Haven, CT; Yale University School of Medicine, Yale Comprehensive Cancer Center, New Haven, CT

Background: It is well known that partial mastectomy for breast cancer is associated with a positive margin rate of 20-40% in most series. This has led some surgeons to advocate for routine cavity shave margins as a means of reducing re-excision rates. Others, however, feel that such a practice may be unwarranted and question the volume of tissue removed, cosmetic outcome and increase in operative time. It is unclear which of these two approaches is optimal; therefore, a prospective randomized controlled trial was proposed. **Methods:** Given the primary endpoint of positive margin rates (defined as a margin of $< 1mm$), the study was powered to find a difference between 30% in the standard partial mastectomy group and 15% in the routine shave margin group. To reach a power of 80% with alpha of 5%, 122 patients were required in each arm; we therefore set N=250 with a 1:1 randomization scheme. Patients are evaluated preoperatively and all patients undergoing a partial mastectomy for stage 0-III breast cancer are eligible; including those who have completed neoadjuvant chemotherapy. Patients are stratified according to stage and randomized within strata. After informed consent, patients undergo a standard partial mastectomy (including specimen radiography as needed). Surgeons may resect additional tissue at that time according to their standard practice. At the completion of this procedure, the randomization envelope is opened in the operating room and surgeons are instructed to either shave (ie., take additional circumferential margins) or close (no shave). Patients will be followed for five years. Outcome measures include: positive margin/re-excision rate, local recurrence, volume of tissue resected, cosmetic outcome, and intraoperative time. To date, over 130 patients have accrued to this trial. Initial results are expected to be reported in 2014. Clinicaltrials.gov identifier: NCT01452399