500 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Clinical and translational results of CALGB 40601: A neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for HER2-positive breast cancer.

Lisa A. Carey, Donald A. Berry, David Ollila, Lyndsay Harris, Ian E. Krop, Douglas Weckstein, Norah Lynn Henry, Carey K. Anders, Constance Cirrincione, Eric P. Winer, Charles M. Perou, Clifford Hudis, Alliance; The University of North Carolina at Chapel Hill, Chapel Hill, NC; The University of Texas MD Anderson Cancer Center, Houston, TX; Case Western/Seidman Cancer Center, Cleveland, OH; Dana-Farber Cancer Institute, Boston, MA; New Hampshire Oncology-Hematology, PA, Hooksett, NH; University of Michigan Medical Center, Ann Arbor, MI; The University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Alliance Statistical Center, Duke University, Durham, NC; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Recent trials in HER2-positive (HER2+) breast cancer (BrCa) demonstrate increased pathological complete response (pCR) using dual HER2-targeting in the neoadjuvant setting and increased progression-free survival in metastatic disease. CALGB 40601 aimed to further quantify the pCR rates of weekly paclitaxel (T) and trastuzumab (H) alone or combined HER2-blockade of H with the small molecule lapatinib (L), and to identify biomarkers of sensitivity to these HER2-targeted agents. **Methods:** Eligible patients had newly diagnosed, noninflammatory stage II-III HER2+ BrCa and were randomized to receive T (80mg/m2/week IV) + H (4mg/kg then 2mg/kg/week IV) alone (TH) or with the addition of L (750 mg/d PO) (THL) for 16 weeks preoperatively. A third arm, T + L (1500 mg/d) (TL), was closed early when negative efficacy and toxicity data emerged from preliminary analysis of ALTTO. After surgery, 4 cycles of adjuvant dose-dense AC and 1 year H was recommended. Tumors were biopsied for research before therapy; post-Rx samples of residual disease were requested. The primary endpoint was in-breast pCR rate; the study had 85% power to detect an increase from 30% (TH) to 50% (THL). **Results:** 305 patients were randomized (118 THL, 120 TH, 67 TL); 68% were clinical stage II and 59% hormone receptor-positive. Grade 3+ toxicity was higher among L-containing arms, including neutropenia (12% TL, 7% THL, 2% TH), rash (15% TL, 14% THL, 2% TH), and diarrhea (20% TL, 20% THL, 2% TH). Breast pCR rates with 95% confidence limits were: 51% (42-60%) THL, 40% (32-49%) TH, 32% (22-44%) TL. pCR rate in the TH arm was higher than previous studies, and was not significantly different from THL ($p=0.11$). We will present molecular subtype, sequence and gene copy number abnormalities in primary tumors and residual disease. **Conclusions:** pCR rate was higher with combined THL compared with standard TH but did not reach statistical significance. These results are qualitatively similar to other neoadjuvant studies in HER2+ BrCa, and contribute to estimates of pCR rates after these agents. Tissue-based studies may illuminate which patients benefit from HER2-targeting using these agents. Clinical trial information: NCT00770809.

501 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Impact of neoadjuvant chemotherapy plus HER2-targeting on breast conservation rates: Surgical results from CALGB 40601 (Alliance).

David W. Ollila, Donald A. Berry, Constance Cirrincione, Lisa A. Carey, Keith D. Amos, Norah Lynn Henry, Eric P. Winer, Clifford Hudis, Mehra Golshan, Alliance for Clinical Trials in Oncology; The University of North Carolina at Chapel Hill, Chapel Hill, NC; The University of Texas MD Anderson Cancer Center, Houston, TX; Alliance Statistical Center, Duke University, Durham, NC; University of Michigan Medical Center, Ann Arbor, MI; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; Brigham and Women's Hospital, Boston, MA

Background: Neoadjuvant systemic therapy improves breast conserving therapy (BCT) rates, but the magnitude of this benefit is unknown in operable breast cancer. We sought to quantify this benefit in CALGB 40601, a phase III trial of paclitaxel (T) + HER2 blockade with either trastuzumab (TH), lapatinib (TL), or both (THL), by requiring the treating breast surgeon to determine BCT eligibility before and after neoadjuvant therapy and examining surgical results. **Methods:** Eligible patients (pts) had operable, newly diagnosed, noninflammatory stage II-III HER2+ breast cancer randomized to receive TH, TL or THL. Prior to, and again after neoadjuvant therapy, the treating breast surgeon determined whether the patient was a BCT candidate based on clinical and radiographic criteria, but the subsequent breast cancer operation was at the discretion of the surgeon and patient. Two endpoints examined were: (1) the conversion rate from BCT-ineligible to BCT-eligible and (2) the rate of successful BCT as determined by tumor-free surgical margins. **Results:** Of 305 pts randomized (118 THL, 120 TH, 67 TL), 294 were evaluable. Prior to neoadjuvant therapy, 136 (46%) patients were candidates and 158 (54%) were non-candidates for BCT. 107/136 (79%) remained BCT candidates following neoadjuvant therapy and 78 chose BCT, of whom 69 (88%) were successful. 29 pts (21%) initially thought to be BCT candidates became non-candidates after neoadjuvant therapy. Conversely, 76/158 (48%) pts considered non-BCT candidates prior to neoadjuvant therapy down-sized sufficiently to be considered BCT candidates; 40 of these opted for BCT with a 75% (30/40) BCT success rate. In total, 183 pts were deemed BCT candidates after neoadjuvant therapy, yet 65 (36%) proceeded directly to mastectomy. **Conclusions:** This is the first neoadjuvant trial to prospectively quantify a nearly 50% conversion rate from BCT-ineligible to BCT-eligible in HER2+ breast cancer pts treated with modern systemic therapy. Neoadjuvant chemotherapy combined with targeted anti-HER2 treatment permits potential BCT in approximately 80% of properly selected patients. Clinical trial information: NCT00770809.

ACOSOG Z1041 (Alliance): Definitive analysis of randomized neoadjuvant trial comparing FEC followed by paclitaxel plus trastuzumab (FEC → P+T) with paclitaxel plus trastuzumab followed by FEC plus trastuzumab (P+T → FEC+T) in HER2+ operable breast cancer.

Aman Buzdar, Vera J. Suman, Funda Meric-Bernstam, A. Marilyn Leitch, Matthew James Ellis, Judy Caroline Boughey, Gary Walter Unzeitig, Melanie Royce, Kelly Hunt, for the Alliance for Clinical Trials in Oncology; The University of Texas MD Anderson Cancer Center, Houston, TX; ACOSOG Statistical Center, Mayo Clinic, Rochester, MN; Simmons Cancer Center, The University of Texas Southwestern Medical Center, Dallas, TX; Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; Mayo Clinic, Rochester, MN; Doctors Hospital of Laredo, Laredo, TX; University of New Mexico Cancer Center, Albuquerque, NM

Background: Neoadjuvant chemotherapy (NAC) and concomitant trastuzumab (T) have produced high pathologic complete response (pCR) rates in HER2+ breast cancers. Z1041 addresses the timing of initiation of T with NAC. **Methods:** Women with operable HER2+ invasive breast cancer were randomized 1:1 to: FEC → P+T (Arm 1) or P+T → FEC+T (Arm 2) where treatment was administered as 5-FU 500 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 day 1 of a 21-day cycle x 4 (FEC); paclitaxel 80 mg/m^2 weekly x 12 and trastuzumab 4 mg/kg once then 2 mg/kg weekly x 11. Eligibility also included: tumor $>$ 2 cm or a positive lymph node and left ventricular ejection fraction $>$ 55%. The primary aim was to compare the pCR rates in the breast (pBCR) between the regimens. Secondary endpoints were pCR rate in the breast and lymph nodes (pBNCR) and safety profile. All pts who began study treatment were included in the analyses. With 128 pts per regimen, a two-sided alpha=0.05 test of proportions would have a 90% chance of detecting a difference of 20% or more in the pBCR rates, when the pBCR rate with the poorer regimen is $\leq$ 25%. **Results:** From September 15, 2007 to December 15, 2011, 282 women (Arm 1: 140 pts) were enrolled. Two pts (Arm 1) withdrew without receiving treatment. The two arms were similar in age, stage, and hormone receptor (HR) status (HR neg: 40%). The severe (grade 3+) treatment-related toxicities included: neutropenia (Arm 1: 24.6%; Arm 2: 32.4%), fatigue (Arm 1: 4.3%; Arm 2: 8.5%), and neurosensory problems (Arm 1: 3.6%; Arm 2: 4.9%). The pBCR rate and pBNCR rates (Table) were not found to differ between the two regimens (Fisher's exact p values: 0.905 and 0.811, respectively). **Conclusions:** High pCR rates can be achieved with trastuzumab in combination with anthracyclines and taxanes. The pBCR or pBNCR was not different between regimens based on the timing of initiation of trastuzumab. Clinical trial information: NCT00513292.

	FEC → P+T	P+T → FEC+T
n	138	142
% pCR in breast	55.1	54.2
(95% CI)	46.4- 63.5	45.7-62.6
% pCR in breast and nodes	50.7	48.6
(95% CI)	42.1 – 59.3	40.1-57.1

503 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Follow-up results of NOAH, a randomized phase III trial evaluating neoadjuvant chemotherapy with trastuzumab (CT+H) followed by adjuvant H versus CT alone, in patients with HER2-positive locally advanced breast cancer.

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Background: The monoclonal antibody trastuzumab (H) has been shown to improve event-free survival (EFS) and pathologic complete response (pCR) in patients with HER2-positive locally advanced or inflammatory breast cancer receiving neoadjuvant chemotherapy with or without one year of trastuzumab in the primary analysis of the NOAH study (Gianni L, Lancet 2010). Updated EFS and overall survival (OS) results are now presented. **Methods:** In this international, multicenter, open-label, randomized phase III trial patients with locally advanced or inflammatory breast cancer were randomized 1:1 to receive CT+H followed by adjuvant H versus CT alone. A parallel cohort of 99 comparable patients with HER2-negative disease was included and treated with the same chemotherapy regimen. The neoadjuvant chemotherapy regimen included doxorubicin, paclitaxel, cyclophosphamide, methotrexate and 5-fluorouracil. The primary objective was to compare EFS defined as time from randomization to disease recurrence or progression [local, regional, distant or contralateral] or death due to any cause). **Results:** After a median follow up of 5.4 years, the EFS benefit with trastuzumab was confirmed. Cardiac tolerability was good despite concurrent administration of trastuzumab with doxorubicin. Two patients (2%) developed reversible symptomatic congestive heart failure and are presently alive. **Conclusions:** Present analysis confirms the significant EFS benefit observed in the primary analysis of the NOAH study, and shows a strong trend towards improved OS with the addition of trastuzumab to chemotherapy. pCR rate may be considered as a possible primary endpoint and early indicator of benefit in future neoadjuvant studies of HER2-targeted agents. Clinical trial information: 86043495.

	HER2-positive			
Parameter	CT+H (N=117)	CT alone (N=118)	HR, p value	HER2-negative (N=99)
5-yr EFS (%)	57.5	43.3	0.64, 0.016	60.5
5-yr EFS in pCR (%)	86.5	54.8	0.29, 0.008	85.9
5-yr OS (%)	73.5	62.9	0.66, 0.055	76.4
5-yr BCSS (%)	77.4	63.9	0.59, 0.023	78.6

Abbreviations: EFS, event free survival; OS, overall survival; BCSS, breast cancer specific survival; HR, hazard ratio.

505 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase III, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3).

Ruth O'Regan, Mustafa Ozguroglu, Fabrice Andre, Masakazu Toi, Guy Heinrich Maria Jerusalem, Sharon Wilks, Claudine Isaacs, Binghe Xu, Norikazu Masuda, Francis P. Arena, Denise Aysel Yardley, Yoon Sim Yap, Pabak Mukhopadhyay, Shyanne Douma, Mona El-Hashimy, Tanya Taran, Tarek Sahmoud, David Edward Lebwohl, Luca Gianni; Georgia Cancer Center for Excellence at Grady Memorial Hospital, Atlanta, GA; Istanbul University, Istanbul, Turkey; Institut Gustave Roussy, Villejuif, France; Graduate School of Medicine Kyoto University, Kyoto, Japan; Centre Hospitalier Universitaire Sart Tilman Liege and University of Liege, Liège, Belgium; Cancer Care Centers of South Texas, San Antonio, TX; Lombardi Comprehensive Cancer Center, Washington, DC; Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; NHO Osaka National Hospital, Osaka, Japan; Arena Oncology Associates, Lake Success, NY; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; National Cancer Centre Singapore, Singapore, Singapore; Novartis Pharmaceuticals Corp, East Hanover, NJ; Novartis Pharmaceuticals, East Hanover, NJ; Novartis Pharmaceuticals, Florham Park, NJ; Global Oncology Development, Novartis Pharmaceuticals Corporation, Florham Park, NJ; San Raffaele Scientific Institute, Milan, Italy

Background: Everolimus (EVE) is an inhibitor of mammalian target of rapamycin (mTOR), a protein kinase central to a number of signaling pathways regulating cell growth and proliferation. Data from preclinical and phase 1/2 clinical studies indicated that adding EVE to trastuzumab (TRAS) plus chemotherapy may restore sensitivity to and enhance efficacy of human epidermal growth factor receptor 2 (HER2)-targeted therapy. The international BOLERO-3 phase 3 study is being conducted to evaluate the addition of EVE to TRAS plus vinorelbine. **Methods:** Adult women with $HER2^+$ advanced breast cancer and who received prior taxane therapy and experienced recurrence or progression on TRAS were randomized 1:1 to receive either EVE or placebo (5 mg/day) in combination with weekly TRAS and vinorelbine (25 mg/m^2). The primary endpoint is progression-free survival (PFS). Secondary endpoints included overall survival, response rate, clinical benefit rate, safety, quality of life, and pharmacokinetics. Final analysis will be conducted after approximately 417 PFS events. **Results:** The trial accrued 569 patients between October 2009 and May 2012. Previous therapy included TRAS (100%), a taxane (100%), and lapatinib (28%). The median age was 54 years, and 76% of patients had visceral metastases, 5% had stable brain metastases, 56% had hormone-receptor–positive disease, 33% had Eastern Cooperative Oncology Group performance status of 1 or 2, and 41% had 3 or more metastatic sites. The median number of prior chemotherapy lines in the metastatic setting was 1. As of February 4, 2013, a total of 396 PFS events were reported. **Conclusions:** Final PFS analysis will be performed in early May 2013; primary and secondary efficacy endpoints will be presented. Clinical trial information: NCT01007942.

Identifying clinically relevant prognostic subgroups in node-positive postmenopausal HR+ early breast cancer patients treated with endocrine therapy: A combined analysis of 2,485 patients from ABCSG-8 and ATAC using the PAM50 risk of recurrence (ROR) score and intrinsic subtype.

Michael Gnant, Mitchell Dowsett, Martin Filipits, Elena Lopez-Knowles, Richard Greil, Marija Balic, John W Cowens, Torsten O. Nielsen, Carl Shaper, Ivana Sestak, Christian Fesl, Jack M. Cuzick, Austrian Breast and Colorectal Cancer Study Group; Comprehensive Cancer Center, Department of Surgery, Medical University of Vienna, Vienna, Austria; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Institute of Cancer Research, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Universitätsklinikum der PMU, Salzburg, Austria; Medical University Graz, Graz, Austria; Nanostring, Seattle, WA; British Columbia Cancer Agency, Vancouver, BC, Canada; MyRAQA Inc., Redwood Shores, CA; Queen Mary, University of London, London, United Kingdom; Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria; Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, London, United Kingdom

Background: Most postmenopausal women with node positive HR+ EBC receive adjuvant chemotherapy. We hypothesized that a molecular-based characterization of residual risk after endocrine therapy using the ROR score and IS may identify node-positive patient subgroups with limited long-term recurrence risk after endocrine therapy better than clinical-pathological risk assessment by clinical treatment score (CTS) alone. **Methods:** Long-term follow-up and tissue samples were obtained from 2,485 postmenopausal HR+ patients from the ABCSG-8 (N=1,478) and transATAC (N=1,007) trials. The PAM50 test was conducted on RNA extracted from paraffin blocks using the NanoString nCounter Analysis system. The ability of ROR, IS and ROR-defined risk groups (ROR-RG) to add prognostic information to CTS was assessed by the likelihood ratio test in a prospectively defined analysis plan. **Results:** Patients in the combined data set were grouped by the number of positive nodes into 1 (N1), 2 (N2), or 2 or 3 (N2-3),Baseline hazards for these subgroups were similar in the two trials. ROR score, IS and ROR-RG added statistically significant prognostic information (10-year distant recurrence risk) beyond CTS in all groups. In patients with one positive node, the absolute 10-year risk of distant recurrence was 6.6% [95% CI: 3.3%-12.8%] in the PAM-50-low risk group (40% of patients) and 8.4 % [5.3%-13.3%] in the Luminal A subgroup (69% of patients). **Conclusions:** The results of this combined analysis demonstrate that a significant proportion of N1 EBC patients have very limited long term recurrence risk and suggest the same for some N2 patients. The PAM50 ROR score, IS and ROR-RG reliably provide additional prognostic information beyond CTS and may be useful in deciding which women with node-positive HR+ EBC can be spared adjuvant chemotherapy.

	N1 (N=331)		N2 (N=145)		N2-3 (N=212)	
	ΔLR χ^2	P value	ΔLR χ^2	P value	ΔLR χ^2	P value
ROR	17.53	<0.0001	12.18	0.0005	14.16	0.0002
IS	12.16	0.0005	7.80	0.0052	8.58	0.0034
ROR-RG	11.32	<0.004	7.95	<0.02	13.15	<0.001

507 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Prognostic impact of the 21-gene recurrence score in patients presenting with stage IV breast cancer.

Tari A. King, Jaclyn P Lyman, Mithat Gonen, Amy Voci, Marina De Brot, Camilla Boafa, Amy Pratt Sing, Eun-Sil Shelley Hwang, Michael Alvarado, Minetta C. Liu, Judy Caroline Boughey, Kandace P. McGuire, Catherine H. Van Poznak, Lisa K. Jacobs, Ingrid M. Meszoely, Helen Krontiras, Gildy Babiera, Larry Norton, Monica Morrow, Clifford Hudis, Translational Breast Cancer Research Consortium; Department of Surgery, Breast Service, Memorial Sloan-Kettering Cancer Center, New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Epidemiology-Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; Genomic Health, Inc., Redwood City, CA; Duke Unversity Medical Center, Durham, NC; University of California, San Francisco, San Francisco, CA; Mayo Clinic, Rochester, MN; Department of Surgery, Division of Surgical Oncology, Magee-Womens Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Vanderbilt-Ingram Cancer Center, Nashville, TN; University of Alabama at Birmingham, Birmingham, AL; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The 21-gene Recurrence Score (Onco*type*DX Breast Cancer Assay) predicts outcome and benefit from chemotherapy (CT) in early stage ER+ BC treated with adjuvant endocrine therapy. We evaluated the association between Recurrence Score (RS), time to progression (TTP), and overall survival (OS) in patients with stage IV BC enrolled in TBCRC 013. **Methods:** TBCRC 013 is a registry study evaluating surgery of the primary tumor in pts presenting with Stage IV BC. From 7/09 - 4/12, 128 evaluable pts were enrolled in two cohorts (A: metastases (mets) with intact primary tumor (n=112); B: mets within 3 months of primary surgery (n=16)). This study includes 110 pts with pre-treatment primary tumor samples available for analysis. Clinical variables, TTP and OS were correlated with RS using long-rank, Kaplan-Meier and Cox regression. **Results:** Median pt age was 52yrs (21-79) and median tumor size 3.1cm (0.7-15). 82 (80%) were ER+, 83 (81%) Her2(-) and 51 (46%) had bone-only mets. Cohorts A and B did not differ. At a median follow-up of 26 mos (1-47), median TTP is 19 mos (95%CI16-25) and surgery is not associated with OS. 102 samples qualified for RS. 23 (23%) had low RS<18, 29 (28%) intermediate RS, 18-30; and 50 (49%) high RS≥31. Age, tumor size or site of 1stmets was not associated with RS. Risk groups were prognostic for TTP in ER+ pts and for 2 yr OS in ER+Her2- pts (Table). In Cox models continuous RS was also prognostic for TTP in ER+ pts (HR 3.5; for 50 point difference (PD) 95%CI 1.5-8.1, p=0.003) and for OS in ER+Her2- pts (HR 21.4, for 50 PD 95%CI 2.2-204.4, p=0.008). In MVA, adjusting for clinical variables, RS remained prognostic for TTP in ER+ pts (p=0.01). Further analysis of surgery in this trial is ongoing. **Conclusions:** The 21-gene RS is independently prognostic for TTP in ER+ Stage IV BC. RS is also prognostic for OS in ER+Her2- BC, suggesting that a high RS may be a surrogate for endocrine resistance and could be used to select pts with ER+ Stage IV BC for CT. A randomized trial to address this hypothesis is warranted. Clinical trial information: NCT00941759.

	RS<18 n=23	RS18-30 n=29	RS≥30 n=50	Log rank, p
Median TTP, mos				
ER+	32 (16-NR)	22 (20-NR)	12 (8-21)	0.002
ER+HER2-	32 (16-NR)	22 (20-NR)	13 (9-26)	0.015
2 yr OS, %				
ER+	100	100	80 (68-98)	0.049
ER+HER2-	100	100	73 (56-96)	0.005

NR, not reached.

508 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

A randomized double-blind phase II study of the combination of oral WX-671 plus capecitabine versus capecitabine monotherapy in first-line HER2-negative metastatic breast cancer (MBC).

Lori J. Goldstein, Celia Tosello Oliveira, Bernhard Heinrich, Salomon M. Stemmer, Carola Mala, Sabine Kastner, Paul Bevan, Lisa Richters, Barbara Schmalfeldt, Nadia Harbeck; Fox Chase Cancer Center, Philadelphia, PA; Instituto Brasileiro Controle Cancer, Sao Paulo, Brazil; Hämatologisch-Onkologische-Praxis Augsburg, Augsburg, Germany; Institute of Oncology, Davidoff Center, Rabin Medical Center, Tel-Aviv University, Tel-Aviv, Israel; Wilex, Munich, Germany; Wilex AG, Munich, Germany; Breast Center University of Cologne, Cologne, Germany; Breast Center University of Munich, Munich, Germany

Background: uPA and its inhibitor PAI-1 play a key role in tumor invasion, metastasis and tumor growth. uPA and PAI-1 are biomarkers validated at highest level of evidence in breast tumors and are recommended for clinical decision making by ASCO. WX-UK1 is a competitive inhibitor of uPA with an inhibition constant in the submicromolar range. WX-671 (upamostat) is an oral prodrug of WX-UK1. **Methods:** Female patients aged >18, with HER2 negative MBC were randomized in a double-blind fashion to receive upamostat (200 mg orally daily for 21 days) plus C (1000 mg/m^2 orally twice daily for 14 days) vs. C (same regimen) in 3 week treatment cycles until progressive disease or unacceptable toxicity. 132 from five countries were enrolled. The primary objective was to evaluate the efficacy of the combination of upamostat and C compared to C alone by assessment of progression free survival (PFS). The study also evaluated the objective response rate and safety as well as pharmacokinetics (PK). Efficacy was evaluated by RECIST by independent central read. **Results:** Median treatment duration was 8 cycles in both arms. In the total study population (intent to treat; ITT) upamostat led to an increase of median PFS from 7.5 months (95% CI: 4.2; 12.8) in the control group to 8.3 months (95% CI: 5.6; 9.6) in the combination therapy. An unexpectedly high rate (50%) of study patients presented within their first two years after initial diagnosis. In patients who had received prior adjuvant chemotherapy, PFS improved from 4.3 months (95% CI: 2.6; 9.7) in the C alone group to 8.3 months (95% CI: 5.6; 10.9) in the upamostat plus C group. The overall response rate was higher in the combination group compared to C alone (20% vs. 12% at Week 24). PK analysis demonstrated no drug-drug interactions between upamostat and C. The combination therapy was safe and well tolerated. **Conclusions:** This is the first proof of efficacy of an anti-uPA therapy in breast cancer. The heterogeneity of the patients in this study may underestimate the potential treatment effects of upamostat. Additional subset analyses will be presented. Future biomarker-stratified strategies may reveal better efficacy. Clinical trial information: NCT00615940.

LBA509 **Clinical Science Symposium, Mon, 1:15 PM-2:45 PM**

Correlation of molecular alterations with efficacy of everolimus in hormone-receptor–positive (HR+), HER2-negative advanced breast cancer: Preliminary results from BOLERO-2.

Gabriel N. Hortobagyi, Martine J. Piccart-Gebhart, Hope S. Rugo, Howard A. Burris, Mario Campone, Shinzaburo Noguchi, Alejandra T. Perez, Ines Deleu, Mikhail Shtivelband, Louise Provencher, Norikazu Masuda, Shaker R. Dakhil, Ian Anderson, David Chen, Amy Damask, Alan Huang, Robert McDonald, Tanya Taran, Tarek Sahmoud, José Baselga; Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; Jules Bordet Cancer Institute, Brussels, Belgium; University of California, San Francisco, San Francisco, CA; Sarah Cannon Research Institute, Nashville, TN; CLCC René Gauducheau, Centre de Recherche en Cancerologie, Nantes Saint Herblain, France; Osaka University, Osaka, Japan; Memorial Cancer Institute, Breast Cancer Program, Hollywood, FL; AZ Nikolaas, Sint-Niklaas, Belgium; Ironwood Cancer and Research Centers, Chandler, AZ; Centre des Maladies du Sein Deschênes-Fabia, Hôpital du Saint-Sacrement, Quebec City, QC, Canada; Osaka National Hospital, Osaka, Japan; Cancer Center of Kansas, Wichita, KS; Redwood Regional Oncology Center, Santa Rosa, CA; Novartis Pharmaceuticals, Oncology, Florham Park, NJ; Novartis Institutes for BioMedical Research, Cambridge, MA; Oncology Translational Medicine, Novartis Institute for Biomedical Research, Cambridge, MA; Novartis Institutes for BioMedical Research, Inc., Cambridge, MA; Novartis Pharmaceuticals Corp, Florham Park, NJ; Novartis Pharmaceuticals Corp, East Hanover, NJ; Memorial Sloan-Kettering Cancer Center, New York, NY

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*.

Predictive markers of everolimus efficacy in hormone receptor positive (HR+) metastatic breast cancer (MBC): Final results of the TAMRAD trial translational study.

Isabelle Treilleux, Monica Arnedos, Claire Cropet, Jean-Marc Ferrero, Sophie Abadie Lacourtoisie, Dominique Spaeth, Christelle Levy, Eric Legouffe, Eric Pujade-Lauraine, Quing WANG, Thomas Bachelot; Centre Léon Bérard, Lyon, France; Institut Gustave Roussy, Villejuif, France; Centre Léon Bérard, Unité de Biostatistique et d'Evaluation des Thérapeutiques, Lyon, France; Centre Antoine Lacassagne, Nice, France; ICO Paul Papin, Angers, France; ORACLE - Centre d'Oncologie de Gentilly, Gentilly, France; Centre François Baclesse, Caen, France; Clinique Valdegour, Nimes, France; Université Paris Descartes, AP-HP, Hôpitaux Universitaires Paris Centre, Site Hôtel-Dieu, Paris, France; Genomic Platform - Translational Research laboratory - Leon Berard Cancer Center, Lyon, France; Department de Cancerologie Medicale, Centre Leon Berard, Lyon, France

Background: Hormone resistance is linked in part to cross-talk between ER signalling and PI3K/Akt/mTOR pathway. Following results of the BOLERO-2 trial, everolimus (E), a potent mTOR inhibitor, has recently been approved in combination with exemestane in women with HR+ MBC refractory to aromatase inhibitor (AI). However, E is frequently associated with specific toxicities, and predictive markers of efficacy are needed. We report here the final results of translational studies within the TAMRAD randomized Phase II trial, comparing tamoxifen (TAM) to TAM+E in AI pre-treated MBC. **Methods:** Tumor samples from 51 patients among the 111 treated in the TAMRAD trial were retrieved. Hot spot mutations of PI3K (exon 9-20), and KRAS (exon 2) were described. TMA analysis evaluated IHC expression of PTEN, pAkt, PI3K, LKB1, S6K, pS6K, 4EBP1, p4EBP1, and eIF4E. Exploratory analysis of E efficacy in each biomarker subgroup (high vs low expression defined by median percentage of marked cells) was done. **Results:** Patients characteristics and treatment efficacy among this sub-population were similar to the results from the whole population: Time to progression was 10 months for the TAM+E treated patients vs. 5.5 months for the TAM treated patients, HR: 0.59 (95% CI 0.33-1.07). PI3K-Akt pathway: All patients derived benefit from E regardless of PI3K mutational status, PTEN or pAkt expression. Surprisingly, E efficacy was greater in patients with low PI3K expression (n=12, HR=0.11, 95%CI 0.01-0.96) than in patients with high PI3K expression (n= 28, HR=0.9; 95%CI 0.49-2.41) PI3K independent pathway: Patients with low expression of the anti-oncogene LKB1 derived greater benefit from E (n=22, HR=0.33; 95%CI 0.13-0.89) than patients with high LKB1 expression (n=25, HR=0.75; 95%CI 0.32-1.74) mTOR downstream effectors: Patients with high p4EBP1 (n=27, HR=0.37; 95%CI 0.15-0.90) or low 4EBP1 (n=21, HR=0.39; 95%CI 0.14-1.08) were the subgroups most likely to benefit from E. **Conclusions:** Those results are in favor of a better efficacy of E for patients with PI3K independent activation of mTOR. If confirmed, they could have important implications for future patient selection. Clinical trial information: NCT01298713.

511 **Clinical Science Symposium, Mon, 1:15 PM-2:45 PM**

Array CGH and DNA sequencing to personalize targeted treatment of metastatic breast cancer (MBC) patients (pts): A prospective multicentric trial (SAFIR01).

Fabrice Andre, Thomas Denis Bachelot, Mario Campone, Monica Arnedos, Veronique Dieras, Magali Lacroix-Triki, Vladimir Lazar, David Gentien, Pascale Cohen, Anthony Goncalves, Ludovic Lacroix, Max Chaffanet, Florence Dalenc, Marie-Christine Mathieu, Ivan Bieche, Sylviane Olschwang, Qing Wang, Frederic Commo, Marta Jimenez, Herve R. Bonnefoi; Institut Gustave Roussy, Villejuif, France; Centre Léon Bérard, Lyon, France; Institut de Cancérologie de l'Ouest/René Gauducheau, Saint-Herblain, France; Institut Curie, Paris, France; Institut Claudius Regaud, Toulouse, France; Institut Paoli Calmettes, Marseille, France; Institut Curie - Hôpital René Huguenin, Saint-Cloud, France; Unicancer, Paris, France; Institut Bergonie Cancer Center, Bordeaux, France

Background: The aim of the present study was to profile the metastatic lesion of pts using high throughput technologies, and to treat them accordingly. **Methods:** SAFIR01 trial aimed to include 400 pts with MBC, selected for not presenting a progressive disease at the time of biopsy. A biopsy was done in a metastatic site. DNA was extracted if the tumor contained >50% cancer cells, and sent to one of the 5 genomic centers who performed array CGH (copy number changes) and sanger sequencing on PIK3CA (exon 10/21) and AKT1 (exon 3). A targeted therapy matched to the genomic alteration was expected to be proposed at the time of progressive disease. The primary endpoint was the % of pts who received a targeted therapy according to the genomic alteration. **Results:** A biopsy of metastatic site was done successfully in 408 out of the 423 included pts. Biopsy was complicated by a serious adverse event in 9 pts. A discrepancy between primary and metastatic lesion was observed in 8% and 19% of pts for Her2 and HR. Array CGH and sequencing were successfully obtained in 277 (68%) and 295 (72%) pts. The main reason for failure of genomic test was the low cellularity (n=93). A targetable genomic alteration was identified in 204 pts. The most frequent genomic alterations were PIK3CA mutations, CCND1, FGF4 and FGFR1 amplifications. 76 pts presented a rare targetable genomic alteration (<5%), including AKT1 mutations, EGFR, FGFR2, PIK3CA, MDM2 amplifications. Early Feb 2013, 46 out of 277 pts with genomic analyses (17%) had received a targeted therapy matched to the genomic alteration, covering twelve different targets. Updated results on number of pts treated, together with efficacy data will be presented. Next generation sequencing on metastatic lesions is ongoing and results will be presented. **Conclusions:** This trial evaluated the concept of personalized medicine for MBC and provided a large scale genomic analysis of metastatic tissue. This study suggests that assessing the biology of metastatic tissue could allow driving pts to targeted therapy. A randomized trial (SAFIR02) testing this approach is expected to start during summer 2013. Clinical trial information: NCT01414933.

512 **Clinical Science Symposium, Mon, 1:15 PM-2:45 PM**

Kinome reprogramming response to MEK inhibition: A window-of-opportunity trial in triple-negative breast cancer (TNBC).

Gary L. Johnson, Keith D. Amos, James S Duncan, Marty Whittle, Jon Zawistowki, Dan Goulet, Xiaping He, Jeanne Noe, Charles M. Perou, Shelton Earp, Lisa A. Carey; University of North Carolina - Lineberger Comprehensive Cancer Center, Chapel Hill, NC; The University of North Carolina at Chapel Hill, Chapel Hill, NC; The University of North Carolina - Lineberger Comprehensive Cancer Center, Chapel Hill, NC

Background: Targeted therapy (Rx) in TNBC is challenging due to heterogeneity and cancer cell kinome "reprogramming" in response to targeted kinase inhibitors (Cell 149:307, 2012). In preclinical TNBC models specific kinases (e.g., DDR1/2, PDGFRbeta, VEGFR2, AXL) are activated in response to MEK inhibition. Our studies define unique kinome reprogramming in basal-like (BBC) versus claudin-low (CL). This study compared kinome profiles of TNBC pre- and post- MEK1/2 inhibition with GSK1120212 (trametinib, T) using multiplexed inhibitor beads coupled with mass spectrometry (MIB/MS). **Methods:** Eligible patients (pts) with untreated TNBC received T (initial dose 1.5mg/d raised after interim analysis of kinome effects to 2mg/d) for 7 days preceding breast surgery. Fresh tumor tissue was obtained before and after T. Kinase activation state was analyzed as post:pre(-)treatment ratio; molecular subtype was by gene expression analysis. **Results:** Kinome response profiling was completed in 7 of 9 pts by abstract submission. Toxicities included grade 2 (2pts) or grade 1 (1pt) rash, grade 1 diarrhea (1pt), and grade 1 nausea (1pt). Two of the 9 pts profiled did not have sufficient pre-treatment tumor for kinome analysis. Molecular subtypes included 6 BBC patients (one of which was CL after T), 2 CL patients (one of which was BBC after T), and 1 normal-like patient (which was BBC after T). MEK1/2 inhibition and kinase reprogramming was seen in 6 of the 7 tumors where both pre- and post T samples could be analyzed. The results show kinome reprogramming in response to MEK1/2 inhibition occurs in human tumors similar to preclinical modeling in TNBC cell lines and credentialed engineered mouse models; the kinase reprogramming pattern differed between BBC and CL. **Conclusions:** MEK1/2 inhibition upregulates and activates specific receptor tyrosine kinases in BBC that are different from CL.A subset of BBC and CL may have plasticity, changing their molecular subtype and kinome profile, and responding heterogeneously to MEK1/2 inhibition. Analysis of kinome reprogramming identifies upregulation of druggable targets for individual patients that suggest rational combinations with MEK inhibition in TNBC. Clinical trial information: NCT01467310.

513 Poster Discussion Session (Board #1), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase II trial of carboplatin (C) and bevacizumab (BEV) in patients (pts) with breast cancer brain metastases (BCBM).

Nancy U. Lin, Rebecca Sue Gelman, W. Jerry Younger, Jessica Sohl, Rachel A. Freedman, A. Gregory Sorensen, Elizabeth Bullitt, Gordon J Harris, Daniel Morganstern, Bryan P. Schneider, Ian E. Krop, Eric P. Winer; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; Siemens Healthcare North America, Malvern, PA; The University of North Carolina at Chapel Hill, Chapel Hill, MA; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

Background: The anti-tumor and anti-edema effects of BEV provide a rationale for testing in BCBM. Carboplatin (C) is associated with CNS responses across multiple tumor types. We evaluated BEV + C in pts with BCBM. **Methods:** Pts with progressive, measurable BCBM (>/= 1 cm in longest dimension) were eligible. Cycle 1: BEV 15 mg/kg on Day 1, followed on Day 8 by carboplatin AUC=5 (plus trastuzumab if HER2+). In subsequent cycles, pts received BEV + C on Day 1 (plus trastuzumab if HER2+) of a 3 week (wk) cycle. Standard brain MRI was obtained at baseline (BL) and every 2 cycles. Non-CNS scans (CT or MRI) were performed after 2 cycles, 4 cycles, then every 4 cycles. Correlative brain imaging was obtained at BL, 12-96 hours after the first dose of BEV, and after 2 cycles. Circulating tumor cells and blood for VEGF polymorphisms were also collected. The primary endpoint was composite CNS objective response rate (CNS ORR). CNS partial response required all of the following: >/= 50% reduction in volumetric sum of target CNS lesions compared to BL, no progression of non-target lesions, no new lesions, stable/decreasing steroid dose, no progressive neurologic signs or symptoms, *and* no progression of non-CNS disease by RECIST 1.0. The study used a 2-stage design to distinguish between ORR 5% vs 20% (responses in >/= 1/12 pts to enter 2ndstage; responses in >/= 4/37 pts needed to be promising). **Results:** 38 pts were enrolled between 11/3/09-8/24/12 (30 HER2+; 8 HER2-negative). Most (76%) pts had received >/=2 lines of metastatic chemotherapy. 97% of pts with HER2+ disease received prior trastuzumab; 73% had prior lapatinib. All but 5 pts progressed after WBRT and/or SRS. As of 1/15/13, 3 pts remain on protocol therapy; 22 patients have died. The composite CNS ORR was 63% (95% CI 46%-78%). CNS ORR by RECIST was 45%. CNS responses were observed in both HER2+ and HER2-negative pts. Of 34 pts with >/= 24 wks potential follow-up time, median number of cycles was 8 (range 1-19). One grade 2 CNS hemorrhage event was reported; there were no cases of grade 3/4 CNS hemorrhage. **Conclusions:** BEV + carboplatin is associated with a high rate of durable CNS response in pts with BCBM. Updated results, including progression-free and overall survival will be presented. Clinical trial information: NCT01004172.

514 Poster Discussion Session (Board #2), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Clinical evidence for drug penetration of capecitabine and lapatinib uptake in resected brain metastases from women with metastatic breast cancer.

Aki Morikawa, David M. Peereboom, Quentin R Smith, Helen Thorsheim, Paul R Lockman, Ahkeem James Simmons, Robert J. Weil, Viviane Tabar, Patricia Schriver Steeg, Andrew David Seidman; Memorial Sloan-Kettering Cancer Center, New York, NY; Cleveland Clinic, Cleveland, OH; Texas Tech University Health Sciences Center, Amarillo, TX; Texas Tech University Health Science Center, Amarillo, TX; Women's Cancers Section, Laboratory of Molecular Pharmacology, National Cancer Institute, Bethesda, MD

Background: Brain metastasis (BM) is a challenging complication of metastatic breast cancer (MBC). Although systemic therapy is not commonly considered as a primary therapeutic approach, its potential in BM management has recently become apparent (Bachelot T et al Lancet Oncol 2013). Capecitabine and lapatinib in particular have been evaluated in HER2+ breast cancer BM (BCBM), but evidence for drug/metabolite CNS penetration is solely derived from preclinical animal models. In this study, we examined capecitabine, its metabolites, and lapatinib uptake in BCBMs resected due to medically indicated craniotomy. **Methods:** Study patients had BCBM requiring surgical resection. Patients with HER2-negative MBC received a single preoperative oral dose of capecitabine (1250mg/m^2) 2-3 hrs before surgery. Those with HER2+ MBC received 2-3 oral doses of lapatinib (1250mg) daily, the last dose 2-3 hrs before surgery. On the day of surgery, serum was collected serially starting just before drug administration, intraoperatively, and through one hour after the conclusion of surgery. The concentration of capecitabine, its metabolites, and lapatinib from serum and BM were measured using liquid chromatography with tandem mass spectroscopy (LC-MS/MS). **Results:** 10 patients enrolled; PK data is available for 9: 6 for capecitabine and 3 for lapatinib. Capecitabine, its intermediate metabolites, 5FU, and lapatinib were detected in all BMs. Tumor capecitabine and 5-FU concentrations ranged from 3% to 129% and from 168% to 1422%, respectively, of serum concentrations. For lapatinib, the range was 21% to 700%. In a number of the BMs, drug concentrations were in the therapeutic range, whereas in others the concentrations were up to 10 fold lower. **Conclusions:** This is the first study to show capecitabine and lapatinib were detected in clinically relevant concentrations in a number of non-irradiated human BCBMs. This provides evidence for their ability to cross the blood-brain barrier, is consistent with prior published clinical activity, and supports further evaluation in a clinical setting prior to whole brain radiotherapy. Clinical trial information: NCT00795678.

515 Poster Discussion Session (Board #3), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

TBCRC 018: Phase II study of iniparib plus chemotherapy to treat triple-negative breast cancer (TNBC) central nervous system (CNS) metastases (mets).

Carey K. Anders, Allison Mary Deal, Vandana Gupta Abramson, Minetta C. Liu, Anna Maria Storniolo, John T. Carpenter, Shannon Puhalla, Rita Nanda, Amal Melhem-Bertrandt, Nancy U. Lin, Paul K. Marcom, Catherine H. Van Poznak, Vered Stearns, Michelle E. Melisko, J. Keith Smith, Olga Karginova, Eric P. Winer, Charles M. Perou, Antonio C. Wolff, Lisa A. Carey, Translational Breast Cancer Research Consortium; The University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, NC; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Vanderbilt-Ingram Cancer Center, Nashville, TN; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Indiana University Simon Cancer Center, Indianapolis, IN; University of Alabama at Birmingham, Birmingham, AL; University of Pittsburgh Medical Center, Magee Women's Cancer Program, Pittsburgh, PA; University of Chicago, Chicago, IL; The University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; Duke University Medical Center, Durham, NC; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC

Background: Nearly half of women with advanced TNBC develop CNS mets. This study evaluated the safety and efficacy of iniparib, a small molecule anti-cancer agent that penetrates the blood brain barrier (BBB), and the topoisomerase I inhibitor, irinotecan, in patients (pts) with TNBC CNS mets. **Methods:** Eligible pts had TNBC with new or progressive CNS mets with at least 1 measurable ($>$ 5mm) lesion. Pts received irinotecan 125mg/m^2 IV days (d) 1, 8 and iniparib (initial dose 5.6mg/kg, later changed to 8mg/kg) IV d 1, 4, 8, 11 every 21d. Tumor response rate (RR) was assessed by brain MRI and body CT every 9 weeks. The Kaplan Meier method estimated the primary endpoint of time to progression (TTP, intracranial [modified RECIST] or extracranial [RECIST 1.1]). Secondary endpoints were RR, PFS, OS, quality of life (QOL) and correlative endpoints. **Results:** Of 37 pts who began treatment, 34 were evaluable for efficacy. Mean age was 48 yrs (34 – 80 yrs). *BRCA* status was known for 16 patients of whom 5 had a mutation (4 *BRCA1*, 1 *BRCA2*). 88% received prior (neo)adjuvant and 68% prior metastatic chemotherapy (median 2 [1–14] lines). While 15% were CNS radiation (RT) naïve, 32% had received whole brain RT, 21% stereotactic RT, and 32% both. The most common grade (gr) 3/4 adverse events were neutropenia (14%), fatigue (5%), leukopenia (5%), hypokalemia (5%). Diarrhea was common (54%), but gr 3/4 was rare (3%). Median TTP (CNS and non-CNS) was 2.1 months (mos) (95% CI 1.7–4.3) and OS was 7.6 mos (95% CI 5.1-10.2). First progression site was CNS in 39%, non-CNS in 29% or both in 32%. CNS best RR was (12%; 0 CRs, 4 PRs); CNS clinical benefit rate (CBR, CR + PR + SD $\geq$ 6 mos) was 30%. Non-CNS RR was 5% (0 CRs, 1 PR) and CBR was 11%. **Conclusions:** Iniparib and irinotecan was well-tolerated among pts with TNBC CNS mets. While TTP was shorter than expected and contribution of iniparib to irinotecan remains uncertain, 30% of pts demonstrated CNS clinical benefit raising the question of whether predictive biomarkers could be identified. QOL, volumetric analysis of CNS lesions and translational studies evaluating molecular subtype, germline *BRCA1/2*, and DNA repair gene expression/methylation are ongoing. Clinical trial information: NCT01173497.

516 Poster Discussion Session (Board #4), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

A phase II randomized trial of lapatinib with either vinorelbine or capecitabine as first- and second-line therapy for HER2 overexpressing metastatic breast cancer (MBC).

Christos A. Papadimitriou, Tomasz Sarosiek, Joanna Pikiel, Boguslawa Karaszewska, Christoph Salat, Christian Caglevic, Piotr Potemski, Etienne Brain, Kathryn Jane Briggs, Michelle DeSilvio, Luca Marini, Wolfgang Janni; Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece; Centrum Medyczne Ostrobramska NZOZ MAGODENT, Warszawa, Poland; Wojewódzkie Centrum Onkologii, Gdansk, Poland; Przychodnia Lekarska "KOMED", Konin, Poland; Hematology Oncology Clinic, Munich, Germany; Fundacion Arturo Lopez Perez, Intop, Chile; Department of Chemotherapy, Medical University of Lodz, Lodz, Poland; Institut Curie, Saint-Cloud, France; GlaxoSmithKline, Uxbridge, Middlesex, United Kingdom; GlaxoSmithKline, Oncology, Collegeville, PA; GlaxoSmithKline, Uxbridge, United Kingdom; Universitaetsklinikum Ulm, Ulm, Germany

Background: Lapatinib (L) is approved for the treatment of human epidermal growth factor receptor 2 (HER2) positive MBC in combination with capecitabine (C) following progression after trastuzumab, anthracyclines and taxanes. Vinorelbine (V) is an important chemotherapy option in MBC. This randomized, open-label, multicenter phase II study (NCT01013740) evaluated the efficacy and safety of L with either V or C in women with HER2+ MBC. The analysis of progression-free survival (PFS) and safety showed comparable rates of efficacy and tolerability between the 2 arms (Janni et al, SABCS 2012). Here we report the results of the overall survival (OS) and crossover analyses. **Methods:** Patients with MBC who had received ≤1 chemotherapy regimen in the metastatic setting were randomized 2:1 to either L 1250 mg orally once daily (QD) continuously + V 20 mg/m^2 intravenously on days 1 and 8, every 3 weeks, or L 1250 mg orally QD continuously + C 2000 mg/m^2/day orally in 2 doses, 12 hours apart on days 1-14 every 3 weeks. Patients were stratified by prior receipt of therapy for MBC and site of metastatic disease. The primary endpoint was PFS. Other endpoints included OS, overall response rate and safety. Patients progressing on one treatment arm were given the option of crossover to the other arm. All analyses were conducted with a descriptive intent only. The control arm of L+C was included in the study design to validate the patient population and lend support to the activity of L+V. **Results:** 112 patients were randomized in the study; 37 to the L+C arm and 75 to the L+V arm. The median OS in the L+C arm was 19.4 months [95% CI: 16.4-27.2] and 24.3 months [95% CI: 16.4-NE] in the L+V arm. At the time of analysis 42 patients had crossed over; 29 patients to L+C and 13 to L+V. Median PFS after crossover was 4 months [95% CI: 2.1-5.8] in the L+C arm and 3.2 months [95% CI: 1.7-5.1] in the L+V arm. **Conclusions:** L+V has shown consistent median OS with that reported in the pivotal study of L+C. The exploratory analysis of patients retreated with L after progression on L supports the biological rationale for maintaining HER2 suppression in HER2+ patients with progression on prior lines of anti-HER2 agents. Clinical trial information: NCT01013740.

517 Poster Discussion Session (Board #5), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase III trial of non-pegylated liposomal doxorubicin (M) in combination with trastuzumab (T) and paclitaxel (P) in HER2+ metastatic breast cancer (MBC).

Lorena De La Pena, Javier Cortes, Alexey Manikhas, Laslo Roman, Vladimir Semiglazov, Mikhail Yu Biakhov, Lokanatha Dasappa, Antonio Llombart, Marcel Rozencweig, Salvatore Forenza, Ronald H. Goldfarb, Jeri Matera, Nozar Azarnia, Clifford Hudis, Jose Baselga; SOLTI, Barcelona, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; City Clinical Oncological Dispensary, St. Petersburg, Russia; Leningrad Regional Oncology Dispensary, St. Petersburg, Russia; N. N. Petrov Research Institute of Oncology, St. Petersburg, Russia; Central Clinical Hospital No.2 Named After N.A. Semashko, Moscow, Russia; Kidwai Memorial Institute of Oncology, Bangalore, India; Fundación Instituto Valenciano de Oncología, Valencia, Spain; Sopherion Therapeutics, LLC., Princeton, NJ; Sopherion Therapeutics, LLC., Forenza, NJ; Sopherion Therapeutics, Inc., Princeton, NJ; Oncology Statistics LLC, Voorhees, NJ; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: M in combination with T has shown promising activity and cardiac safety in MBC patients (pts). We conducted a randomized Phase III trial of first-line M plus T and P (MTP) versus T plus P (TP) in HER2+ MBC pts. **Methods:** Pts with HER2+ (by FISH) MBC $\geq$ 18 years and ECOG 0-1, who had received no prior chemotherapy for metastatic disease, were eligible. Left ventricular ejection fraction should be within normal institutional limits. Prior (neo-) adjuvant anthracyclines, T or P were permitted, if completed $>$1 year before the start of the study. Pts received M 50 mg/m^2 q3w for 6 cycles, T 4 mg/kg loading dose followed by 2 mg/kg qw, and P 80 mg/m^{2}qw, or T+P at the same doses until progression or toxicity. Primary outcome was progression-free survival (PFS). Enrollment of 332 pts would provide 80% power with a 5% significance to detect an improvement in PFS with MTP, assuming a median PFS of 8 months in TP and a hazard ratio (HR) of 0.70. **Results:** 363 pts enrolled (MTP 181, TP 183), 360 received treatment. The two groups were well balanced for demographics, pretreatment characteristics and extent of disease. One third of the pts had prior exposure to anthracyclines, but almost none to trastuzumab (1% and 2% in MTP and TP arms, respectively). Six cycles of M could be given to 72% of the pts. With a median follow-up of 31 months, median PFS was 16.1 and 14.5 months with MTP and TP, respectively (HR 0.84, P=0.174). In pts with ER and PR-negative tumors, PFS was 20.7 and 14.0 months, respectively (HR, 0.68; 95% CI 0.47–0.99). Median overall survival (OS) was 33.6 and 28.9 months, respectively (HR, 0.79, P=0.083). In ER and PR-negative tumors, OS was 38.2 and 27.9 months, respectively (HR, 0.63; 95% CI 0.42–0.93). The incidence of NYHA Class III/IV congestive heart failure was 3% with MTP and there were 2 cardiac deaths with TP. The frequency of adverse events was higher with MTP, especially myelosuppression, stomatitis and gastrointestinal intolerance. **Conclusions:** The trial failed to demonstrate a significant clinical improvement with the addition of M to TP. The clinical benefit observed in an exploratory analysis in the ER and PR-negative population deserves consideration for further clinical trials. Clinical trial information: NCT00294996.

518 Poster Discussion Session (Board #6), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

A phase Ib study of an anti-HER2 inhibitor, lapatinib, in combination with a c-MET and VEGFR inhibitor, foretinib, in HER2-positive metastatic breast cancer (MBC): Results from NCIC CTG IND.198.

Stephen K. L. Chia, Susan Ellard, Mihaela Mates, Stephen Welch, Catalin Liviu Dragos Mihalcioiu, Wilson H. Miller, Karen A. Gelmon, Caroline A. Lohrisch, Vikaash Kumar, Sara Kristina Taylor, Linda Hagerman, Elizabeth A. Eisenhauer, Penelope Ann Bradbury; British Columbia Cancer Agency, Vancouver, BC, Canada; Cancer Centre for Southern Interior, Kelowna, BC, Canada; Cancer Centre of Southeastern Ontario, Kingston, ON, Canada; London Regional Cancer Program, London, ON, Canada; Royal Victoria Hospital, Montreal, QC, Canada; Department of Oncology, McGill University, Montreal, QC, Canada; Cancer Center of Southeastern Ontario, Kingston, ON, Canada; British Columbia Cancer Agency, Centre for the Southern Interior, Kelowna, BC, Canada; NCIC Clinical Trials Group, Kingston, ON, Canada; NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada

Background: The mechanisms of resistance to targeted anti-HER 2 therapy are unclear. Proposed pathways include MET, VEGF and AXL. Multi-targeted pathway inhibition may delay or prevent acquired resistance to HER2 inhibition. Foretinib, an oral multi-kinase inhibitor of MET and VEGFR2, as well as PDGFRB, AXL, FLT3, TIE-2, RET and RON kinases, has pre-clinical anti-tumor activity in breast tumor models. This phase 1b study sought to establish the associated toxicities, pharmacokinetics (PK) and recommended phase II doses (RP2D) of this combination of oral tyrosine kinases inhibitors in a cohort of HER-2 positive MBC patients. **Methods:** Women with HER2 positive (determined locally) MBC, PS 0-2, and no limit on number of prior chemotherapies or lines of anti-HER2 therapies were enrolled. A 3+3 dose escalation design was utilized. 4 dose levels were planned with starting doses of foretinib 30 mg and lapatinib 750 mg PO OD (dose level 1) on a q 4 weekly cycle. Correlative studies from primary archival tissue are planned. **Results:** 19 patients were enrolled, all of whom were evaluable for toxicity assessment and 16 were evaluable for response. Median age was 60 years (34-86), 95% were PS 0-1, 53% were ER- and 95% had at least one prior anti-HER2 based regimen. A median of 2 cycles (range: 1-20) was delivered across 4 dose levels. At the 4^{th} dose level (foretinib 45 mg/lapatinib 1250 mg) dose limiting toxicities were documented in 4/7 patients. These included grade 3 fatigue (2 cases); grade 3 ALT elevation; grade 3 diarrhea and grade 2 joint effusion. There was only one grade 4 non-hematological toxicity (grade 4 vomiting: dose level 1) across all dose levels. One patient discontinued treatment due to toxicity with grade 3 limb edema and grade 3 proteinuria. PK of both drugs from DL1-3 did not appear to demonstrate a significant interaction. The RP2D was declared to be foretinib 45 mg and lapatinib 1000 mg PO OD. The full efficacy data and correlative studies will be presented at the meeting. **Conclusions:** The combination of foretinib and lapatinib can safely be delivered together, though at lower doses than either agent alone.

519 **Poster Discussion Session (Board #7), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

A phase II trial of an oral CDK 4/6 inhibitor, PD0332991, in advanced breast cancer.

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Background: The G1/S checkpoint of the cell cycle is frequently dysregulated in breast cancer (BC). Initial efficacy of PD0332991, a potent oral inhibitor of cyclin-dependent kinases (CDKs) 4/6 was shown in a variety of solid tumors and in combination with letrozole in a randomized phase II trial. **Methods:** We performed a phase II, single arm trial of PD0332991 in women with advanced BC. The primary objectives were safety and efficacy. Eligible patients had histologically-confirmed, stage IV BC with primary or metastatic tumor positive for retinoblastoma (Rb) protein expression, measureable disease by RECIST and adequate organ function/performance status. PD0332991 was given at 125 mg orally, days 1 – 21 of a 28-day cycle. Tumor was assessed every 2 cycles. A two-stage statistical design was employed. Secondary objectives included predictive biomarker assessment. **Results:** 36 patients were enrolled; 28 who completed cycle 1 are reported: 18 (64%) HR+/Her2-, 2 (7%) HR+/Her2+ and 8 (29%) HR-/Her2-. 90% had prior chemotherapy for metastatic disease (median 3 lines); 78% had prior hormonal therapy (median 2 lines). Grade 3/4 toxicities were limited to transient neutropenia (50%) and thrombocytopenia (21%). One episode of neutropenic sepsis occurred in cycle 1 in patient with 6 prior chemo regimens. All other toxicities were grade 1/2. Treatment was interrupted in 7 (25%) and dose reduced in 13 (46%) pts for cytopenias. For response data see table. Responses occurred at dose levels as low as 50 mg. Median PFS (months, 95% CI) was 4.1 (2.3,7.7) for ER+/Her2-, 18.8 (5.1,∞) for ER+/Her+ and 1.8 (0.9,∞) for ER-/Her2-. 27/28 patients discontinued study for progressive disease (PD); 1 due to patient preference. **Conclusions:** Therapy with PD0332991 alone is well-tolerated and demonstrates response or prolonged stable disease (SD) in patients with BC despite prior hormonal and chemotherapy. Expansion within subtypes and molecular predictors of response are being investigated. Clinical trial information: NCT01037790.

Response	HR+/Her2- (n=18)	HR+/Her2+ (n=2)	HR-/Her2- (n=8)	Total (n=28)
Partial response (PR)	1 (6%)	1 (50%)	0	2 (7%)
SD > 6 months	3 (17%)	0	1 (13%)	4 (14%)
SD < 6 months	9 (50%)	1 (50%)	0	10 (36%)
PD	5 (27%)	0	7 (87%)	12 (43%)
Clinical benefit (PR + SD>6 months)	4 (23%)	1 (50%)	1 (13%)	6 (21%)

520 Poster Discussion Session (Board #8), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

The relationship between quantitative HER2 gene expression by the 21-gene RT-PCR assay and adjuvant trastuzumab (H) benefit in NCCTG (Alliance) N9831.

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Background: There is considerable interest in developing HER2 testing criteria for adjuvant H. We used the 21-gene assay to examine the relationship of HER2 mRNA to benefit from H. **Methods:** N9831 compared adjuvant chemotherapy AC-T to concurrent chemotherapy-trastuzumab AC-TH in stage I-III HER2+ breast cancer. Recurrence Score (RS) and HER2 mRNA expression were determined by Onco*type* DX (neg$<$10.7, equiv 10.7 to $<$11.5, and pos $\geq$11.5 $\log_2$ expression units). Cox regression was used to assess the association of HER2 expression with H benefit for distant recurrence. **Results:** Median follow-up: 7.4 yrs. Of 1,940 total pts, 901 had consent and sufficient tissue. HER2 by RT-PCR was neg in 130 (14%), equiv in 85 (9%), and pos in 686 (76%) pts. Concordance between HER2 assessments was 95% for RT-PCR vs central IHC ($>$10% + cells = +), 91% for RT-PCR vs central FISH ($\geq$2.0 = pos) and 94% for central IHC vs central FISH. In the primary analysis, the association of HER2 expression with H benefit was marginally non-significant (P=0.057). In hormone receptor pos pts (local IHC) the association was significant (P=0.002). The association was nonlinear with the greatest estimated benefit at lower and higher HER2 mRNA expression levels. The observed treatment benefit in low HER2 pts was not due to imbalance between arms in RS and individual gene expression values. **Conclusions:** Concordance among HER2 assessments by central IHC, FISH, and RT-PCR was high. Association of HER2 mRNA expression with H benefit was marginally non-significant. A consistent benefit of trastuzumab irrespective of mHER2 levels was observed in the pts with either IHC+ or FISH+ tumors. Benefit was observed in pts with high HER2 by RT-PCR but also observed for the small groups of pts with negative results by quantitative RT-PCR or FISH (Table). Plausible mechanisms for this observation will be discussed.

H benefit Cox hazard ratios (95% CI) by central HER2 status (adjusted for nodes).

	Neg	Equivocal	Pos
IHC	0.31 (0.05, 1.37) P=0.127	0.85 (0.27, 2.31) P=0.763	0.49 (0.33, 0.71) P<0.001
FISH	0.33 (0.09,0.93) P=0.034		0.54 (0.37,0.78) P<0.001
RT-PCR	0.31 (0.09,0.83) P=0.017	0.44 (0.09,1.59) P=0.217	0.55 (0.37,0.81) P=0.002

521 Poster Discussion Session (Board #9), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Combination trastuzumab and chemotherapy to induce immunity to multiple tumor antigens in patients with HER2-positive metastatic breast cancer: NCCTG (Alliance) studies N0337 and N98-32-52.

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Background: The addition of trastuzumab to chemotherapy improves responses to therapy and extends survival among patients with metastatic HER2 breast cancer. Several mechanisms have been proposed for the activity of this combination therapy. Trastuzumab, specifically, is thought to activate NK cells and blunt HER2 signaling. Prior work from us has shown that combination trastuzumab and chemotherapy induces HER2-specific antibodies which correlate with response to therapy. Despite that, it remains unclear whether the immunity that was induced was due to complexing of non-tumor derived HER2 or antigen derived from the tumor site. In the present work, we addressed this question by assessing if combination therapy induced epitope spreading to tumor antigens other than HER2. **Methods:** Pre-and post-treatment sera were obtained from 56 women enrolled in 2 NCCTG clinical trials, N0337 and 98-32-52. IgG antibodies to HER2 intracellular domain (HER2), p53, IGFBP2, CEA and tetanus toxoid (TT) were examined using ELISAs. Sera from an age-matched group (N=56) of controls and 12 patients treated in the adjuvant setting were also examined. **Results:** Prior to therapy, metastatic patients had higher IgG levels ($\geq$ 2-fold) to p53 and HER2 but not CEA, IGFBP2 and TT, relative to the controls. Similarly, adjuvant patients had elevated IgGs to multiple tumor antigens prior to therapy, relative to controls. Following therapy, levels of IgG to IGFBP2, HER2, and p53 increased in 81% of metastatic patients, with mean increases of 3.2 ($\pm$0.6 sem), 6.2 ($\pm$2.7) and 2.7 ($\pm$0.7) fold, respectively ($p<0.05$). Levels of antibodies to TT and CEA were not elevated by treatment. In contrast, IgGs were not increased in adjuvant patients; consistent with the idea that immunity depends on the presence of threshold levels of antigens. **Conclusions:** These results show that combination treatment induces adaptive immunity to antigens released by tumor and that metastatic patients remain capable of responding immunologically to their cancer. Thus, in metastatic breast cancer patients, combination trastuzumab and chemotherapy may behave as a vaccine.

522 Poster Discussion Session (Board #10), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Generation of adaptive HER2-specific immunity in HER2 breast cancer patients by addition of trastuzumab to chemotherapy in the adjuvant setting: NCCTG (Alliance) study N9831.

Keith L. Knutson, Edith A. Perez, Karla V. Ballman, Courtney L. Erskine, Nicholas Fox, Christie-Ann McCarl, Nadine Norton, Susan V. Sumrall, Donald W. Northfelt, Winston Tan, Carmen Julia Calfa, Mark D. Pegram, Raphael Clynes; Mayo Clinic, Rochester, MN; Mayo Clinic, Jacksonville, FL; Columbia University, New York, NY; Mayo Clinic, Scottsdale, AZ; Memorial Cancer Institute, Hollywood, FL; Stanford University, Stanford, CA

Background: In the adjuvant setting, patients with HER2 breast cancer treated with trastuzumab and chemotherapy have superior survival compared to patients treated with chemotherapy alone. We previously showed that trastuzumab and chemotherapy induces HER2-specific antibodies which correlate with response to therapy in patients with HER2+ metastatic breast cancer. It remained unclear from those studies, however, whether the HER2-specific immunity played a role and if antibody immunity was associated with improved disease free survival in the adjuvant setting. In the present study, we addressed these questions by analyzing sera samples from a subset of patients enrolled in the NCCTG adjuvant trial, N9831, which includes an arm (Arm A) in which trastuzumab was not used. Arms B and C received trastuzumab sequentially or concurrently to chemotherapy, respectively. **Methods:** Pre-and post-treatment initiation sera were obtained from 50 women enrolled in N9831 (22 Arm A; 14 Arm B, and 14 Arm C). Lambda IgG antibodies (to avoid detection of trastuzumab) to HER2 were measured and presented as an index (>0.2 was considered a positive response). **Results:** Prior to therapy, across all three arms, N9831 patients had similar mean HER2 IgG levels (0.19 units in Arm A, 0.14 in Arm B, and 0.23 in Arm C, $P=0.85$). Following treatment, the mean levels of antibodies increased in Arm B to 0.35 units and in Arm C to 0.56 units and were higher ($p<0.001$) than in Arm A where levels did not increase. The proportion of patients who demonstrated antibody immunity increased by 9% in Arm A, 50% in Arm B and 28% in Arm C ($P=0.026$). Although the event rate was low in this cohort, Cox modeling suggested that larger increases in antibodies were associated with improved disease free survival ($HR=0.23$; $p=0.04$). **Conclusions:** These results show that the increased antibody immunity observed in adjuvant patients treated with combination trastuzumab and chemotherapy is clinically significant and results from the inclusion of trastuzumab. The findings may have important implications for improving treatment outcomes in patients treated with trastuzumab.

523 Poster Discussion Session (Board #11), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Treatment (tx) patterns and clinical outcomes for patients (pts) with de novo versus recurrent HER2+ metastatic breast cancer (MBC).

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Background: Use of adjuvant trastuzumab (T) in pts with HER2+ early breast cancer is associated with decreased recurrence. As fewer patients relapse, the proportion of pts with de novo metastatic disease in the first-line (1L) setting will increase, which could have implications for the design/interpretation of results from HER2+ MBC trials. To date, little data exist on potential differences in prognosis and outcomes between pts with recurrent vs de novo HER2+ MBC. **Methods:** registHER is an observational cohort of pts with HER2+ MBC diagnosed ≤6 mo from enrollment and followed until death, disenrollment, or June 2009 (median follow-up: 27 mo). Demographics and 1L tx patterns (using descriptive analyses), as well as clinical outcomes (median PFS and OS estimated by Kaplan-Meier method) were examined for pts with de novo vs recurrent HER2+ MBC. De novo was defined as disease-free interval (DFI) between initial and metastatic diagnosis ≤90 days; recurrent was defined as DFI >90 days. Cox regression analyses were used to generate hazard ratios (HRs). **Results:** Pts with de novo HER2+ MBC (327 of 1001 enrolled) were more likely to be younger and non-white; have lymph, bone, and/or liver metastases and >4 sites of metastatic disease; less likely to have lung or CNS metastases; and have received 1L regimens of TCH or AC more frequently vs pts with recurrent disease (who received T + vinorelbine more frequently). PFS and OS were longer in the de novo vs recurrent group (Table). **Conclusions:** Despite presenting with more advanced-stage disease accompanied by higher tumor burdens, pts with de novo HER2+ MBC had more favorable clinical outcomes vs those with recurrent disease. Differences in disease characteristics and tx patterns resulting in more refractory disease (including acquired resistance from adjuvant tx) may account for these observations. Clinical trial information: NCT00105456.

Clinical outcomes.

	De novo (n=327)	Recurrent (n=674)
Median PFS,[a] mo (95% CI)	12.5 (11.6–13.8)	9.4 (8.2–10.2)
Cox HR	0.740 (0.640–0.855)	
Unadjusted	0.711 (0.613–0.824)	
Adjusted		
Median OS, mo (95% CI)	41.7 (36.1–47.2)	32.8 (29.3–36.7)
Cox HR	0.775 (0.643–0.935)	
Unadjusted	0.750 (0.619–0.908)	
Adjusted		

[a] PFS as reported by physicians' standard practice.

524 Poster Discussion Session (Board #12), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Is the proportion of patients with synchronous stage IV breast cancer surviving > 2 years increasing over time?

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Background: Studies have shown a moderate increase in survival over time among pts with stageIV breast cancer. Median survival is approximately 2 yrs. The aim of this study was to evaluate trends over time of pts with synchronous stage IV disease who survive >2 yrs. **Methods:** Using the SEER registry we identified female pts with synchronous stage IV breast cancer diagnosed between 1990-2007. Pts were divided into 3 groups according to year of diagnosis(1990-1995, 1996-2000, 2001-2007). Probability of surviving more than >2 yrs was computed within each group. A multivariable logistic regression model was then fitted to determine the association between year of diagnosis and the probability of surviving >2 yrs after adjusting for other prognostic factors. **Results:** 22,492 pts were identified of whom 9,388 (41.7%) had a survival of >2 yrs. The probability of surviving >2 yrs was 36.2%, 40.1%, and 44.2% among pts diagnosed in periods 1990-1995, 1996-2000, and 2001-2007 respectively (p-value < 0.0001). The probability of surviving >2 yrs was 55.3% and 29.3% among pts with ER+ and ER- disease respectively (p-value <0.0001) and was 32.9% and 43.5% among pts of black and white race respectively (p-value <0.0001). In the multivariable model the probability of surviving >2 yrs increased with increasing year of diagnosis (OR 1.04, 95% CI 1.03-1.05, p <0.0001). Other factors significantly associated with an increased probability of surviving >2 yrs included radiation therapy, lower grade, younger age, hormone receptor (HR) positive disease and non-inflammatory disease. Interaction term between race and year of diagnosis was marginally significant, such that black pts had a more slowly increasing probability of surviving >2 yrs compared to whites (OR 0.97, 95% CI 0.96-1.00, p = 0.037). Interaction term between HR status and year of diagnosis was not significant. **Conclusions:** Our results indicate that among pts with synchronous stage IV breast cancer the probability of surviving >2 yrs has increased over time reflecting the introduction and FDA approval of multiple efficacious chemotherapeutic and endocrine therapeutic options. Of concern, the probability of surviving >2 yrs has increased more slowly among pts of black race.

525 Poster Discussion Session (Board #13), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Long-term (8 years) assessment of trastuzumab-related cardiac events in the HERA trial.

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Background: Trastuzumab-related cardiac dysfunction may occur in patients (pts) treated with adjuvant therapy and it is mostly reversible. We report the long-term outcome of pts with cardiac dysfunction treated with adjuvant trastuzumab (T) in the Herceptin Adjuvant (HERA) trial. **Methods:** HERA is a three-arm, randomized trial that compared 1 year or 2 years of T with observation (Obs) in women with HER2-positive early breast cancer (EBC). Eligible pts had a left ventricular ejection fraction (LVEF) $\geq$ 55% at study entry (i.e. after completion of (neo)adjuvant chemotherapy with or without radiotherapy). Cardiac function was closely monitored throughout the trial. This analysis at 8-year median follow-up considers pts randomly assigned to 1 year or 2 years of T therapy or observation. **Results:** 5102 pts were randomized to HERA. The "as treated" safety population is considered: 2 years T (N=1,673), 1 year T (N=1,682) and Obs (N=1,744). Cardiac events leading to T discontinuation in the 1-year and 2-year arms were observed in 5.2% and 9.4% of pts, respectively. Cardiac death, severe congestive heart failure (CHF) and confirmed significant LVEF drop remained low in all three arms (Table). In the 1 year T arm, 71.4% of pts with severe CHF, and 81.2% of pts with confirmed LVEF drop recovered cardiac function (at least 2 sequential LVEF assessments $>$ 50%). The median time to recovery was 9.7 months and 6.3 months, respectively. In the 2 years T arm, 87.5% of pts with confirmed LVEF drop recovered cardiac function and median time to recovery was 8.3 months. **Conclusions:** At 8-year median follow-up the incidence of cardiac events during adjuvant T remains low and these events are mostly reversible. These results confirm low cardiac events when T is given as part of the adjuvant therapy for pts with HER2-positive EBC. Clinical trial information: NCT00045032.

Summary of cardiac events in HERA.

	Obs* (N= 1,744)	1 year T (N= 1,682)	2 years T (N= 1,673)
Cardiac death	2 (0.1%)	0 (0%)	3 (0.2%)
Severe CHF[1]	0 (0%)	14 (0.8%)	13 (0.8%)
Confirmed significant LVEF drop[2]	15 (0.9%)	69 (4.1%)	120 (7.2%)

[1] NYHA class III or IV. [2] LVEF $<$ 50% and at least 10 EF points below baseline confirmed by repeat assessment. *Cardiac events in the Obs group are only those reported prior to start of any T as part of the selective crossover.

526 Poster Discussion Session (Board #14), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

ACOSOG Z1041 (Alliance): Cardiac events (CE) among those receiving neoadjuvant anthracyclines (A) and taxanes with trastuzumab (T) for HER2+ breast cancer.

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Background: Z1041 randomized women with HER2+ operable breast cancer to: FEC → P+T (Arm 1) or P+T → FEC+T (Arm 2). Treatment administered as 5-FU 500 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 day 1 of a 21-day cycle x 4; paclitaxel 80 mg/m^{2}weekly x 12 and T 4 mg/kg once then 2 mg/kg weekly x 11. T was to continue q3 weeks post-op for 40 weeks. A secondary aim was to examine the cardiotoxicity (CE). **Methods:** Ejection fraction (EF) was measured at baseline (BL), between regimens (wk 12), prior to surgery (wk 24) and PRN. Eligibility: BL EF ≥ 55%. CEs included decline in EF of > 15%, or >10% points to a value < LLN. Reversibility was adjudicated by blinded investigators as reversible (R: recovery of EF to ≤ 5% below BL), partially reversible (PR: recovery of > 10% points from nadir, but ≤ 5% points below BL), indeterminate (IN: no additional EF data), or irreversible (IRR:follow-up EF studies showed no improvement). **Results:** Of the 280 patients (Arm 1: 138) who began treatment, 15 pts (Arm 1: 10; Arm 2: 5) did not receive T. The number of weeks of T was 13 (range: 1-18) in Arm 1 and 24 (range: 1-31) in Arm 2. Changes in EF and severe treatment related cardiac toxicities prior to surgery (sx) are tabled below. There were 271 pts (Arm 1: 131) who had post-BL EFs. Prior to sx, there were 11 CE (8.3%) in Arm 1 and 13 CE (9.2%) in Arm 2. CEs were R in 12 pts (Arm 1: 5; Arm 2: 7); PR in 6 pts (Arm 1: 4; Arm 2: 2); IN in 4 pts (Arm 1: 2; Arm 2: 3) and IRR in 1 Arm 2 pt. **Conclusions:** The number of CE events in arms 1 and 2 showed no significant difference; greater scatter was observed in arm 2 patients. While concern for late cardiac events makes ongoing cardiac surveillance prudent due to A, concomitant use of A and T appear to not be associated with increased cardiac risk. Clinical trial information: NCT00513292.

EF changes and percent of Pts with cardiac toxicity.

	Toxicities					
	Arm 1 (n=138)			Arm 2 (n=142)		
Grade	2	3	4	2	3	4
Cardiac ischemia	0	0	0	0	0	0.7
Hypertension	2.1	0.7	0	1.4	0.7	0
Left ventricular systolic dysfunction	2.9	0	0	3.5	0.7	0
Sinus tachycardia	0.7	0	0	0.7	0	0
Atrial fibrillation	0	0	0	0	0.7	0
Median (n; range)	EF					
Baseline	65% (53 to 79%)			65% (53 to 83%)		
Change at 12 weeks	-2% (130; 12 to -16%)			-3% (137; 14.0 to -25%)		
Change at 24 weeks	-3% (128; 20 to -20%)			-5% (139; 17.0 to -22%)		

527 Poster Discussion Session (Board #15), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

TBCRC 002: A phase II, randomized, open label trial of preoperative letrozole versus letrozole (LET) in combination with bevacizumab (BEV) in post-menopausal women with newly diagnosed stage II/III breast cancer.

Andres Forero-Torres, Hope S. Rugo, Christos Vaklavas, Nancy U. Lin, Lisa A. Carey, Minetta C. Liu, Rita Nanda, Shannon Puhalla, Anna Maria Storniolo, Helen Krontiras, Mansoor N. Saleh, Yufeng Li, Albert F. LoBuglio, Jennifer F. De Los Santos, on behalf of the Translational Breast Cancer Research Consortium (TBCRC); University of Alabama at Birmingham, Birmingham, AL; University of California, San Francisco, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA; University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; University of Chicago, Chicago, IL; University of Pittsburgh Medical Center, Magee Women's Cancer Program, Pittsburgh, PA; Indiana University Simon Cancer Center, Indianapolis, IN; Georgia Cancer Specialists PC, Atlanta, GA

Background: A study from UAB Breast SPORE showed that expression of vascular endothelial growth factor (VEGF) in MCF7 breast tumor xenografts imparts tamoxifen resistance, increases tumor growth and metastatic potential. We postulated that anti-VEGF therapy would enhance anti-estrogen therapy. **Methods:** Randomized 2:1 phase II selection trial of LET (2.5 mg/day) with/without BEV (anti-VEGF monoclonal antibody; 15 mg/kg q3 weeks) for 24 weeks prior to surgery in post-menopausal patients with stage II/III, ER+/HER2- breast cancer. Primary objective was pathologic complete remission (pCR). Secondary objectives included response rates, down-staging, and toxicity. The trial was not powered to compare arms, but sized to estimate pCR rates to a certain precision (SE$<$5% for combination, SE$<$2% for single agent). Biopsies of the tumor and circulating tumor cells were collected. **Results:** 75 patients were randomized; 50 in the combination and 25 in the LET alone arm; 45 and 24 patients underwent surgery, respectively. Median age was 61 and 65 years, respectively. 5 patients in the combination arm had a pCR (11%; CI 1.9-20.1%) (no evidence of invasive cancer) , and 3 a near pCR (7%; 0%-14.5%) (microscopic disease only); thus pCR/near pCR rate 18% (6.8-29.2%). No patient treated with LET alone achieved a pCR/near pCR. The objective response rate was 64.5% in the combination arm and 37.5% in the single agent arm. 45% of the patients in the combination arm attained stage 0/I; 25% in the letrozole alone arm attained stage I, none attained stage 0. Therapy was well tolerated in both arms with no grade 4/5 toxicity. The most common AEs in the letrozole arm were hot flashes, fatigue, arthralgias/stiffness, myalgias, nausea/vomiting, and night sweats; in the combination arm they were hypertension, arthralgias/stiffness, hot flashes, headache, fatigue, proteinuria, dyspnea, rash, and myalgias. **Conclusions:** Neoadjuvant therapy with LET and BEV was well-tolerated and resulted in increased objective responses and down-staging. "Next-Gen" genomic analysis of the biopsies will allow for a trial with a targeted patient enrolment. Clinical trial information: F061229006.

528 Poster Discussion Session (Board #16), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

The prognostic role of androgen receptor in early-stage breast cancer patients: A meta-analysis.

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Background: Androgen receptor (AR) expression has been observed in ~70% of breast cancer (BC) patients, but its prognostic role is not established yet. To assess this we performed a meta-analysis of studies that evaluated the impact of AR on disease free survival (DFS) and/or on overall survival (OS) in early stage BC. **Methods:** Published studies were identified by an electronic search on PubMed using the MeSH terms ″breast neoplasm″ and ″androgen receptor″ (up to June 2012). Identified studies were assessed against the following criteria for inclusion in the analysis: early stage BC and reported results of AR status in correlation with clinical outcome. We report combined HRs with 95% confidence intervals (CI) using AR negative patients as reference. **Results:** Twenty studies were eligible for the meta-analysis out of 493 initially identified and 12 among them, including 6,525 patients, were considered as evaluable (i.e., reporting enough information to allow aggregation of results). AR positivity was associated with lower risk of relapse in all breast cancer patients, and better overall survival in both univariate (U) and multivariate (M) analysis. AR prognostic impact in different subtypes was also assessed (see Table). **Conclusions:** Our analysis demonstrated that AR delivers prognostic information overall, serving as a positive prognostic factor in early stage BC. Further studies are needed to delineate its prognostic impact within the different subtypes of the disease.

	HR	95% CI	P
Overall			
U DFS (12 studies, N=5,658)	0.65	0.50-0.76	<0.001
M DFS (5 studies, N=3,207)	0.37	0.29-0.47	
U OS (12 studies, N=6,525)	0.60	0.47-0.78	
M OS (6 studies, N=4,671)	0.44	0.27-0.72	
Subtypes (univariate analysis)			
ER+ DFS (5 studies, N=2,048)	0.52	0.42-0.65	<0.001
ER+ OS (5 studies, N=3,047)	0.58	0.47-0.71	<0.001
ER- DFS (2 studies, N=316)	0.33	0.04-2.49	0.45
ER- OS (3 studies, N=620)	1.38	1.01-1.88	0.04
HER2+/ER- DFS (3 studies, N=358)	1.21	0.86-1.7	0.28
HER2+/ER- OS (3 studies, N=358)	1.50	1.01-2.22	0.04
TN DFS (5 studies, N=536)	0.52	0.34-0.79	0.002
TN OS (4 studies, N=495)	0.49	0.28-0.86	0.01

TN, triple-negative.

529 Poster Discussion Session (Board #17), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Relative effectiveness of letrozole alone or in sequence with tamoxifen for patients diagnosed with invasive lobular carcinoma.

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Background: BIG 1-98 is a randomized, phase III study that compares five years of tamoxifen (tam) or letrozole (let), (monotherapy arms), or their sequences (tam-let or let-tam) in post-menopausal women with ER+ early BC. In the monotherapy arms, the magnitude of benefit of adjuvant let compared with tam varies by histology (greater in invasive lobular carcinoma (ILC) than invasive ductal carcinoma (IDC)). In this analysis we investigate the magnitude of benefit of let compared to tam-let and let-tam according to histology (IDC and ILC) at 96 months of median follow-up. **Methods:** There were 4,634 patients enrolled in the let, tam-let and let-tam arms of BIG-98. This analysis includes patients with centrally-reviewed histological subtype (n=4,223); classified as classic ILC or IDC (n=3,790); and with centrally reviewed ER, PgR and Ki67 (n=3,212). **Results:** The 8-year DFS and OS univariate estimates (±SE) for IDC and ILC are presented in the Table. When correcting for classic clinicopathological variables, treatment assignment was not a significant predictor of DFS and OS. **Conclusions:** We observed a trend toward greater magnitude of benefit in favor of let monotherapy for ILC than IDC. In the ILC subset, improvements for both DFS and OS were seen for let when compared to tam-let or let-tam, though not statistically significant. This may be due to the reduced number of ILC patients across subgroups. The present analysis is consistent with previous data from the monotherapy arms where let was associated with better DFS and OS than tam for ILC, and suggests that let might be the preferred upfront regimen for patients diagnosed with ILC. Clinical trial information: NCT00004205.

	IDC (N= 2,849)			ILC (N=363)		
	Let	Tam-Let	Let-Tam	Let	Tam-Let	Let-Tam
Number of patients	941	972	936	123	113	127
8-Year DFS	79 ± 1.4	79 ± 1.3	79 ± 1.4	85 ± 3.6	76 ± 4.5	75 ± 4.1
No. of events	202	209	206	22	27	33
Let vs tam-let HR(95%CI)		0.99 (0.82-1.20)			0.71 (0.41-1.25)	
Let vs let-tam HR(95%CI)		0.97 (0.80-1.18)			0.66 (0.38-1.13)	
8-Year OS	88 ± 1.1	86 ± 1.2	88 ± 1.1	90 ± 3.0	85 ± 3.6	89 ± 3.0
No. of events	117	135	114	12	17	15
Let vs tam-let HR(95%CI)		0.89 (0.70-1.14)			0.61 (0.29-1.28)	
Let vs let-tam HR(95%CI)		1.02 (0.79-1.32)			0.82 (0.39-1.76)	

530 Poster Discussion Session (Board #18), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Preoperative letrozole plus lapatinib/placebo for HR+/HER2 negative operable breast cancer: Biomarker analyses of the randomized phase II LET-LOB study.

Valentina Guarneri, Antonio Frassoldati, Daniele Giulio Generali, Alberto Bottini, Katia Cagossi, Giancarlo Bisagni, Corrado Boni, Luigi Cavanna, Federico Piacentini, Stefania Raffaella Bettelli, Guido Ficarra, Antonino Maiorana, Luca Marini, Pier Franco Conte; Department of Oncology, Hematology, and Respiratory Diseases, Modena University Hospital, Modena, Italy; Clinical Oncology AOU of Ferrara Itay, Ferrara, Italy; U.O. Multidisciplinare di Patologia Mammaria, A.O. Istituti Ospitalieri di Cremona, Cremona, Italy; Division of Medical Oncology, Ramazzini Hospital, Carpi, Italy; Division of Oncology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy; "S. Maria Nuova" Hospital, Reggio Emilia, Italy; Piacenza Hospital, Piacenza, Italy; Department of Pathology, Modena University Hospital, Modena, Italy; GlaxoSmithKline, Uxbridge, United Kingdom; Istituto Oncologico Veneto, University of Padova, Padova, Italy

Background: This is a randomized, double-blind, placebo controlled study aimed to evaluate the clinical and biological effects of letrozole + lapatinib or placebo as neoadjuvant therapy in previously untreated hormone receptor positive/HER2 negative operable breast cancer. **Methods**: 92 postmenopausal patients with stage II-IIIA breast cancer were randomly assigned to 6 months letrozole-lapatinib (Arm A, n=43) or letrozole-placebo (Arm B, n= 49). Clinical response was evaluated according to RECIST. The following biomarkers were centrally evaluated by IHC on diagnostic core biopsy and on surgical specimens: HER2, Ki-67, EGFR, pAKT, PTEN. PIK3CA mutations were evaluated by pyrosequencing. **Results:** 81 patients were evaluable by USG, 8 were assessed with mammography and/or palpation. Three patients who discontinued therapy and withdrew consent were counted as non-responders according to the ITT analysis. No differences in terms of objective response rate (partial+complete response) were observed between the two arms (70% vs 63%). The percentage of patients achieving disease progression, disease stabilization, partial response and complete response were 2%, 23%, 58%, 12% respectively in the letrozole-lapatinib arm, and 6%, 29%, 61%, 2% respectively in the letrozole-placebo arm. No patients achieved pCR. All the patients were centrally confirmed as having HER2 negative disease. A significant decrease in Ki67 and pAKT expression from baseline to surgery was observed in both arms. A trend for a greater Ki67 suppression was observed in responding patients (mean Ki67 suppression -8.8 in responders vs -3.6 in non responders, p= 0.06). A mutation in PIK3CA exon 9 or 20 was observed in 37% of the patients. Overall, no differences in response were observed according to PIK3CA mutations, however, in the letrozole-lapatinib arm, the probability of achieving a clinical response was significantly higher in the PIK3CA mutation subgroup (ORR 93% vs 63% in PIK3CA WT, Pearson's chi2 p=0.040). **Conclusions:** This is the first trial showing a significant correlation between PIK3CA mutation and response to letrozole-lapatinib in Hormone Receptor +/HER2- disease. Clinical trial information: NCT00422903.

531 Poster Discussion Session (Board #19), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase II randomized study of the EGFR, HER2, HER3 signaling inhibitor AZD8931 in combination with anastrozole (A) in women with endocrine therapy (ET) naive advanced breast cancer (MINT).

Stephen R. D. Johnston, Mark Basik, Roberto Hegg, Wirote Lausoontornsiri, Lukasz Grzeda, Mark Clemons, Lydia Mary Dreosti, Serban Ghiorghiu, Helen Mann, Donal Landers, Mary Stuart, Massimo Cristofanilli; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Jewish General Hospital Segal Cancer Centre, Montreal, QC, Canada; Hospital Perola Byington, Sao Paulo, Brazil; Bankok Cancer Hospital, Bangkok, Thailand; NZOZ Magodent, Centrum Medyczne Ostrobramska, Warsaw, Poland; Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; University of Pretoria and The Steve Biko Academic Hospital, Gauteng, South Africa; AstraZeneca, Macclesfield, United Kingdom; Fox Chase Cancer Center, Philadelphia, PA

Background: Preclinical data suggest a key role for EGFR inhibition in delaying acquired resistance to ET in ER+ breast cancer (BC). Retrospective analyses of 2 Phase II studies suggested adding gefitinib to ET delayed PFS in ET naive (ETN) BC. This randomized, double-blind, placebo-controlled multi-center study (NCT01151215) was conducted to prospectively test the hypothesis that adding AZD8931, an inhibitor of EGFR, HER2 and HER3 signaling, to A would be beneficial in delaying endocrine resistance in an advanced ETN BC population. **Methods:** Post-menopausal women with ER+ and/or PR+, ETN, HER2-negative, advanced BC were randomized (1:1:1) to receive A (1 mg od) plus AZD8931 20 or 40 mg bd or placebo (P). The primary endpoint was PFS (ITT population). Data presented are from an interim analysis (data cutoff 31 Aug 2012; 39% pts had a progression event). **Results:** Between Jun 2010 and Jun 2012, 359 pts (median age 61 years) were randomized to A combined with AZD8931 20 mg (n=118), 40 mg (n=120) or P (n=121). At the interim analysis, median PFS in the AZD8931 20 mg, 40 mg and P arms was 10.9, 13.8 and 14.0 months, respectively; PFS HR (95% CI) for AZD8931 20 mg:P was 1.37 (0.91–2.06, $P=0.135$) and for AZD8931 40 mg:P was 1.16 (0.77–1.75, $P=0.485$). Deaths were reported for 20 (17%), 16 (13%) and 12 pts (10%) in the AZD8931 20 mg, 40 mg and P arms, respectively. Grade ≥3 AEs were reported for 22 (19%), 44 (37%) and 18 (15%) pts in the AZD8931 20 mg, 40 mg, and P arms, respectively, the most frequent being rash (0% vs 8% vs 2%), acneiform dermatitis (0% vs 7% vs 0%) and hypertension (3% vs 3% vs 2%). Serious AEs were reported for 12%, 14% and 9% pts in the AZD8931 20 mg, 40 mg and P arms, respectively, and discontinuation (of AZD8931 or P) due to an AE in 5%, 8% and 2% pts, respectively. **Conclusions:** Co-blockade of EGFR, HER2, HER3 in combination with aromatase inhibition does not appear to delay endocrine resistance to ETN BC. Based on the low probability of demonstrating superior efficacy with addition of AZD8931 to A and the overall risk/benefit, the study was closed at the recommendation of the IDMC and pts discontinued AZD8931. Clinical trial information: NCT01151215.

532 Poster Discussion Session (Board #20), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Breast cancer evaluation and targeted investigational therapy (BEAT-IT): A pilot prospective tissue testing to guide clinical trial selection.

Lajos Pusztai, Danielle Mattair, Naoto T. Ueno, Vicente Valero, Stacy L. Moulder, James L. Murray, Ricardo H. Alvarez, Mariana Chavez-Mac Gregor, Lumarie Santiago, Rony Avritscher, Aysegul A. Sahin, Gabriel N. Hortobagyi, William Fraser Symmans, Funda Meric-Bernstam, Elizabeth M Burton, Ana M. Gonzalez-Angulo; Yale Cancer Center, New Haven, CT; 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: An increasing number of molecularly targeted drugs are now available in Phase I and II clinical trials. Many of these drugs target specific molecular abnormalities such as mutated, amplified or rearranged genes. Our hypothesis is that cancers that carry a molecular abnormality that corresponds to the mechanism of action of a given investigational drug are more sensitive to that particular drug than other cancers. The objective of this study is to perform molecular analysis of metastatic breast cancer biopsies (bx) using methods already established within CLIA approved laboratories, and to use the results to triage pts to various therapeutic clinical trials or standard of care therapy. **Methods:** Four core needle biopsies (CNB) and 4 fine needle aspirations (FNA), or 8 FNA are obtained from the most safely accessible metastatic site in a single bx session. Pathological confirmation of successful aspiration is performed. Two core bx (or 4 FNA passes) are formaldehyde fixed and paraffin embedded for Immunohistochemistry (IHC), FISH and mutation analysis (CMS11 or CMS46) and 4 FNA are placed in RNA-later and snap-frozen for transcriptional profiles and storage. Samples are transferred to the Molecular Diagnostic, IHC, and Cytogenetics Laboratories. All reports are included in the electronic medical record. **Results:** FromFeb 2012 to Jan 2013, 142 pts referred, 128 pts registered, 101 bx completed and 78 (77%) bx with available results. Bx sites included: liver (37), lymph node (26), soft tissue (16), bone (13), lung (5), other (4). Successful results were obtained for IHC: PTEN (73%), AR (78%), MET (73%), FISH: EML4-ALK (78%) and MET (74%), and mutation analysis (76%). To date, there have been no reported hospitalizations, ER visits, bleeding, pain, infection or organ dysfunction at the bx sites. 16 pts have been treated on trials with investigational agents hypothesized to result in response based upon the molecular profile of the tumor. **Conclusions:** Prospective tissue collection to determine the molecular targets and to evaluate pts for clinical trial selection is feasible and safe.

533 Poster Discussion Session (Board #21), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Impact of routine tumor genotyping on enrollment in targeted therapy trials for metastatic breast cancer (MBC): 4-year review.

Aditya Bardia, Steven J. Isakoff, Dejan Juric, Darrell R. Borger, Dora Dias-Santagata, Anthony John Iafrate, Keith Flaherty, Beverly Moy, Leif William Ellisen; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Major barriers to enrollment in therapeutic clinical trials (<5% in United States) include low response rate in phase 1/2 trials and low enthusiasm among oncologists. Stratified clinical trial enrollment based on molecular profiling of tumors represents a potential paradigm shift in drug development. Here we assess the clinical utility of tumor genotyping for identification of oncogenic driver mutations and enrollment in therapeutic clinical trials for patients with MBC. **Methods:** A robust, high-throughput tumor genotyping assay (Snapshot), was developed at our institution to assess for presence of potentially actionable oncogenic driver mutations (15 genes, 130 mutations) using DNA derived from formalin-fixed, paraffin-embedded (FFPE) tissue. The tumor genotyping assay was ordered by oncologists in clinic for patients with MBC. Relevant clinical information was gathered from chart reviews. Descriptive statistics were used for analysis. **Results:** From 2009-2012, 347 breast tumors were prospectively genotyped in the study population (median age = 50, range 27-90). PIK3CA mutation (23.3%) was the most common mutation detected overall, albeit at varying frequency in tumor subtypes: HR+ (29.1%, N= 210), HER-2+ (21.5%, N = 65), TN (8.3%, N = 72). Unanticipated mutations in KRAS, BRAF, IDH, and HER-2 were also discovered. Clinical genotyping helped identify breast origin for carcinomas of unknown primary and revealed changes in mutation profile in metastatic tumors from primary tumors. Enrollment in clinical trials for MBC almost quadrupled from 2005-2008 to 2009-2012, with 35.5% of patients undergoing tumor genotype testing enrolling in trials, particularly phase-1 genotype-directed targeted therapy, such as PI3K inhibitors, Akt inhibitors, and combined PI3K/MEK inhibitors. **Conclusions:** Routine tumor genotyping can be successfully incorporated into clinical practice to significantly enhance therapeutic clinical trial enrollment and potentially accelerate development of genotype-directed targeted therapies for MBC.

534 Poster Discussion Session (Board #22), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Frequent LOH of CYP2D6 in ER+ breast cancer determined by next-generation sequencing (NGS).

Mark J. Ratain, James Sun, Yusuke Nakamura, Nancy J Cox, Tarek Sahmoud, Phil Stephens, David Chen, Vincent A. Miller, Jeffrey S. Ross, Roman Yelensky; The University of Chicago, Chicago, IL; Foundation Medicine, Inc, Cambridge, MA; Global Oncology Development, Novartis Pharmaceuticals Corporation, Florham Park, NJ; Foundation Medicine, Inc., Cambridge, MA; Albany Medical College, Albany, NY

Background: The role of CYP2D6 genetic variation in predicting response to tamoxifen in ER+ breast cancer is a subject of ongoing debate. There has been great variability in approaches to both genotyping and phenotyping, and in particular many investigators have extracted DNA from breast cancer samples rather than peripheral blood. We hypothesized that CYP2D6 gene copy number alterations are common in ER+ breast cancer, affecting genotype results, and used NGS to characterize CYP2D6 in patients with ER+ disease. **Methods:** CYP2D6 sequencing was performed as part of a comprehensive NGS profile of cancer-related genes for 261 predominantly relapsed and metastatic ER+ breast cancer FFPE specimens. Sequence data were resolved into genotypes according to the * allele nomenclature. Tumor LOH was determined at CYP2D6, and its error impact on genotyping methods was estimated. To assess biological significance, the prevalence of CYP2D6 alleles and LOH in ER+ disease was compared against a control set of 99 ER- tumors. **Results:** CYP2D6 allele frequencies in our full cohort (ER+, 261; ER-, 99) were consistent with prior studies; 64.4%, 16.8%, 9.0% vs. 63.1%, 17.2%, 7.0% for *1/*2, *4, and *41 respectively, and 1%-2% for the rarer alleles *9, *10, and *5. The rate of CYP2D6 LOH was higher in ER+ disease (41% vs. 26%, $p<0.01$), with all excess arising from copy-loss (as opposed to copy-neutral) changes (22% vs. 7%, $p<0.002$). The estimated impact of LOH on germline genotype assessment from tumor was considerable; an assay sensitive at >20% minor allele frequency (e.g., Sanger sequencing) can misclassify >10% of heterozygotes, leading to significant Hardy-Weinberg disequilibrium (e.g., $p=8.3x10^{-8}$ for *4). Interestingly, an enrichment of reduced or non-functional CYP2D6 alleles in ER+ samples was observed (61% vs. 47%, $p<0.03$). **Conclusions:** Our results demonstrate the distorting effect of extensive LOH on genotype assessment of CYP2D6 in breast cancer. Therefore, tumor DNA should not be routinely used for determination of germline 2D6 genotype, although it appears possible to use NGS. The apparent association between reduced function CYP2D6 alleles and ER+ breast cancer in our dataset requires further investigation.

535 Poster Discussion Session (Board #23), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Integration of Ki67 with residual cancer burden (RCB) compared to Ki67 or RCB alone to predict long-term term outcome following neoadjuvant chemotherapy.

Amna Sheri, Roger A'Hern, Robin Lewis Jones, William Fraser Symmans, Ashutosh Nerurkar, Margaret Hills, Simone Detre, Stephen R. D. Johnston, Mitchell Dowsett; The Royal Marsden NHS Foundation Trust, London, United Kingdom; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, London, United Kingdom; Seattle Cancer Care Alliance, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom

Background: RCB and Ki67 after neoadjuvant chemotherapy have each been shown to predict long-term outcome. Their combined use might provide greater prognostic information. RCB requires collection of data beyond that in routine pathological work-up of residual disease, which may not be required when Ki67 is added. Aims: (i) To test the hypothesis that combining Ki67 and RCB as the residual proliferative cancer burden (R-P-CB) provides significantly more prognostic information than either alone. (ii) To determine if a simplified algorithm integrating Ki67 and standard characteristics of residual disease can provide as much information. **Methods:** Cases at the Royal Marsden Hospital between 2002-2010 were identified and residual disease assessed. The primary endpoint of the study was time to recurrence. The primary analysis compared the prognostic information from Ki67, RCB and R-P-CB. Analyses employed a Cox proportional hazards model. Prognostic indices (PIs) were also created adding Ki67, grade and ER to the RCB and AJCC staging. Leave-one-out cross validation was used to reduce bias. The overall change in chi-square ($\Delta X2$) of the best model for each index was used to compare the prognostic ability of the different indices a $\Delta X2$ of more than 3.84 indicates statistical significance. **Results:** A total of 222 evaluable patients were included in the study, median age was 50 with a median follow up of 60 months. The addition of Ki67 improved the prognostic power of all indices. The R-P-CB ($\Delta X2=69.5$) was significantly more prognostic than the RCB alone ($\Delta X2=35$) and Ki67 alone ($\Delta X2=41.4$). A novel proliferative residual cancer index (PRECI) using post-treatment values of T size, number of involved lymph nodes, grade, ER status ($\pm$) and Ki67 gave $\Delta X2=81.1$ and performed similarly to a model including the RCB, Ki67, ER and grade ($\Delta X2=80.2$). **Conclusions:** Addition of Ki67 to RCB improved prediction of long-term outcome. In this study, a novel index the PRECI provided as much prognostic information as a more complex assessment involving RCB and warrants further investigation for estimating post-neoadjuvant risk of recurrence.

536 Poster Discussion Session (Board #24), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Association of ERCC1 (rs11615) and DNASE2B (rs3738573) polymorphisms with pathologic complete response to neoadjuvant chemotherapy for HER2-overexpressing breast cancer.

Agnes Ducoulombier, Aurelie Dumont, Emmanuelle Tresch, Jinying Chen, Diane Pannier, Francoise Revillion, Jacques Bonneterre, Jean-Philippe Peyrat; Centre Oscar Lambret, Lille, France; Université Lille Nord de France, Lille, France

Background: Pathological complete response (pCR) is the main prognostic factor after preoperative chemotherapy. Predictive factors of pCR are mainly histological type, hormonal status, HER2 overexpression. Single nucleotide polymorphisms (SNP) in genes encoding drug transporters, drug metabolizing enzymes and target genes can affect drug efficacy and may explain therapeutic failures. The aim of the study was to identify SNPs associated with pCR in breast cancer (BC) patients (PTS) with HER-2 overexpression and treated with sequential neoadjuvant chemotherapy. **Methods:** Among PTS treated with NCT and included between 2007 and 2012, 46 PTS had HER-2 overexpressing BC, mostly ductal carcinoma (91.3%), greater than or equal to T2 (97.7%) and N1 (65.2%).91.3% of PTS received 3 FEC 100 - 3 Taxotere and 18 cycles of trastuzumab (3-18). Genotyping of 46 SNPs was performed on germline DNA using real time PCR. pCR was correlated with clinicopathologic features and genotypes using logistic regression. **Results:** pCR was evaluable for 45 PTS according to Sataloff criteria: pCR rate was 40% (95% CI 25.7-55.7%) and was significantly associated with hormonal status: 60.9% in negative hormone receptor tumors and 18.2% in positive hormone receptor tumors ($p = 0.004$). Four SNPs were significantly associated with pCR. All patients homozygotes CC for *ERCC1-rs11615* respond to NCT ($p=0.024$). The response rate was higher for patients homozygotes TT for *NQO2-rs1143684* (59.1%; $p=0.018$), PTS carrying one or two C allele for *DNASE2B-rs3738573* (50%; $p=0.025$) and PTS carrying one or two C allele for *MDR1-rs1045642*(51.5%; $p=0.012$). **Conclusions:** In this pilot study 4 SNPs were significantly associated with pCR and may be useful to predict response to NCT (Anthracyclines/Taxanes/Trastuzumab regimen) for HER-2 overexpressing breast tumors. Moreover, *DNASE2B-rs3738573* and *ERCC1-rs11615*, two polymorphisms located in genes involved in DNA reparation, have never been described as predictive markers for BC neoadjuvant chemotherapy. (The first 3 authors contributed equally to this work.)

537 Poster Discussion Session (Board #25), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Freedom from progression (FFP) by adding paclitaxel (T) to doxorubicin (A) followed by CMF as adjuvant or primary systemic therapy: 10-yr results of a randomized phase III European Cooperative Trial in Operable Breast Cancer (ECTO).

Milvia Zambetti, José Baselga, Wolfgang Eiermann, Vicente Guillem, Vladimir Semiglazov, Ana Lluch, Dolores Sabadell, Alla Bozhok, Mikhail J. Byakhov, Belen Ojeda, Mauro Mansutti, Gabriella Mariani, Angela Moliterni, Hernan Cortes-Funes, Marian Colozza, Tadeusz Pienkowski, Domenico Magazzu, Pinuccia Valagussa, Gianni Bonadonna, Luca Gianni; San Raffaele Hospital, Milan, Italy; Memorial Sloan-Kettering Cancer Center, New York, NY; Interdisziplinäres Onkologisches Zentrum München, Munich, Germany; Instituto Valenciano de Oncología, Valencia, Spain; N. N. Petrov Research Institute of Oncology, St. Petersburg, Russia; Hospital Clínico Universitario de Valencia- INCLIVA Health Research Institute, University of Valencia, Valencia, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; N.N. Petrov Research Institute of Oncology, St. Petersburg, Russia; Central Clinical Hospital named N.A.Semashko, Moscow, Russia; Hospital de la Santa Creu i Sant Pau, Departement of Medical Oncology, Barcelona, Spain; Department of Oncology, University Hospital of Udine, Udine, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain; Azienda Ospedaliera, Perugia, Italy; Department of Oncology, Postgraduate Medical Center, Warsaw, Poland; Fondazione Michelangelo, Milan, Italy

Background: At the time the ECTO was designed in 1996, taxanes were only indicated for patients with metastatic breast cancer. However, paclitaxel and docetaxel were still to be tested in the adjuvant setting. In addition there was relatively scarce information on the comparative efficacy of neoadjuvant and adjuvant regimens. The ECTO trial was designed to evaluate the addition of paclitaxel to an anthracycline-based adjuvant regimen and to compare this combination with the same regimen given as primary systemic (neoadjuvant) therapy. **Methods:** A total of 1,355 women with operable breast cancer were randomized to one of three treatments: 1) surgery followed by adjuvant single agent doxorubicin (A) followed by CMF (arm A); 2) surgery followed by adjuvant paclitaxel plus doxorubicin (AT) followed by CMF (arm B); 3) AT followed by CMF followed by surgery (arm C). The two co-primary objectives were to assess the effects on freedom from progression (FFP) of: 1) the addition of paclitaxel to post-operative chemotherapy (arm B versus arm A); and 2) primary versus adjuvant chemotherapy (arm B versus arm C). **Results:** At 10 years, in the adjuvant setting FFP remained statistically significant in favor of AT followed by CMF (arm B, HR 0.77, P=0.045). Distant FFP was similarly improved but overall survival was not (HR 0.82, P=0.24). There was no significant difference in FFP when chemotherapy was given after surgery compared with the same regimen given before surgery (arm B vs arm C, HR 0.79, P=0.07). In the primary chemotherapy arm, patients who achieved a pathological complete remission (pCR) had improved distant FFP ($P < 0.001$) compared to patients who did not achieve pCR. When given as primary systemic therapy, the paclitaxel-containing regimen allowed breast-sparing surgery in a significant percentage of patients, which did not translate in an increased risk of ipsilateral breast recurrence compared to the risk observed in patients in the adjuvant arms. **Conclusions:** Incorporating paclitaxel into anthracycline-based adjuvant therapy resulted in a significantly improved FFP and DFFP.

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

Expression of enhancer of zeste homologue 2, correlated with HIF-1α, to refine relapse risk and predict poor outcome for breast cancer.

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Background: Overexpression of enhancer of zeste homologue 2 (EZH2), a key component of polycomb proteins, has been linked to aggressive tumor behavior for breast cancer. In vitro, hypoxia-inducible factor 1 alpha (HIF-1α) transcriptionally activates EZH2 and promotes breast tumor initiating cells progression. Here, we characterized the clinicopathological effect of HIF-1α and EZH2 in breast cancer patients. **Methods:** Tumor specimens from 410 luminal subtype breast cancer patients were used to construct tissue microarray. EZH2 and HIF-1α level were examined by immunohistochemistry staining and Western blot analysis. With the 5-year follow up, the prognostic effect of EZH2 was subjected to multivariate analysis. **Results:** EZH2 and HIF-1α were highly expressed in 99 (24.1%) and 272 (70.6%) patients, respectively. EZH2 overexpression was associated with high histological grade ($P=0.030$), lymphatic invasion ($P=0.025$), HER2 overexpression ($P=0.005$) and hypoxic condition ($P<0.001$). Forced expression of EZH2 predicted a poor 5-year overall survival (OS, 74.8% vs. 93.4%, $P=0.001$), disease-free survival (DFS, 72.2% vs. 88.6%, $P=0.031$), local failure-free survival (LFFS, 95.7% vs. 97.9%, $P=0.045$) and distant metastasis-free survival (DMFS, 75.4% vs. 90.5%, $P=0.039$). However, the prognostic effect of HIF-1α was not detected for breast cancer. Cox multivariate analysis confirmed that EZH2 was an independent prognostic factor for OS, DFS and LFFS. Moreover, a positive correlation was detected between EZH2 and HIF-1α ($r=0.299$, $P<0.001$). Importantly, tumors with HIF-1α and EZH2 co-overexpression were correlated with a worsened OS ($P=0.007$). **Conclusions:** EZH2 was an independent negative prognostic biomarker for luminal subtype breast cancer. Targeting HIF-1α transcriptionally regulated EZH2 pathway might be of benefit in the treatment of luminal subtype of breast cancer.

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

Extended adjuvant tamoxifen for early breast cancer: A meta-analysis.

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Background: Hormone receptor positive breast cancer is characterized by the potential for disease recurrence many years after initial diagnosis. Endocrine therapy has been shown to reduce the risk of such recurrence, but the optimal duration of endocrine therapy remains unclear. **Methods:** We conducted a systematic review and meta-analysis to quantify the relative and absolute benefits and harms of extended adjuvant tamoxifen (>5 years of therapy) compared with adjuvant tamoxifen (≤5 years of therapy). Odds ratios (ORs), 95% confidence intervals (CIs), absolute risks, and the number needed to treat (NNT) were computed for pre-specified events including disease recurrence, distant recurrence, all-cause death, endometrial carcinoma, cardiovascular death and treatment discontinuation. Subgroup analyses by timing of recurrence and baseline lymph node and menopause status were carried out. **Results:** Six trials comprising 25,326 patients were included. Extended adjuvant tamoxifen was associated with a non-significant reduction in the risk of recurrence (OR 0.89, 95% CI 0.77-1.04, p=0.14, NNT 74). Similar results were seen for distant recurrence (OR 0.88, 95% CI 0.75-1.04, p=0.14, NNT 70). There was no association between extended adjuvant tamoxifen and all-cause death (OR 1.06, 95% CI 0.86-1.31, p=0.58). There was no reduction in risk during extended adjuvant therapy (i.e. between years 5 and 9), but a potential reduction in the risk of recurrence after completion of extended adjuvant tamoxifen (i.e. beyond 10 years after diagnosis). Subgroup analysis suggested benefit in lymph node positive patients. Endometrial carcinoma was substantially more frequent with extended adjuvant tamoxifen (OR 1.81, 95% CI 1.45-2.25, p<0.001, NNT 102), but among those with endometrial carcinoma, the odds of death were lower among the extended tamoxifen group (OR 0.50, 95% CI 0.28-0.90, p=0.02). **Conclusions:** Extended adjuvant tamoxifen is not associated with a significant reduction in recurrence or death in unselected patients. Patients with lymph node positive breast cancer may derive more benefit. Reduction in the risk of recurrence only appears after completion of extended adjuvant therapy.

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

Pro-COL11A1: A biomarker to predict malignant relapse of breast intraductal papillomas.

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Background: Breast cancer is currently the most frequent tumor among women. Despite the huge progress achieved in its early diagnosis, there are still many unsolved clinical issues, being the diagnosis, prognosis and treatment of papillary diseases (and specifically intraductal papilloma), one of the highest challenges. Because of its unpredictable clinical behavior, treatment of intraductal papilloma has generated a great controversy. Even though considered as a benign lesion, it presents high rate of malignant recurrence. This is the reason why there are clinicians supporting a complete excision of the papillary lesion, while others support an only expectant follow up. Previous results of our group have suggested that pro-Collagen 11 alpha 1 (pro-COL11A1) expression in cancer associated fibroblasts (CAFs) correlates with an infiltrating phenotype in breast lesions. We have analyzed the correlation between the differential expression of pro-COL11A1 in intraductal papilloma and their risk of malignant recurrence. **Methods:** Immunohistochemistry of pro-COL11A1 (clone 1E8.33, ONCOMATRIX, Bilbao, SPAIN) was performed in formalin fixed, paraffin embedded Core Needle Biopsy samples of 51 patients with intraductal papilloma. All patients had a minimum follow-up of 5 years. **Results:** Twenty-three out of 51 cases showed positive staining for COL11A1. Nine patients out of the positive cases relapsed as infiltrating carcinoma, two as intraductal papilloma and the rest had not recurred after five years of follow up. Only one case out of the 28 negative cases relapsed as invasive carcinoma. There were significant differences ($p=0.0013$) when comparing staining of individuals with malignant recurrence versus non recurrence and benign relapse patients, with a sensitivity of 90% and specificity of 66%. **Conclusions:** These data suggest that COL11A1 expression in CAFs is a highly sensitive biomarker to predict malignant relapse of intraductal papilloma. The low specificity might be biased by the complete excision of this lesion as the routine treatment or by a short follow-up of the patients.

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

A phase II study of combined fulvestrant and everolimus in metastatic estrogen receptor (ER)+ breast cancer after aromatase inhibitor (AI) failure.

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Background: Fulvestrant, an ER downregulator, can be effective in metastatic ER+ breast cancer but resistance is a problem. Everolimus inhibits mTOR; a key pathway in endocrine resistance. We hypothesized that everolimus may delay resistance to fulvestrant and thus improve its efficacy. **Methods**: We enrolled postmenopausal women with ER+ breast cancer who experienced disease relapse or progression within 6 months of AI use and had measurable/evaluable disease. Fulvestrant was given at 500 mg IM on day1, 250 mg d14, d28, and monthly thereafter. Everolimus was given at 10 mg po daily. Primary endpoint was time to progression (TTP) and secondary endpoints included safety, response, and biomarker analysis. A sample size of 40 patients was calculated to meet a median TTP of 7 vs. 3.7 months for fulvestrant alone as reported in the EFECT trial. Tumor blocks were collected and biopsies done for accessible disease. **Results**: 33 patients were enrolled. 2 were ineligible and are excluded from analysis. Median age was 54 years (range 40-85). Most common disease sites were bone 84%, liver 62%, and lung 55%. 81% of patients received prior tamoxifen, 71% had prior chemotherapy and 23% had multiple AIs. Median TTP is currently 7.4 months with 4 patients remaining on therapy. Responses include complete response 3%, partial response 10%, and stable disease 42%. 32% of patients had primary refractory disease and 13% discontinued therapy before disease assessment. Most common adverse events were elevated AST 81% or ALT 68%, hyperglycemia 61%, anemia 61%, elevated cholesterol 60%, hypokalemia 52%, mucositis 48%, and weight loss 48%. The majority of adverse events were grade I/II. Fasting lipid profile data is summarized. **Conclusions**: These results suggest that adding everolimus to fulvestrant improves its efficacy in heavily pretreated ER+ metastatic breast cancer. Toxicity was manageable but needs close monitoring. Biomarker analysis is ongoing in order to identify patients not likely to benefit from this treatment strategy. Clinical trial information: NCT00570921.

	Baseline median	2 months median	Wilcoxon signed rank test
Total cholesterol	178.5	241.5	P<0.0001
LDL	112	149	P<0.0001
HDL	39	43	P= 0.007
Triglycerides	127	226.5	P= 0.0007

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

Predictors of patient-reported toxicities from endocrine therapy: Importance of illness perceptions, treatment beliefs, and fear of recurrence.

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Background: Numerous studies have documented the toxicities of endocrine therapy (ET) for early breast cancer (EBC) and their deleterious impact on quality of life and adherence. However, little is known about the factors that underlie patient's susceptibility to report toxicities. The identification of risk factors for toxicities from ET is important as it would allow early targeting of symptom management interventions for women more vulnerable to adverse effects of ET. This prospective study aims to examine the impact of pre-treatment perceptions of EBC, ET beliefs and fear of breast cancer (BC) recurrence (FBCR) on toxicities reported after 6 months of ET. **Methods:** Women diagnosed with EBC completed a survey prior to initiating endocrine therapy, then at 3, 6 and 12 months. Standardized self-report instruments were used to assess EBC perceptions, ET beliefs, FBCR and toxicities. Clinical and treatment variables were also evaluated. Univariate analyses and mulitivariate regression were conducted to identify factors associated ($p<0.1$) with side effects at 6 months. **Results:** Since 9/2010, 173 patients have consented and 84 (mean age = 60 y) have completed the questionnaires at baseline and after 6 months of ET. Controlling for age, none of the clinical or treatment variables (stage of disease, type of surgery, receipt of chemotherapy and radiation therapy) were significant univariate predictors of toxicities. In multiple regression, stronger perceptions that BC has serious consequences on their lives ($\beta=0.218$, $p<0.05$), greater concerns about the adverse effects of ET ($\beta=0.215$, $p<0.05$) and higher levels of FBCR ($\beta=0.316$, $p<0.01$) at baseline were associated with higher levels of reported toxicities. **Conclusions:** Baseline psychological factors predicted level of patient-reported toxicities to a larger extent than clinical/treatment factors. How patients perceived their illness, their beliefs about ET side effects and their fear of cancer recurrence are strongly associated with side effects experienced after 6 months of ET. These results could facilitate the identification of a subgroup of patients for early interventions to improve symptom management.

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

Factors predicting endoxifen levels in breast cancer patients taking standard-dose tamoxifen and following dose escalation.

Peter Fox, Bo Gao, Bavanthi Balakrishnar, Alexander M Menzies, Shang Heng Yeap, Sayed Sahanawaz Ali, Val Gebski, Pamela Provan, Sally Coulter, Christopher Liddle, Rina Hui, Richard Kefford, Jodi Lynch, Nicholas Wilcken, Rosemary L Balleine, Howard Gurney; Westmead Hospital, Sydney, Australia; Westmead Hospital, University of Sydney, Sydney, Australia; Melanoma Institute Australia, Westmead Hospital, University of Sydney, Sydney, Australia; Johns Hopkins Singapore International Medical Centre, Tan Tock Seng, Singapore; The Canberra Hospital, Canberra, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; University of Sydney, Westmead Hospital, Sydney, Australia; Westmead Millennium Institute, Sydney, Australia; Storr Liver Unit, Westmead Millennium Institute, University of Sydney, Westmead Hospital, Sydney, Australia; Westmead Hospital and Melanoma Institute Australia, Westmead, Australia; St George Hospital, Sydney, Australia; Sydney West Cancer Network, Westmead Millennium Institute, Sydney Medical School-Westmead, Sydney, Australia

Background: Tamoxifen (TAM) is transformed via CYP2D6 to its major active metabolite endoxifen (Endox). Recent data suggest that 15nM Endox may be a therapeutic threshold for breast cancer. This study identified predictors of achieving specified Endox target levels (15nM and 30nM) on standard dose TAM, and following dose escalation. **Methods:** Baseline Endox was measured in 122 breast cancer pts on TAM 20mg pd. Pts with baseline Endox <30nM underwent incremental dose escalation to a maximum of 60mg pd until Endox reached 30nM or dose limiting toxicity. Clinical data were collected and *CYP2D6* genotype was used to specify extensive, intermediate or poor metabolizer categories (EM, IM, PM). Multiple regression analyses examined associations between Endox and potential predictive factors. **Results:** Baseline Endox ranged from 3.1-72.2nM (mean 27.6nM). In 19% (n=23), baseline Endox was below 15nM and 62% (n=76) were below 30nM. Low baseline Endox was associated with CYP2D6 genotype (IM or PM, $p<0.001$) and younger age ($p=0.02$). Following dose escalation, 96% (n=117) attained an Endox level of 15nM and 76% (n=93) reached 30nM. Baseline Endox level was the only variable independently associated with achieving both targets ($p=0.02$, $p<0.001$ respectively). *CYP2D6* genotype did not independently predict attainment of Endox targets following dose escalation ($p>0.4$). The ratio of Endox to its precursor N-desmethylTAM, an indicator of CYP2D6 activity, was stable with dose escalation, suggesting that CYP2D6 was not saturated. **Conclusions:** Although IM/PM predict for low Endox on 20mg TAM, only low baseline Endox predicted failure to achieve both 15nM and 30nM targets following dose escalation. These results suggest a role for Endox level monitoring to determine optimal TAM dose. Clinical trial information: NCT01075802.

15 or 30nM Endox targets according to baseline Endox and CYP2D6 phenotype.

			Dose escalation		
Baseline Endox (nM)	n	Mean baseline Endox (nM)	Mean maximum Endox (nM)	% reached 15nM target	% reached 30nM target
All patients	122	27.6	37.4	95.9	76.2
0-10	12	6.6	16.8	66.7	0
10-15	11	12.6	31.9	100	54.5
15-20	21	18.0	39.0	-	94
20-30	32	24.3	37.2	-	81.3
>30	46	43.3	-	-	-
CYP2D6					
PM	17	12.3	22.9	76.5	23.5
IM	37	23.2	36.7	100	78.4
EM	68	33.8	41.5	98.5	88.2

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

Single nucleotide polymorphisms to predict for neoadjuvant chemotherapy in breast cancer according to estrogen receptor (ER) status.

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Background: Neoadjuvant chemotherapy (NCT) using anthracyclines and taxanes is a standard treatment for locally advanced breast cancer and pathologic complete response (pCR) is a major prognostic factor for survival. Gene polymorphisms have been identified as modulators of chemotherapy response. Our study investigated constitutional variants of genes associated with a change in the response to neoadjuvant chemotherapy using taxanes and/or anthracyclines in patients with breast adenocarcinoma. **Methods:** From November 2007 to January 2012, 118 women with breast adenocarcinoma histologically proven, with no Her2 surexpression, receiving or having received a neoadjuvant chemotherapy with taxanes and/or anthracyclines were included in the study. NCT associated 3 FEC100 then 3 Docetaxel every 21 days. Genotyping of 46 SNPs was performed on germline DNA using real time PCR. pCR was correlated to clinical characteristics and genotypes using univariate logistic regression. **Results:** 21.2% had a pCR according to Sataloff classification. pCR is increased in SBRIII ($p=0.009$), estrogen receptor negative ($p=0.005$) and triple negative ($p=0.006$) tumors. 7 SNP are significantly associated with pCR in ER+ breast tumors (pCR=13.5%). Among these SNP, pCR is increased for patients carrying almost one G allele for *SLCO1B3-rs11045585* (pCR=28.6%; $p=0.032$), for homozygotes GG for *SHTM1-rs1979277* (pCR=24.3%, $p=0.006$) and for homozygotes CC for *CYP1B1-rs1056836* (pCR=25.7%; $p=0.003$). Moreover, 4 SNPs are significantly associated with pCR in ER- breast tumors: *ERCC1-rs11615* (carriers of almost one C allele: pCR=50%; $p=0.030$), CD24-rs52812045 (Homozygotes CC pCR=56.3%, $p=0.033$), *CYP2B6-rs2279343*(carriers of one or two G allele: pCR=52.6%; $p=0.046$) and *GSTP1-rs1695* (carriers of one or two G allele: pCR=48%; $p=0.050$). **Conclusions:** Besides ER status, polymorphisms could be useful markers to predict response to anthracyclines/taxanes NCT in breast cancer. Furthermore, this work is the first describing *ERCC1-rs11615, SLCO1B3-rs11045585* and *SHTM1-rs1979277* as new potential genetic markers for NCT in breast cancer. (The first 3 authors contributed equally to this work.)

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

Clinical significance of ERβ mRNA expression in ERα-negative and triple-negative breast cancers.

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Background: Previously at the 2012 ASCO meeting, we reported significant ERβ mRNA expression in ERα-negative (ERα-) and triple negative breast cancers (TNBC). In this study, we analyzed its clinical outcome and correlation with other clinical parameters. **Methods:** A total of 141 cases consisted of 69 ERα-BC including 41 TNBC and 72 ERα+ BC were obtained from patients aged 29 to 97 years old between 2003 and 2010. Treatments included surgery, hormone, chemo- or radiotherapy, or any combinations. The follow-up period ranged from 1 to 132 months. ERβ mRNA was analyzed from formalin-fixed tumor tissues by RT-PCR. ERα, PR, Her-2, Ki-67, AIB-1, NFk/p65, p-c-jun, Ki-67, TIF-2, SRC-1, CK5/6 and p53 were tested by immunohistochemistry. The correlation was deemed significant if p value less than 0.05 from Chi-square. Overall survival (SVR) was defined from the date of diagnosis to last follow-up or death attributed to BC and was analyzed by the Kaplan-Meier curves and Wilcoxon rank sum. **Results:** Single or combination of ERβ isoform(s) was highly expressed in both ERα- and TNBC and ERβ2 was the most frequent (48.8%) and ERβ5, the least (30.2%). In contrast, ERβ5 was the most frequent in ERα+BC. Presence of all or any ERβ isoform was associated with significantly higher SVR in all cases, and in TNBC (ERβ total, Wilcoxon $p = 0.0177$, ERβ2, $p= 0.0329$), and also with negative LN ($p< 0.0001$). ERβ2 and ERβ5 were expressed in 63.2% and 30 %, respectively, in 20 patients died in 1 to 60 months. Over expression of AIB-1, NF-kB/p65 and TIF-2 was associated with ERβ1 and ERβ2 ($p<0.05$). Ki-67 + cells were mostly ERβ + BC than ERα+. ERα mRNA expression was up-regulated, and ERβ,down- regulated, with the ERα: ERβ+ ratio of 3-1000:1. There was no association between ERβ expression and the stage, age, tumor size, and postmenopausal status. **Conclusions:** Specific ERβ isoform appears to be a significant discriminating factor for SVR and negative node. ERβ2 is the predominant isoform in ERα- but ERβ5 in ERα+BC, suggesting a distinct role of ERβ isoform in ERα- and ERα+BC. ERβ isoform may be a selective therapeutic target in this cohort. ERβ+/ Ki-67+cells appear to be a sub-population of BC arising from basal-myoepithelial cells in this cohort.

546 General Poster Session (Board #2A), Sat, 1:15 PM-5:00 PM

A new 5-gene signature predictive of risk of relapse in early breast cancer.

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Background: The aim of this study was look for the ″core-genes″ of published Signatures in order to find a simpler one **Methods:** To select candidate genes we used data of NCBI Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/) including 408 breast cancer cases. Raw intensity data of Affymetrix HU133A and HU133B arrays of the two datasets (GSE1456 and GSE3494) were preprocessed using R/Bioconductor and the supercomputer Michelangelo (www.litbio.org). The candidate genes were selected from the "70-gene signature" (van 't Veer, Nature 2002), the "21-gene recurrence score" (Paik, NEJM 2004), the "two-gene–ratio model" (Ma, Cancer Cell 2004) and the "15-gene Insuline Resistence" signature (Gennari , JCO, Vol 25, No 18S, 2007: 10597), for a total of 98 genes.The 20 mRNA more significantly related to DFS were evaluated by quantitative reverse transcriptase PCR on 261 consecutive breast cancer cases, from paraffin embedded sections, split into a training (n 137) and a validation set (n 124). **Results:** The signature was developed on the training set and a multivariate stepwise Cox analysis selected 5 genes independently associated with DFS: *FGF18* (HR=1.13, p=0.05) , *BCL2* (HR=0.57, p=0.001), *PRC1* (HR=1.51, p=0.001), *MMP9* (HR=1.11, p=0.08), *SERF1a* (HR=0.83, p=0.007). These 5 genes were combined into a linear score weighted according to the coefficients of the Cox model, (0.125 *FGF18* - 0.560 *BCL2* + 0.409 *PRC1* + 0.104 *MMP9* - 0.188 *SERF1A).* The linear score was highly associated with DFS (HR=2.7, 95%CI=1.9-4.0, p<0.001). The signature was then evaluated on the validation set assessing the discrimination ability by a Kaplan Meier analysis, using the same cut offs classifying patients at low, medium or high risk of relapse as defined on the training set. The score resulted highly associated with DFS also in the validation set (p<0.001). **Conclusions:** Overexpression of BCL2 and SERF1A are related to a higher probability of relapse; overexpression of FGF18, PRC1 and MMP9 to a higher probability of survival without recurrence. The signature has a good discriminating ability and a further clinical validation is planned.

547 **General Poster Session (Board #2B), Sat, 1:15 PM-5:00 PM**

Final results of a phase II trial of trabectedin (T) in patients with hormone receptor-positive, HER2-negative advanced breast cancer, according to xeroderma pigmentosum gene (XPG) expression.

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Background: Hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (BC) is currently associated with 3-4 years survival and, after ≥2 relapses, therapeutic approaches are reduced. XPG expression is frequently modified in BC. T forms cytotoxic complexes with XPG inducing apoptosis, thus, the inhibitory effects of T may depend on XPG presence. In fact, a better response to T in BC pts with XPG RNA overexpression has been observed. **Methods:** Pts withHR positive, HER2 negative advanced BC, pretreated with anthracyclines and/or taxanes, who had progressed after 2-5 chemotherapy lines, were stratified according to their XPG expression from paraffin embedded tumor samples, to stratum A (XPG high [>3]) or to stratum B (XPG low [≤3]) (threshold was selected from median XPG expression values observed in a previous trial) and treated with T (1.3 mg/m^2 in 3-hour iv infusion every 3 weeks). Primary endpoint: to evaluate the efficacy of T as progression free survival rate at 4 months (PFS4) according to XPG expression. Secondary endpoints: Comparison of PFS, overall response rate, duration of response, overall survival and safety in XPG high and XPG low pts. Statistical methods: A 2-stage design was chosen: at a 1st stage, 20 pts were enrolled in each stratum. A futility analysis (O'Brien Fleming boundary) based on the primary endpoint was done once 40 evaluable pts were recruited. If ≥ 7 out of 20 pts achieved PFS4, recruitment would continue to a maximum of 50 pts per stratum. **Results:** 44 pts (21 XPG high and 23 XPG low) were enrolled from three countries and five centers. Efficacy is shown in the Table. Most frequent AEs were nausea (54%) and fatigue (70%). ALT increase G4 occurred in 7% of pts and neutropenia G4 in 28%. **Conclusions:** Trabectedin showed modest activity in advanced HR-positive, HER2-negative BC previously treated with anthracyclines and taxanes, with an acceptable safety profile. XPG does not seem to be a predictor of outcome to T treatment in this patient population. Clinical trial information: 2010-022968-13.

	XPG high N=21		XPG low N=23		Total N= 44	
	N	%	N	%	N	%
PFS4	4	19	6	26	10	23
PR	1	5	2	9	3	7
SD >3 mos.	7	33	6	26	13	30
Median PFS/95% CI	1.9	(1.6-3.5)	1.9	(1.7-3.8)	1.9	(1.8-3.5)

548 General Poster Session (Board #2C), Sat, 1:15 PM-5:00 PM

Phase II randomized, open-label study of YM155 (sepantronium bromide) plus docetaxel versus docetaxel alone as first-line treatment for HER2 negative metastatic breast cancer.

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Background: YM155 (YM) is a small molecule survivin suppressant. In a phase I/II study of YM plus docetaxel (D) in solid tumors evidence of anti-tumor activity was observed in women with human epidermal growth factor 2 non-overexpressing (HER2 negative) metastatic breast cancer (mBC). **Methods:** This was a randomized study of YM plus D versus D as 1st line treatment in subjects with HER2 negative mBC. Eligibility criteria were: ECOG < 1, no prior chemotherapy for mBC, and at least one measurable lesion. Primary endpoint was progression free survival (PFS); secondary endpoints were: objective response rate (ORR), overall survival (OS), duration of response (DOR), clinical benefit rate (CBR), time to response (TTR) and safety. YM was administered at 5 mg/m^2/day as a 168 hr continuous infusion followed by 14 Day (d) observation and D was administered at 75 mg/m^{2}over 1 hr on d1 every 21d. In the control arm, D was dosed per investigator choice q 21d. **Results:** 101 subjects were randomized (50 YM + D; 51 D). Median (m) age 55 (range: 25 – 79), 25% had triple negative disease, $> 60\%$ had bone and lymph mets, 86% had prior therapy for BC. mPFS (days) was 251 (95%CI: 176 – 333) YM + D vs 252 (95%CI: 202-433) D ($p=0.34$). ORR, CBR and TTR (YM+D; D): 26% vs. 25.5%; 82% vs. 84.3% and 45 vs 59 d. OS data are immature but showed no difference ($p=0.911$). Adverse events [AEs ($> 25\%$)] [YM + D% vs D %]: neutropenia 83 vs 84, alopecia 62.5 vs 53, fatigue 50 vs 41.2, nausea 35.4 vs 41.2, leucopenia 27 vs 33 and dyspnoea 33 vs 14. Common ($>10\%$) serious AEs [YM + D% vs D%]: febrile neutropenia 21 vs 8 and neutropenia 10 vs 8. **Conclusions:** Preclinical and clinical evidence suggested the combination of YM + D may offer additional benefit to D alone in subjects with mBC. This study showed no difference in efficacy, but the combination appeared to be well tolerated. Clinical trial information: NCT01038804.

549 General Poster Session (Board #2D), Sat, 1:15 PM-5:00 PM

Luminal A and Luminal B subtypes in patients with breast cancer 65 years of age and older.

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Background: In 2011, the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer (bc) suggested the distinction between Luminal A and Luminal B subtypes. In Luminal A patients (pts) endocrine therapy seems to be sufficiently effective, whereas in Luminal B pts the additional application of chemotherapy should be considered. It is currently unknown, whether the risk stratification into Luminal A and B is comparably or more discriminatory than the established pathologic tumor size (pT) and lymph node (pN) status in pts $\geq$ 65 years. This analysis evaluates the discriminatory capacity of the new distinction between Luminal A and B and the established prognostic factors in bc pts $\geq$ 65 years treated with endocrine therapy only. **Methods:** Clinico-pathological data of 190 bc pts $\geq$ 65 years diagnosed between 1998 and 2004 were retrospectively analyzed. Pts were classified as Luminal A [ER (+) and/ or PR (+) and Her/2neu (-) and Ki-67 $<$ 14%] or Luminal B [ER (+) and/ or PR (+) and Her2 (-) and Ki-67 $\geq$ 14%]. The Kaplan-Meier method was used to assess the progression-free survival (PFS) and overall survival (OS) estimates. Differences in survival between groups were tested for significance by the log-rank test. **Results:** Median age was 74 years (65–92 years) and median time of follow-up was 69 months (0–134 months). 68.9% and 31.1% pts had Luminal A and B subtypes, respectively. 73.3% and 26.7% of pts had pT1 and pT2 tumors, respectively. 79.7% and 20.3% of pts had pN0 and pN1 status, respectively. Overall, median PFS was 33 months. No significant difference regarding PFS could be detected between Luminal A and B pts, between pT1 and pT2 tumors and between pN0 and pN1 status (p=0.458; 0.172; 0.156), respectively. Overall, median OS was not reached. No significant difference regarding OS could be detected between Luminal A and B pts, between pT1 and pT2 tumors and between pN0 and pN1 status (p=0.328; 0.951; 0.976), respectively. **Conclusions:** In bc pts $\geq$ 65 years treated with endocrine therapy only, neither the recently consented dichotomization into Luminal A and B subtypes nor pathologic tumor size and lymph node status could be confirmed to be discriminative as propagated in the 2011 St. Gallen Consensus for the overall bc population.

550 General Poster Session (Board #2E), Sat, 1:15 PM-5:00 PM

Post-surgical highly sensitive C-reactive protein (hsCRP) and prognosis in early stage in breast cancer (BC).

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Background: Obesity, commonly associated with inflammation, is associated with poor prognosis in BC. Previous research suggests CRP, an obesity-associated marker of systemic inflammation, may mediate the adverse prognostic effects of obesity and be associated with fatigue. We examined the association of hsCRP with obesity-related factors, fatigue and distant disease-free and overall survival (DDFS, OS) in an early BC cohort. **Methods:** 501 non-diabetic women with T1-3, N0-1, M0 BC diagnosed 1989-96 provided fasting blood (mean 7.7 ± 4.3 weeks after surgery, prior to systemic therapy, stored at -80°C) which was analyzed for hsCRP (Roche Elecsys immunochemistry). 359 women also completed the EORTC QLQ-C30 (mean 8 ± 3.9 weeks post-surgery). Women were followed prospectively to 2007. Data were analyzed using Spearman's rank correlation coefficients (r) and Cox models. **Results:** Mean age was 50.5 ± 9.7 years; 282/159/24/36 subjects had T1/T2/T3/TX cancers; 350 were N0; 306 had ER+ and 278 PgR+ cancers (HER2 was not performed); 76/208/142 cancers were grade 1/2/3; adjuvant treatment involved radiation (369 subjects), chemotherapy (196), tamoxifen (107). Median hsCRP was 0.9 mg/L ($25^{th}/75^{th}$ percentiles: 0.4/2.4 mg/L). hsCRP was correlated (all $p < 0.0001$) with age ($r = 0.25$), Body Mass Index (BMI, $r = 0.6$), insulin ($r = 0.44$), Homeostasis Model Assessment ($r = 0.45$) and leptin ($r = 0.54$), but not with EORTC fatigue ($r = 0.02$), T or N stage, grade or ER/PgR status (any + vs. both -). Median follow-up was 12 years. hsCRP was not associated with DDFS or OS in univariate analyses (Q4 vs. Q1 HR 1.03, 95% CI 0.69-1.52, $p = 0.9$ and HR 1.27, 95% CI 0.86-1.86, $p = 0.24$ respectively) or multivariate analyses adjusting for age, T, N, grade, ER/PgR status, treatment (HR 1.02, 95% CI 0.66-1.59, $p = 0.93$ and HR 1.17, 95% CI 0.76-1.81, $p = 0.48$ respectively). **Conclusions:** hsCRP (measured post-op, prior to systemic therapy) was associated with age, BMI and obesity associated physiologic factors; it was not associated with fatigue, DDFS or OS. Funded by The Breast Cancer Research Foundation (New York), The Canadian Cancer Society Research Institute (formerly The Canadian Breast Cancer Research Initiative).

551 **General Poster Session (Board #2F), Sat, 1:15 PM-5:00 PM**

Ki-67 level in hormone reptor positive breast cancer patients: A retrospective review of 9,061 Korean women.

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Background: Although young age breast cancer represents poor prognosis, no definitive explanation could have been made for the phenomenon. A tumor proliferation marker Ki67 is known to be a marker for both prognosis and prediction for chemotherapy responsiveness, and its level varies widely depending on the breast cancer subtype. This study was aimed to analyze Ki67 in relationship with age in hormone receptor positive breast cancer patients. **Methods:** We retrospectively reviewed 9061 consecutive cases of hormone receptor positive invasive breast cancer from data base at Seoul National University Hospital (SNUH) (between 2000 and 2012), Samsung Medical Center (SMC) (between 2004 and 2010), and National Cancer Center (NCC) (between 2001 and 2010) in Korea. Patients with estrogen receptor (ER) or progesterone receptor (PR) positive tumors were included irrespective of HER2 amplification. A multicenter data of Ki67 level identified by immunohistochemistry (IHC) and age at diagnosis were analyzed. Patients who underwent neoadjuvant systemic therapy were excluded. **Results:** Total 6222 cases from SNUH, 976 from SMC and 1863 from NCC were included. The three datasets were analyzed separately due to variable IHC methods in each institute. Mean ages were 49.30 years (range 20-86), 47.75 years (range 22-81) and 45.31 years (range 25-59), and mean Ki67 levels were 4.66% (range 1-100), 22.98% (range 1-97) and 14.58% (range 1-90), at SNUH, SMC, NCC respectively. Ki67 level was inversely proportional with age at diagnosis in all three datasets, and the level was significantly higher for patients <40 years compared to ≥ 40 years (mean Ki67: 5.97 vs 4.41, $p<0.001$; 28.60 vs 21.88, $p<0.001$; 17.01 vs 14.03, $p<0.001$, respectively). There was an inverse relation with age as well when Ki67 level was categorized into '$<10\%$ vs $\geq 10\%$ ($p<0.001$)', '$<20\%$ vs $\geq 20\%$ ($p=0.03$)' and '$<14\%$ vs $\geq 14\%$ ($p<0.001$)' respectively. **Conclusions:** Despite the variability of assessing Ki67 expression, Ki67 level was significantly higher in young age hormone receptor positive breast cancer from all three analyses. This could partly explain the poor prognosis and substantial responsiveness to chemotherapy in this age group of patients.

552 General Poster Session (Board #2G), Sat, 1:15 PM-5:00 PM

Impact of body mass index (BMI) on the prognosis of women with high-risk early breast cancer (BC) receiving adjuvant chemotherapy (CT).

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Background: Obesity has been shown to impact the prognosis of early BC; this effect was not consistently observed across the different biological subtypes, and is less clear when aggressive tumor phenotypes are considered. The aim of this study was to evaluate the influence of BMI (kg/m2) on the prognosis of women with high risk early BC enrolled into a phase III clinical trial of adjuvant CT. **Methods:** The relationship between BMI and Disease Free (DFS) or Overall Survival (OS) was assessed in 1066 early BC patients with rapidly proliferating tumors (Thymidine Labeling Index $>$ 3% or G3 or Ki67 $>$ 20%), randomized to receive adjuvant CT with or without anthracyclines (Epirubicin $\rightarrow$ CMF vs CMF $\rightarrow$ Epirubicin vs CMF). BMI was defined as follows: normal $<$ 25 kg/m2, overweight 25-30 kg/m2, obese $>$30 kg/m2. DFS and OS were calculated by Kaplan-Meier estimation; multivariate Cox analysis was performed according to menopausal status, type of CT, hormonal, HER-2 and nodal status. **Results:** Information on BMI at baseline, was available on 959 women. Of these, 430/959 (44.8%) were normal, 331 (34.5%) were overweight and 198 (20.7%) were obese. Median age was 52 years (range 26 to 70); 48% was node positive, 62% was ER positive and 33% was HER-2 positive. At a median follow-up of 69 mos (range 1-119), 5-year DFS was 80% (95% CI 78-83) and 5-year OS was 94% (95% CI 90–94). 5-year DFS was 81% (95% CI 77-85), 82% (95% CI 77-86) and 76% (95% CI 70-83), in normal, overweight and obese women, respectively (p 0.6). 5-year OS was 92% (95% CI 89-95), 94% (95% CI 91-96) and 89% (95% CI 84-93), respectively (p 0.4). By multivariate analysis only ER, HER-2 and nodal status were significantly associated with differences in DFS and/or OS. **Conclusions:** BMI at baseline was not associated with the prognosis of early BC patients with rapidly proliferating tumors, receiving adjuvant CT. These results confirm those achieved in triple negative BC and suggest that neither dietary restriction or medical interventions aimed at reducing BMI and/or underlying insulin resistance nor specific anticancer strategies seem to be appropriate in this subgroup.

553 General Poster Session (Board #2H), Sat, 1:15 PM-5:00 PM

Patient-reported physical, emotional, and social functioning in advanced breast cancer: Insights from BOLERO-2.

Denise Aysel Yardley, Gabriel N. Hortobagyi, Fabienne Lebrun, J. Thaddeus Beck, Patrick Neven, José Baselga, Katarina Petrakova, Shaker R. Dakhil, Silvia Sabatini, Anna Komorowski, Edmond Emilien Chouinard, Robyn R. Young, Michael Gnant, Kathleen I. Pritchard, Jie Zhang, Ryan Ziemiecki, Ashok Panneerselvam, Tanya Taran, Tarek Sahmoud, Shinzaburo Noguchi; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; The University of Texas MD Anderson Cancer Center, Houston, TX; Institut Jules Bordet, Brussels, Belgium; Highlands Oncology Group, Fayetteville, AR; Hospital Gasthuisberg, Leuven, Belgium; Massachusetts General Hospital Cancer Center, Boston, MA; Masaryk Memorial Cancer Institute, Brno, Czech Republic; Cancer Center of Kansas, Wichita, KS; Santa Maria Hospital, Terni, Italy; Hematology Oncology Associates of Rockland, Nyack, NY; Cambridge Memorial Hospital, Cambridge, Ontario, ON, Canada; The Center for Cancer and Blood Disorders, Fort Worth, TX; Comprehensive Cancer Center, Department of Surgery, Medical University of Vienna, Vienna, Austria; Odette Cancer Centre, Sunnybrook Health Sciences Centre; University of Toronto, Toronto, ON, Canada; Novartis Pharmaceuticals Corp, Florham Park, NJ; RTI Health Solutions, Research Triangle Park, NC; Novartis Pharmaceuticals, Florham Park, NJ; Global Oncology Development, Novartis Pharmaceuticals Corporation, Florham Park, NJ; Osaka University, Osaka, Japan

Background: The phase 3 BOLERO-2 study at 18 months' median follow-up showed that everolimus (EVE) + exemestane (EXE) significantly improved progression-free survival (PFS) vs EXE alone in 724 hormone-receptor–positive (HR^+) advanced breast cancer (ABC) patients with recurrence/progression during/after nonsteroidal aromatase inhibitor (NSAI) therapy. A higher rate of grade 3/4 adverse events was noted with EVE + EXE, but was not associated with deterioration in quality of life (QOL) based on the EORTC QLQ-C30 Global Health Status scale. Additional patient-reported *post hoc* analyses of QOL are reported herein. **Methods:** During BOLERO-2, QOL (EORTC QLQ-C30 and QLQ-BR23) was assessed at baseline and q 6 wk thereafter until progression or discontinuation. Physical, emotional, and social functioning subscales of QLQ-C30 were analyzed. Time to definitive deterioration (TTD) was defined based on either a 5% (protocol specified) or 10-point (more stringent) decrease from baseline for each subscale and analyzed by Kaplan-Meier methods. The difference between treatments was assessed by a log-rank test stratified by randomization factors. **Results:** QLQ-C30 compliance was $> 80\%$ at week 48. Among the 3 protocol-specified QLQ-C30 subscales, analyses based on a 5% decrease in QOL showed a longer TTD for both physical and emotional functioning in the EVE + EXE group vs EXE alone (log-rank $P = .0120$ and $P = .0277$, respectively). The TTD for social functioning was similar in both treatment arms (log-rank $P = .3374$). Analyses based on a 10-point decrease indicated a longer TTD for physical functioning in the EVE + EXE group (15.2 mo) vs EXE alone (9.7 mo; log-rank $P = .0211$). The TTDs for emotional and social functioning were similar between EVE + EXE and EXE alone: 13.9 vs 13.8, respectively (log-rank $P = .4023$), and 11.5 vs 9.5, respectively (log-rank $P = .2507$). **Conclusions:** The treatment goal for ABC is to maximize clinical benefit with minimal negative effects on QOL. These additional BOLERO-2 QOL analyses confirmed that the more than doubling of PFS with EVE + EXE was accompanied by maintained physical, emotional, and social functioning compared with EXE alone in patients with HR^+ ABC progressing after NSAI. Clinical trial information: NCT00863655.

554 General Poster Session (Board #3A), Sat, 1:15 PM-5:00 PM

MDS/AML risk post-breast cancer and association with age: SEER data 2001-2009.

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Background: Increased acute myeloid leukemia (AML) incidence has been identified post chemotherapy and radiation treatment for primary breast cancer (BC). Risk has not been evaluated in large populations or included myelodysplastic syndrome (MDS). **Methods:** We used 2001-2009 Surveillance, Epidemiology and End Results (SEER) database records to identify a cohort of first primary stage I-III BC patients. We identified subsequent MDS/AML diagnoses in the BC cohort, using SEER to query appropriate ICD-O-3 codes. We compared observed MDS/AML rates in the BC cohort to expected rates, estimated for first primary MDS/AML in the entire population, and calculated observed/expected rate ratios with 95% confidence intervals (CI) with age adjustment. Due to SEER data limitations, disease stage was used as a proxy for likelihood of radiation and chemotherapy treatment. **Results:** BC case distribution by stage was 51% stage I, 39% stage II and 11% stage III. Age distribution was 26% 20-49, 38% 50-64 and 36% 65+ years. Out of 306,691 BC cases, 470 had a subsequent diagnosis of MDS or AML (.15%) with 19% among women age 20-49 years, 36% women age 50-64 and 45% among women age 65+ years. Age adjusted number of expected myeloid leukemia cases is 171. Follow up time to myeloid leukemia diagnosis was on average 2.92 years post BC diagnosis (range .25-8.75 years). Myeloid leukemia cases were 56% AML and 44% MDS. We found an overall increased risk of MDS/AML among all age (20-65+)/all stage (I-III) breast cancer cases compared to the general population (RR=2.75, 95% CI 2.51, 3.00). Risk increased with increasing BC stage: stage I (RR=1.87, 95% CI 1.61, 2.16), stage II (RR=3.57, 95% CI 3.12, 4.06), and stage III (RR=5.66, 95% CI 4.45, 7.07) and decreased with increasing age with the highest risk among women age 20-49 (RR=10.60, 95% CI 8.57, 12.92) (age 50-64 (RR=5.60, 95% CI 4.79, 6.49), age 65+ (RR=1.81, 95% CI 1.57, 2.06)). **Conclusions:** Patients with stage I-III breast cancer have a significant high risk of MDS/AML post BC diagnosis increasing with higher stage cancer, most likely the result of radiation and/or chemotherapy treatment. Younger age women, 20-49 years, appear to be the most susceptible to this outcome.

555 General Poster Session (Board #3B), Sat, 1:15 PM-5:00 PM

A prognostic factor (PF) index for overall survival in a HER2-negative endocrine-resistant metastatic breast cancer (MBC) population: Analysis from the ATHENA trial.

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Background: Chemotherapy is the standard of care for patients (pts) with HER2-negative endocrine-resistant MBC. The considerable variability in overall survival (OS) within this population relates essentially to prognostic factors (PF). Increasingly, large studies based on progression-free survival (PFS) as a primary endpoint are now being questioned. An accurate PF index may help in designing innovative trials with appropriate pts selection according to overall survival (OS) prognosis. **Methods:** The ATHENA trial assessed the safety of first-line bevacizumab combined with non-anthracycline-containing therapy in 2264 pts treated in 37 countries from 2006 to 2009. Pt characteristics, safety, and efficacy have been reported [Breast Cancer Res Treat 2011;130:133-43]. Sixty-one HER2-positive pts were excluded. A multivariate Cox regression model selected PF generating a simple PF index. Of note, skin, lymph node, ipsi-/contra- breast, or other soft tissue involvement was scored as a single organ. **Results:** After a median follow-up of 20.1 months and 1171 OS events (53% of pts), median OS for the entire sample and triple-negative (TNBC) and non-TNBC subgroups was 25.2 (95% CI 23.9–26.3), 18.3 (16.3–19.7) and 27.3 (26.3–29.3) months, respectively. PF most closely associated with poorer OS were: liver mets or >2 involved organs (HR 1.6; 95% CI 1.5–1.8); DFI ≤24 months (HR 1.7; 1.5–2.0); adjuvant anthracyline and/or taxane (HR 1.1; 1.2–1.4); and TNBC (HR 1.6; 1.4–1.8). A predictive model was designed stratifying by number of PF present (0/1 vs 2 vs 3/4). The model was consistent in both TNBC and non-TNBC populations (Table). **Conclusions:** A PF index may estimate figures and balance arms in future trials considering OS as primary objective. A well-defined group of non-TNBC accounting for 37% of patients has an OS estimate similar to the most aggressive TNBC.

PF	N (%)	Deaths, %	Median OS, mo	95% CI
Non-TNBC (N=1,618)				
0/1	1016 (62.8)	42.9	32.8	29.9–35.2
2	480 (29.8)	60.4	22.3	20.5–24.8
3	122 (7.5)	68.0	15.9	13.5–19.0
TNBC (N=585)				
1	102 (17.4)	37.3	34.1	21.1–39.2
2	179 (30.6)	51.4	24.8	19.6–30.0
3/4	304 (52.0)	76.3	13.7	11.7–15.8

556 General Poster Session (Board #3C), Sat, 1:15 PM-5:00 PM

Prognostic impact of estrogen receptor (ER) level changes during progression for patients with both ER-positive (ER+) primary breast cancer and paired recurrence.

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Background: We have previously reported that ER+ breast cancer (BC) patients (pts) who become ER-negative at relapse have a poorer overall survival (OS) as compared to those still ER+ at relapse [Dieci et al., Ann Oncol 2013]. Our aim is to evaluate whether, among the group of patients with an ER+ status on both primary and recurrence, changes in the level of ER expression may be of prognostic value. **Methods:** A total of 81 pts with ER+ primary BC and ER+ paired recurrence who underwent relapse biopsy at Modena University Hospital were studied. ER status was assessed by IHC and the cutoff for ER-positivity was >=10%. Samples were defined as ER-high (>50%) and ER-low (>=10% and <=50%). HER2-status was defined according to IHC and/or FISH results. OS was calculated as the time interval between primary BC diagnosis and death or last follow up. **Results:** Biopsied recurrences were: distant (86%) and local relapses (14%). Fifteen percent of primary and 21% of recurrent tumors were HER2-positive. Sixty-two pts maintained the same ER level (i.e. high or low) on both primary and relapse (ER-level concordant), whereas 19 changed from ER-high to ER-low or viceversa (ER-level discordant). No difference in OS was observed between the ER-level concordant and the ER-level discordant groups (p=0.3). However, we identified those pts whose ER-high primary BC turned into ER-low as having a particularly poor outcome. Indeed, 10yrs-OS rates were 51% for the ER-level concordant group, 50% for pts changing from ER-low to ER-high and 14% for pts changing from ER-high to ER-low (p=0.0019). Finally, we focused on the subset of pts starting from an ER-high primary BC and showing an ER+/HER2-negative phenotype on both primary and relapse (n=51). The drop of ER-level expression below the 50% cut-off at relapse was confirmed as a poor prognostic factor, as compared to pts maintaining an ER-high level (10yrs-OS 53% vs 17%, p=0.0063). **Conclusions:** We demonstrated that, even in the case of maintenance of the same single-receptor status (ER+) and/or tumor phenotype (ER+/HER2-negative) between primary BC and recurrence, relapse biopsy may provide relevant prognostic information.

557 General Poster Session (Board #3D), Sat, 1:15 PM-5:00 PM

Characterization of patients who received prior chemotherapy for advanced breast cancer (ABC) in BOLERO-2.

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Background: In patients with hormone-receptor–positive (HR^+) breast cancer, endocrine therapy is the standard of care both in the adjuvant setting and as first-line treatment for ABC. For selected HR^+ patients with ABC, chemotherapy (CT) may be utilized if disease burden is high and rapid symptom control is required (Barrios CH. *GAMO*.2010). In the phase 3 BOLERO-2 study (NCT00863655), 1 line of prior CT in the ABC setting was allowed. This subset analysis examined disease characteristics and the efficacy of everolimus (EVE) plus exemestane (EXE) in patients who received CT for ABC prior to BOLERO-2 study entry. **Methods:** In BOLERO-2, 724 patients with HR^+, human epidermal growth factor receptor-2–negative ($HER2^-$) ABC whose disease recurred or progressed during/after a nonsteroidal aromatase inhibitor were randomized 2:1 to EVE (10 mg/d) + EXE (25 mg/d) or placebo (PBO) + EXE. The primary endpoint was progression-free survival (PFS) by local investigator review and confirmed by blinded independent central review. **Results:** A subset of 186 patients (26%) received prior CT for ABC: 125 in the EVE + EXE group and 61 in PBO + EXE. In this subset, 54% (67 of 186) of patients received prior CT only in the advanced setting and 46% (58 of 186) of patients received prior CT in both the neoadjuvant/adjuvant and advanced settings. Incidences of visceral metastases (67% vs 56%), multiple metastases (79% vs 66%), and $\geq$ 4 metastatic sites (18.3% vs 15%) were higher in ABC patients with prior CT for ABC at study entry versus those with no prior CT for ABC. Disease recurrence $<$ 6 months from initial diagnosis was recorded in 32.2% (n = 60) of prior CT patients versus 17.3% (n = 93) of patients with no prior CT. Median PFS (by local assessment) in patients who received prior CT for ABC was substantially longer with EVE + EXE versus PBO + EXE (6.1 vs 2.7 mo; HR = 0.38; 95% CI, 0.27-0.53). PFS by central review showed similar results (7.1 vs 2.8 mo, respectively; HR = 0.42; 95% CI, 0.27-0.65). **Conclusions:** These results demonstrate that patients with HR^+, $HER2^-$ ABC who received previous CT in the advanced setting had a higher tumor burden and derived clinically significant benefit from combination treatment with EVE + EXE. Clinical trial information: NCT00863655.

558 General Poster Session (Board #3E), Sat, 1:15 PM-5:00 PM

Clinical management and resolution of stomatitis in BOLERO-2.

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Background: In BOLERO-2, adding everolimus (EVE) to exemestane (EXE) more than doubled progression-free survival without affecting quality of life vs EXE alone in postmenopausal women with hormone-receptor–positive advanced breast cancer who had recurrence or progression on/after nonsteroidal aromatase inhibitor therapy. Although mTOR inhibitors are generally well tolerated, stomatitis is one of their most clinically relevant and potentially dose-limiting toxicities (Sonis *Cancer*2010). The incidence, grade, and clinical course of stomatitis among patients (pts) participating in the BOLERO-2 study are described. **Methods:** Pts were randomized 2:1 to receive EVE+EXE or placebo (PBO)+EXE. Stomatitis incidence, severity, consequent dose interruptions/adjustments, study drug discontinuations, and time to resolution were recorded. **Results:** The median duration of EVE+EXE treatment exposure was 30 wk (range, 1-123 wk). Stomatitis (any grade) occurred more frequently with EVE+EXE than with PBO+EXE (59% vs 12%, respectively). Grade 3 stomatitis occurred in 8% vs 1% of pts receiving EVE+EXE vs PBO+EXE, respectively; no grade 4 was reported. Onset of grade ≥2 stomatitis after treatment initiation was earlier in the EVE+EXE arm vs the PBO+EXE arm: median time was 15d vs 24d, respectively. In the EVE+EXE arm, 97% of pts with grade 3 stomatitis (n=38) improved to ≤1 after a median of 13 d. Complete resolution was observed in 82% of these pts after a median of 38 d. In the PBO+EXE arm, all pts with grade 3 stomatitis (n=2) improved to ≤1 after a median of 18 d. Complete resolution was observed after a median of 29 d. Overall, 24% of pts in the EVE+EXE arm required dose interruptions/adjustments vs 1% of pts in the PBO+EXE arm, and 3% of pts (n=13) discontinued EVE+EXE vs <1% of pts (n=1) discontinuing PBO+EXE, all related to stomatitis. **Conclusions:** The BOLERO-2 data foster a new era of combining targeted and endocrine therapies. In the study, treatment-emergent stomatitis was of mild to moderate intensity, occurred shortly after treatment initiation, and was generally reversible. Most incidents were successfully managed with palliative interventions and temporary dose modifications. Oral hygiene and other preventive measures are recommended. Clinical trial information: NCT00863655.

559 General Poster Session (Board #3F), Sat, 1:15 PM-5:00 PM

Tissue sampling frequency and breast pathology diagnoses following mammography: Time trends and age group analysis from the Breast Cancer Surveillance Consortium (BCSC).

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Background: Pathology diagnoses in a well-characterized population of women can be used to identify tissue sampling and diagnosis trends following mammography. **Methods:** Screening and diagnostic mammography, patient characteristics, and pathology reports from the BCSC performed from 1996-2008 were identified. Diagnosis was based on the most severe pathology interpretation in the same breast within 60 days of a post-mammogram tissue sample. Age, mammogram year and type, breast density, and family history of breast cancer were evaluated for associations with tissue sampling and most severe pathology diagnosis. **Results:** 4,022,506 mammograms (88.5% screening; 11.5% diagnostic) were performed in 1,288,886 women; 76,567 (1.9%) were followed by tissue sampling (1.2% screening; 7.1% diagnostic). Tissue sampling frequency following diagnostic mammography increased over time in women over 50 but remained stable following screening mammography. The frequency of invasive cancer increased with age and was more common following a diagnostic (29.3%) vs screening (19.8%) mammogram; the frequency of high risk lesions (ADH; lobular neoplasia) was highest in women aged 50-59. For tissue sampling following screening mammograms, the frequency of DCIS increased over time while benign diagnoses decreased. No significant time trends were noted for diagnoses associated with diagnostic mammograms. Women aged 40-59 with dense breasts and a tissue sampling following screening mammogram had a significantly higher frequency of DCIS (40-49: 4.8% vs 3.2%, $P < 0.001$; 50-59: 7.0% vs 5.7%, $P = 0.007$). Women aged 40-59 with $>$ 1first degree relative with breast cancer vs none that had a tissue sampling following screening mammogram had a significantly higher frequency of invasive cancer (40-49: 11.4% vs 9.4%, $p = 0.008$; 50-59: 19.8% vs 18.2%, $p = 0.086$) and DCIS (40-49: 6.2% vs 4.0%, $p < 0.001$; 50-59: 8.2% vs 6.2%, $p < 0.001$). **Conclusions:** There was an increase in DCIS and a decrease in benign diagnoses in tissues samples after screening mammography over time. No trends were seen following diagnostic mammography. DCIS was also more frequent in women with dense breasts.

560 General Poster Session (Board #3G), Sat, 1:15 PM-5:00 PM

Ethnic differences in tumor proliferation in women with early-stage breast cancer.

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Background: Hispanic women have a higher mortality rate and lower incidence of breast cancer (BC) compared to Caucasian women. Studies report higher tumor proliferation in African American (AA) women compared to Caucasian women. The 21-gene assay (Onco*type*DX) Recurrence Score (Score) is based on the expression of 16 cancer related genes, including 5 proliferation genes that are grouped to provide the proliferation axis score (PAS). We evaluated the differences in the Score and PAS between Hispanic and Caucasian women with early-stage BC in a matched cohort analysis. **Methods:** Women with early-stage BC who had a Score obtained from 2005- 2011 were identified. Hispanic women were matched to Caucasians in a 1:2 ratio, based on age (+/- 10 years), stage, and nodal status. Lymphovascular invasion (LVI) and grade were collected. The Score result, 10-year distant recurrence, ER/PR/HER2 expression, and PAS were obtained from the Onco*type*DX assay. Assuming equal variances, we expected $>$ 90% power to detect a difference in the mean PAS between Hispanic and Caucasian women **Results:** We identified 219 women who had Onco*type*DX testing (74 Hispanic: 145 Caucasian). Of the 74 Hispanic women, 84% were from the Dominican Republic or Puerto Rico. Mean age was similar between groups (56.3 and 56.8). All but 8 patients were node(-). Mean PAS was higher in Hispanic (5.53, range: 3.9-7.8) vs Caucasian women (5.26, 3.7-7.3) ($p=0.03$, 95% CI: 0.03-0.51). The mean Score was 18.3 (0-54) and 16.3 (1-50) for Hispanic vs Caucasian women. There was no statistical difference in Score ($p= 0.17$) or 10-year distant recurrence ($p=0.13$) between groups. No differences were observed in median ER (9.8% vs 9.9%: Hispanic vs Caucasian), PR (7.3% vs 7.6%), or HER2 (9.1% vs 9.0%) by RT-PCR. Rates of LVI and grade 3 tumors were also not statistically different. **Conclusions:** Similar to higher PAS in AA women, Hispanic women with ER/PR(+), HER2(-) early-stage BC have higher tumor proliferation markers, measured by RT-PCR in the Onco*type* DX assay, than Caucasian women. This may contribute to ethnic differences in BC mortality. We plan to evaluate ethnic differences in the 5 single PAS genes (CCNB1, MKI17, MYBL2, BIRC5, AURKA) to determine which are driving proliferation differences.

561 General Poster Session (Board #3H), Sat, 1:15 PM-5:00 PM

Incidence, management, and resolution of noninfectious pneumonitis in BOLERO-2.

Yoshinori Ito, Shinzaburo Noguchi, Ines Deleu, José Baselga, Gabriel N. Hortobagyi, Thomas Denis Bachelot, Norikazu Masuda, Barbara Pistilli, Kathleen I. Pritchard, Hiroji Iwata, Michael Gnant, J F Eakle, Tibor Csõszi, Vichien Srimuninnimit, Puttisak Puttawibul, Fausto Roila, Ashok Panneerselvam, Tanya Taran, Tarek Sahmoud, Hope S. Rugo; Cancer Institute Hospital, Japanese Foundation for Cancer Research Breast Medical Oncology, Breast Oncology Center, Tokyo, Japan; Department of Breast and Endocrine Surgery, Osaka University, Osaka, Japan; AZ Nikolaas, Sint-Niklaas, Belgium; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; Centre Léon Bérard, Lyon, France; Osaka National Hospital, Osaka, Japan; Ospedale di Macerata, Macerata, Italy; Odette Cancer Centre, Sunnybrook Health Sciences Centre; University of Toronto, Toronto, ON, Canada; Aichi Cancer Center Hospital, Nagoya, Japan; Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; Florida Cancer Specialists, Fort Myers, FL; Department of Medical Oncology, Szolnok, Hungary; Siriraj Hospital, Mahidol University, Bangkok, Thailand; Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand; Oncologia Medica, Ospedale S. Maria, Terni, Italy; Novartis Pharmaceuticals Corp, Florham Park, NJ; Novartis Pharmaceuticals Corp, East Hanover, NJ; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: The BOLERO-2 trial showed that adding everolimus (EVE) to exemestane (EXE) more than doubled progression-free survival (PFS) without reducing quality of life versus placebo (PBO) + EXE alone in postmenopausal women with hormone-receptor–positive (HR^+), HER2-negative ($HER2^-$) advanced breast cancer (ABC) progressing on/after nonsteroidal aromatase inhibitor (NSAI) therapy. Although generally well tolerated, mTOR inhibitors such as EVE have been associated with noninfectious pneumonitis (NIP). **Methods:** Patients (pts) were randomized 2:1 to receive EVE+EXE or PBO+EXE. Incidence and severity of NIP, consequent dose interruptions/adjustments, study drug discontinuations, and time to resolution were recorded. **Results:** Median duration of exposure to EVE was 24 weeks with median dose intensity of 8.6 mg/d. Pulmonary adverse events (AEs) of any grade (NIP, interstitial lung disease, lung infiltration, pneumonia, or pulmonary fibrosis) were recorded in 97 of 482 pts (20%) in the EVE+EXE arm versus 1 of 238 pts (<1%) in the PBO+EXE arm. Of these, 16% of pts (77 of 482) in the EVE+EXE arm versus 0 in the PBO+EXE arm had a diagnosis consistent with NIP. In the EVE+EXE arm, grade 1 (no symptoms), grade 2 and 3 NIP occurred in 7%, 6% and 3% of pts, respectively, and no grade 4 events were reported. Complete resolution of NIP to grade ≤1 was recorded for all but 4 pts for whom NIP was still observed at last follow-up before study discontinuation. Overall, in the EVE+EXE arm, NIP was recorded as the reason for dose interruption and treatment discontinuation in 7.5% and 5.6% of pts, respectively. **Conclusions:** Data from BOLERO-2 support the combination of EVE and EXE to significantly prolong PFS in postmenopausal women with HR^+, $HER2^-$ ABC progressing on/after NSAI. The incidence of NIP in this study was generally consistent with reports from other oncology settings, was of mild to moderate severity, and was generally reversible with appropriate interventions and temporary dose modifications. Patient and healthcare provider education for early diagnosis and management of NIP are highly recommended. Clinical trial information: NCT00863655.

562 General Poster Session (Board #4A), Sat, 1:15 PM-5:00 PM

Phase II trial evaluating the use of 21-gene recurrence score (RS) to select preoperative therapy in hormone receptor (HR)-positive breast cancer.

Amelia Bruce Zelnak, Sujatha Murali, Toncred Marya Styblo, Grant Walter Carlson, Sheryl G. A. Gabram, Monica Rizzo, Mylin Ann Torres, Mary Newell, Yuan Liu, Ruth O'Regan; The Winship Cancer Institute of Emory University, Atlanta, GA; Department of Surgery, Emory University, Atlanta, GA; Department of Radiation Oncology, Emory University, Atlanta, GA; Emory University School of Medicine, Atlanta, GA; Emory University School of Public Health, Atlanta, GA; Department of Hematology and Medical Oncology, Emory University, Atlanta, GA

Background: Hormone receptor (HR)- positive breast cancer patients (pts) typically have lower pathological responses to pre-operative chemotherapy than HR-negative breast cancers. Objective: We evaluated the pathologic and radiologic response rates to pre-operative endocrine therapy or chemotherapy, as directed by RS, in pts with HR-positive resectable breast cancers. **Methods:** Pts with HR-positive breast cancers had RS performed on the initial diagnostic biopsy. Pts were treated pre-operatively as follows based on RS: $\leq$10, exemestane +/- goserelin for 6 to 12 months (ET); 11 to 25 randomized to ET or docetaxel-cyclophosphamide (TC) for 6 cycles (CT); $\geq$ 26, CT. **Results:** From 4/2009 to 12/2012, 66 pts signed consent for RS testing and 46 are evaluable for efficacy analysis. Median age is 57 (40 to 78); one-third of pts are African-American; 41% have clinically node positive disease. RS ranged from 2 to 57. 28 pts received CT: Pathologic complete response (PCR) rate was 10% and 60% of cancers were down-staged based on initial T-stage. Radiologic response is available for 20 pts: complete radiologic response (CRR) 15%, partial RR (PRR) 40%, progressive disease (PD) 5%. In 11 pts with RS 11 to 25: PCR 0%, down-staged 45%, up-staged 18%, radiologic responses: CRR 17%, PRR 50%, PD 17%. In 17 pts with RS $\geq$ 26: PCR 18%, down-staged 71%, up-staged 0%, radiologic responses: CRR 14%, PRR 36%, PD 0%. 18 pts received ET for between 6 to 22 months, 5 remain on study and have not had surgery: PCR 0%; down-staged 38%; up-staged 15%; radiologic responses: CRR 13%, PRR 40%, PD 0%. There was no correlation between RS and efficacy of ET. To date, 3 pts have relapsed, all of whom received CT. **Conclusions:** This is the first prospective use of the 21-gene RS to select pre-operative therapy for pts with HR-positive breast cancer. Pre-operative CT results in tumor down-staging in the majority of cancers with RS $\geq$ 11, though it appears to be more effective with RS $\geq$ 26. ET was moderately effective in down-staging cancers with RS $\leq$ 25. Updated results will be presented. Clinical trial information: NCT00941330, NCT00832338.

563 General Poster Session (Board #4B), Sat, 1:15 PM-5:00 PM

Eribulin mesylate (Erib) plus capecitabine (X) for adjuvant treatment in post-menopausal estrogen receptor–positive (ER+) early-stage breast cancer: Phase II, multicenter, single-arm study.

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Background: Erib and X have both shown single agent activity in MBC; and X also has activity in ER+ adjuvant tx. This study was designed to evaluate the feasibility of the combination in the adjuvant setting. **Methods:** Female pts stage I-II, HER2 negative, ER+ BC received Erib at 1.4 mg/m^2 iv D1 and D8 and X at 900 mg/m^2 po bid on days 1-14 of 21 day cycle, for 4 cycles. The study was considered feasible if 80% of pts are able to achieve the target relative dose intensity (RDI) of at least 85% of the regimen and lower 95% confidence boundary (LCI) is above 70%. **Results:** Final results of 67pts enrolled are reported here. 88% pts completed 4 cycles of tx. Pt characteristics: Median age 62 yrs (range 28-80), ECOG 0(90%), stage 2(52%). 64/67 pts were evaluable for feasibility. The study met its primary endpoint demonstrating feasibility rate of 81%(95% LCI:71%) with average RDI of 91%. Results were mainly affected by X dose adjustments (Erib RDI-93%, X RDI-88%). X related dose reductions(24, (36%)), missed doses (57,(85%)) and discontinuations due to AE (11(16%)) were higher compared to that with Erib(14(21%), 5(8%) and 7(10%)), respectively. Most common AEs with dose reductions were gr 3/4 hand foot syndrome (HFS) (12%), neutropenia(8%), neuropathy(8%), and GI disorders(6%); and drug discontinuation were HFS(8%), neutropenia(3%), neuropathy(2%), and GI disorders(3%). Tx related AEs and SAE are reported in the Table. 14(21%) pts had an SAE with 12(18%) requiring hospitalization. **Conclusions:** Adjuvant tx with the Erib-X combination can be given safely with the majority of the patients able to achieve full dosing regimen. We plan to explore an alternative schedule of X(7wk on/off) with this regimen to see if it will further improve tolerability and the RDI. Clinical trial information: NCT01439282.

Tx-related AEs (≥30%)	Alopecia 78%; 46% gr1 Fatigue 57% Nausea 51% HFS 40% Diarrhea 37% Neutropenia 36% Constipation 30% Neuropathy 33%; 8% gr3/4
Most common SAEs (≥2%)	Pulmonary embolism 5% Diarrhea 3% Febrile/neutropenia 3%

564 General Poster Session (Board #4C), Sat, 1:15 PM-5:00 PM

Competing risks of death in NCIC CTG MA.27 adjuvant exemestane versus anastrozole.

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Background: Our group previously examined if baseline patient/tumor characteristics, or prior treatment affected cause of death in MA.17, a placebo controlled extended adjuvant trial of the aromatase inhibitor (AI) letrozole. We now examine factor effects on all cause mortality in MA.27. **Methods:** MA.27 was an adjuvant phase III superiority trial of 5 yrs of exemestane vs anastrozole, in ER+ postmenopausal breast cancer accrued between 2003 and 2008; event free survival was similar. We examined by intention-to-treat, the multivariate time-to-breast cancer-specific (BrCa), cardiovascular (Cardio), and other causes (OT) of death with log-normal survival analysis adjusted by treatment and stratification factors (lymph node status, adjuvant chemotherapy, celecoxib, aspirin, and trastuzumab). We tested whether factors were associated with 1) all cause mortality, and if so, 2) cause-specific mortality. We also fit step-wise forward cause-specific adjusted models. **Results:** 7,576 women (median age 64.1 years; 5417 (71.5%) $<$70 yrs and 2159 (28.5%) $>$70 yrs) were enrolled and followed for a median of 4.1 yrs. The 432 deaths comprised: 187 (43.3%) BrCa, 66 (15.3%) Cardiovascular, and 179 (41.4%) OT MA.27 therapy was not associated with mortality ($p=0.84$). Five baseline factors were differentially associated with cause of death. Older age was associated with greater BrCa ($p=0.03$), Cardio ($p<0.001$), and OT ($p<0.001$) mortality. Pre-existing cardiovascular history led to worse Cardio mortality ($p<0.001$). Worse ECOG performance status led to worse OT death ($p<0.001$). T1 tumors were associated with less BrCa mortality ($p<0.001$). PgR+ tumors were also associated with less BrCa mortality ($p<0.001$). There were fewer BrCa deaths with Node –ve disease ($p<0.001$), ER+ tumors ($p=0.001$) and without adjuvant chemotherapy ($p=0.005$); there was worse Cardio mortality ($p=0.01$) with receipt of trastuzumab; worse OT ($p=0.03$) for non-whites, and without adjuvant radiotherapy ($p=0.003$). **Conclusions:** 56.7% of deaths in MA.27 patients were non-breast cancer related. We showed baseline patient and tumor characteristics, and prior treatment differentially affected cause of death. Clinical trial information: NCT00066573.

565 General Poster Session (Board #4D), Sat, 1:15 PM-5:00 PM

Initial results from the 21-gene breast cancer assay registry: A prospective observational study in patients (pts) with ER+, early-stage invasive breast cancer (EBC).

Jeffrey L. Vacirca, Michaela L. Tsai, Adam Brufsky, Richard Alan Michaelson, Frederick P. Smith, Lee Steven Schwartzberg, Steven M Butler, Farid Jamshidian, Amy Pratt Sing; North Shore Hematology Oncology Associates, PC, East Setauket, NY; Park Nicollet Institute, Frauenshuh Cancer Center, St. Louis Park, MN; Division of Hematology and Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA; St Barnabas Medical Center, Livingston, NJ; Frederick P. Smith, M.D., P.C., Chevy Chase, MD; The West Clinic, Memphis, TN; Genomic Health, Inc., Redwood City, CA

Background: Genomic assays such as the 21-gene breast cancer assay (Onco*type* DX), have improved the ability to individualize pt treatment based on their individual tumor's biology. Since 2004, when the 21-gene assay became commercially available, more than 300K assays have been ordered. While several studies have been conducted assessing the impact of having the Recurrence Score (Score) result on treatment decisions, most have been retrospective or evaluating the treatment recommendation. The Onco*type* DX Breast Cancer Registry is a large prospective study conducted in clinical practices evaluating the types of pts having the assay ordered and the actual treatments delivered. We report here the first set of analyses. **Methods:** Pts with ER+ EBC were eligible to enroll. Data collected at baseline (BL) included age, size, grade, ER, PR and HER2 status. Data collected at the 6-month visit included Score and treatment given. Pt demographics, Score distribution, and associations with clinicopathologic (CP) factors are described. **Results:** A total of 890 pts were enrolled at 15 U.S. sites between 11/09-3/12. 803 eligible pts were included in the analyses. The Table shows BL characteristics, Score distribution and %CT given. Distribution of Score values across the CP factors was similar to the cohort overall. 30% of pts received CT. Among low Score patients, CT was given in 17% of pts <50y, 9% of Grade 3 tumors and 11% of tumors >2cm. **Conclusions:** A large, prospective registry for pts with EBC receiving the 21-gene breast cancer assay examined the application of the Score to treatment. The Score distribution is consistent with other retrospective cohorts. The association between the Score and the CP factors was modest. The CP factors did not predict the Score. In general, CT decisions followed the Score with the exception of younger pts; 17% received CT despite a low Score. These findings from a real-world cohort underscore the importance of understanding breast cancer biology in order to make more informed and individualized treatment decisions.

	N	%CT
All pts	803	30
Age		
<50	171	43
>70	135	15
Grade		
1	201	13
3	134	53
Size		
<1cm	209	27
>2cm	201	35
RS		
Low	55	7.5
Intermed	35	47
High	10	86

566 General Poster Session (Board #4E), Sat, 1:15 PM-5:00 PM

Characteristics and clinical outcome of T1 breast cancer: A national multicenter retrospective cohort study.

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Background: T1N0M0 breast cancer (BC) are generally considered as carrying good prognosis and cancer-specific survival rates after 5 to 10 years are as high as 90 or 95% in many studies. However, they constitute a heterogeneous group and many studies identified biologically-defined at-risk patients within T1 BC. The objectives of our study were to describe the main characteristics of T1a, b, and c (11-15mm) BC and to identify prognostic factors for survival. **Methods:** We retrospectively collected the medical files of all patients diagnosed with BC who underwent sentinel lymph node biopsy (SLNB) between January 1999 and December 2008 in 13 French sites and examined overall survival (OS) and Relapse-free survival (RFS) in T1a, T1b and T1c 11-15 mm. **Results:** Among 8,100 women operated, 5,423 had T1 tumors (708 T1a, 2,208 T1b and 2,508 T1c 11-15mm). T1a differed significantly from T1b tumors with respect to several parameters : younger age, more frequent negative hormonal status and positive HER2 status, less frequent lymphovascular invasion (LVI), exhibiting a mix of favorable and poor prognosis factors. After a median follow-up of 60.5 months, OS rate was 97.6% (95CI: 97.1-98) at 60 months, 95.4%(94.5-96.4) at 84 months and 90.7% (85.2-96.4) at 120 months. No significant difference was observed between T1a, T1b and T1c tumors ($p=0.335$). RFS rates were 94% (95CI: 93.8-95.2), 92.1% [91.1-93.2] and 83.8% (77.6-90.5) at 60, 84 and 120 months respectively. RFS was significantly higher in T1b tumors (95.9%, 95CI: 95-96.9) as compared to T1a (93.2%, 91-95.4) or T1c tumors (93.8%, 92.8-94.9), $p=0.0099$. In multivariate analysis, SBR tumor grade, hormone therapy and LVI were independent prognostic factors for RFS, while hormone therapy and SBR grade were independently associated with OS. **Conclusions:** Relatively poor outcome of patients with T1a tumors might be explained by a high frequency of risk factors in this subgroup (frequent negative hormone receptors and HER2 overexpression) and by a less frequent administration of adjuvant systemic therapy (endocrine treatment and chemotherapy). Tumor size might not be the main determinant of prognosis in T1 breast cancer.

567 General Poster Session (Board #4F), Sat, 1:15 PM-5:00 PM

Phase I clinical trial of bavituximab (Bavi) and paclitaxel (P) in patients (pts) with HER2-negative metastatic breast cancer (MBC).

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Background: Bavituximab is a novel tumor vascular targeting agent. It is an unconjugated, chimeric immunoglobulin G1 monoclonal antibody directed against phosphatidylserine (PS). PS is externally expressed on endothelial cells when exposed to hypoxia and/or other physiological stressors frequently observed in tumor-associated vasculature. On attaching to PS, Bavi triggers antitumor effects by inducing antibody-dependent cellular cytotoxicity and promoting antitumor immunity. **Methods:** We conducted a phase I clinical trial of Bavi in combination with P in pts with HER-2 negative MBC. Pts were treated with weekly P (80mg/m^2 for 3/ 4 weeks) and weekly Bavi (3mg/kg for 4/ 4 wks). Microparticle generation, activation and circulating endothelial cell apoptotic markers were measured by flow cytometry. **Results:** 14 pts with MBC were enrolled. Median age at MBC diagnosis was 50yrs. Seven pts had triple negative MBC; 4 pts presented with de-novo metastatic disease. Prior treatments included chemotherapy in the adjuvant/ neoadjuvant setting (8); metastatic setting (2); adjuvant hormonal therapy (3). Best responses to date include complete response (1), partial response (6), stable disease (1), progressive disease (2) and too early to evaluate (4). Bavi related toxicities include grade2/3 infusion related reactions in 2 pts (1 discontinued Bavi). Bone pain, fatigue, headache and neutropenia were the most common adverse effects. 1 pt had a catheter associated upper extremity thrombosis requiring anticoagulation. Laboratory correlative studies revealed no evidence of platelet activation of PAC-1 or P-Selectin. Median platelet and endothelial microparticles decreased from baseline in response to therapy. **Conclusions:** Bavi is a novel vascular targeting agent that is well tolerated in combination with P. Early results show promise in terms of clinical responses with 8 of 10 evaluable patients having clinical benefit. Early biomarker results suggest no effect of therapy on platelet activation but decreases in circulating microparticles is observed. Clinical trial information: NCT01288261.

568 General Poster Session (Board #4G), Sat, 1:15 PM-5:00 PM

Periodontal health in early-stage postmenopausal breast cancer survivors on aromatase inhibitors.

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Background: Aromatase inhibitors (AIs) are associated with profound estrogen deprivation resulting in reduced bone mineral density (BMD). Periodontal diseases and tooth loss are associated with estrogen withdrawal and decreased systemic BMD. Little is known as to the impact of AIs on oral health. To investigate oral health as a breast cancer (BCA) survivorship concern, a prospective study was initiated to determine the prevalence of periodontal diseases in postmenopausal early stage (I-IIIA) BCA survivors on adjuvant AI therapy. Baseline assessments are presented here. **Methods:** Women within 6 months of initiating adjuvant AI for hormone receptor positive BCA were eligible to participate in this study of serial assessments of oral health. A control group of women without BCA and not on AI underwent parallel assessments. Periodontal status was evaluated by the following established dental techniques; (1) periodontal pocket depth (PD), (2) number of teeth with bleeding on probing (BOP), (3) the number of teeth with clinical attachment loss (CAL). Questionnaires regarding socio-demographic and dental utilization were administered to all participants. Linear regression modeling was used to analyze the outcomes. **Results:** The study met its target accrual of 58 postmenopausal women; 29 with BCA on AI and 29 controls. Demographics were similar regarding age, education, income level, frequency of dental visits, and dental insurance status across both groups. Baseline assessments demonstrated no differences in PD (2.0 mm vs. 2.0 mm; $p < 0.95$) or the number of teeth (26.6 vs 26.1; $p< 0.39$). Interestingly, the AI group had significantly more sites of BOP (27.9 vs 16.7; $p < 0.02$), and higher CAL (5.2 mm vs 4.0 mm; $p < 0.01$) than did controls. In linear regression analysis adjusted for income, AI use increased CAL by 1 mm (95% CI: 0.15 -1.88). There was also a trend for decreased CAL in subjects with incomes over $75,000 per year ($p< 0.06$). **Conclusions:** This first investigation of the periodontal status of women initiating adjuvant AI therpay identifies this population to have signs of increased risk for periodontal disease. Serial oral health assessments are being conducted to assess AI therapy and periodontal changes over time. Clinical trial information: NCT01693731.

569 General Poster Session (Board #4H), Sat, 1:15 PM-5:00 PM

Aromatase inhibitor pain syndromes: Classification and determination of specific risk factors—A prospective multicenter cohort study.

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Background: Pain is frequent during Aromatase Inhibitors (AIs) treatment for breast cancer and several pain syndromes have been reported but not precisely defined. We developed a prospective multicentre study aiming at classifying AIs-related pain syndromes, comparing their impact on daily life, and identifying their specific determinants for a more targeted prevention approach. **Methods:** A one-year multicenter cohort prospective study, with 5 pre-scheduled visits, was carried out in early stage breast cancer women, free of pain, starting an AI treatment, recruited from 4 oncology centres. At baseline, clinical data (demography and psychosocial, cancer characteristics and treatments, pain, sleep, rheumatologic examination, cancer-related quality of life), biological data (sex hormones, vitamin D, bone biomarkers, oxidative stress, immunological and inflammatory markers), and genetic polymorphism for pain mechanisms (opioid and serotonin pathways) were recorded. **Results:** A cohort of 135 women was evaluated. Among them, 77 (57%) developed a pain syndrome along the study period, leading to AIs discontinuation in 12 cases. Five main different types of pain syndromes were identified: joint pain, in 48 women overall over the follow-up (36%), diffuse pain, in 30 women (22%), tendinitis, in 29 women (22%), and neuropathic pain, in 12 women (9%) and mixed types, which were frequent and often transient. Analyses demonstrated that risk factors for developing pain syndromes were baseline anxiety and impaired quality of life, while cancer features, genetic background, inflammation, immunological and sex hormone levels were not involved. **Conclusions:** In pain-free women with breast cancer starting an AI, risks for developing pain during the first year of treatment are slightly greater than 50%. We identified 5 main pain syndromes, joint and widespread pain being the most frequent. In all instances, initial psychological dimensions (personality, impaired quality of life and anxiety) are identified as major risk factors for pain development.

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

Comparative analysis of bone marrow micrometastases with sentinel lymph node status in early-stage breast cancer.

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Background: A definitive relationship between bone marrow (BM) micrometastases (M) and sentinel lymph node (SLN) status has not been established in Breast Cancer (BRCa). Hence, a retrospective study was done to examine the relationship between BMM and SLN status in BRCa patients (pts). **Methods:** T1/T2 BRCa pts underwent SLN biopsy and definitive surgery for primary tumors. At the operation, BM aspiration from bilateral post-superior iliac spines was performed. BM samples were examined using a Cytokeratin Detection Kit using CAM 5.2 monoclonal antibody and visualization achieved with a Ventana iView V-Red detection system. An Automated Cellular Imaging System was applied to identify metastatic BRCa cells. Pts with +ve BM underwent repeat BM analysis 6 months after completing initial treatments. Data was collected for T-stages, SLN, BM, ER/PR receptor and Her-2/neu statuses and analyzed using Chi-Square Analysis or Fischer's Exact Test. **Results:** We analyzed 458 consecutive pts, of which SLN metastasesv(mets) were detected in 22.9% and BMM were detected in 8.1%. BMM were found 23% bilaterally and 77% unilaterally. BMM were detected in 11.4% of SLN +ve pts versus 7.1% of SLN -ve ptsv($p=0.15$) and 6.8% of T1 pts versus 12.3% of T2 ptsvv($p=0.07$). BMM were found in 8.7% of ER/PR +ve pts versus 4.5% of ER/PR –ve ptsvv($p=0.1$) and 9.5% of HER2/neu +ve pts versus 7.7% of HER2/neu –ve ptsv ($p=0.5$) (Table). Repeat BM analysis detected BMM only in 6.6% pts. **Conclusions:** Bilateral BM aspirate resulted in a significant increase in detection of micrometastases. BM metastases may occur independently of lymphatic metastasis. Therefore, evaluation for the presence of BMM may help identify high risk pts with node negative disease in early stage BRCa.

Comparison of bone marrow status versus four variables.

Variable (No. of pts)	BM +VE (37)	BM –VE(421)	P value
SLN +VE(105)	12 (11.4%)	93 (88.6%)	0.15
SLN-VE (353)	25 (7.1%)	328 (92.9%)	OR-1.6 (0.8-3.3)
T1 (352)	24 (6.8%)	328 (93.2%)	0.07
T2 (106)	13 (12.3%)	93 (87.7%)	OR-1.9 (0.93-3.8)
ER/PR +VE (391)	34 (8.7%)	357 (91.3%)	0.1
ER/PR –VE (67)	3 (4.5%)	64 (95.5%)	OR-2 (0.6-6.8)
HER2/NEU +VE(95)	9 (9.5%)	86 (90.5%)	0.5
HER2/NEU –VE(363)	28 (7.7%)	335 (92.3%)	OR-1.2 (0.5-2.7)

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

Relationship of tumor and stromal autophagy and endocrine responsiveness in breast cancer tissues.

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Background: Neoadjuvant endocrine therapy has been employed to improve surgical outcomes for endocrine responsive breast cancers in post-menopausal women. Endocrine responsiveness is estimated by the expression levels of hormone receptors although heterogeneity in the response is well recognized. To improve the clinical outcome, it is critical to understand how cancer tissues react to the endocrine treatment. **Methods:** Pre-treatment biopsy samples and post-treatment surgical samples were obtained from 116 patients enrolled onto the multicenter prospective study of neoadjuvant exemestane therapy, JFMC34-0601. Fifty-four paired samples were available for the study. Estrogen receptor, progesterone receptor, HER2, Ki-67 by immunohistochemistry and pathological response were centrally evaluated. Apoptosis was assessed by TUNEL (Roche Diagnostics, Mannheim) and M30 (Roche Diagnostics, Mannheim). Autophagy was assessed by anti-beclin 1 (Novus Biologicals, CO) and anti-LC3 (MBL, Nagoya). Clinical response was assessed based on the RECIST criteria. The Wilcoxon rank-sum test and chi-square test were used for the statistical analysis. **Results:** The expression of autophagy markers, beclin and LC3, in cancer cells showed significant increases by exemestane (beclin $p=0.016$; LC3 $p=0.0004$) whereas TUNEL did not show any change and M30 expression decreased ($p=0.01$). The increase of beclin expression was associated with the clinical response: responders showed an increase ($p=0.039$) while non-responders did not. Importantly, the treatment increased autophagy markers not only in cancer cells but in stromal cells (beclin $p<0.0001$; LC3 $p=0.024$) while it did not change TUNEL in stromal cells. Patients with stromal beclin-positive showed poor clinical response (3/12) and poor pathological response (0/12) while those with stromal beclin-negative showed good clinical response (26/39) and good pathological response (16/38) (clinical response $p=0.011$; pathological response $p=0.0064$). **Conclusions:** This study suggested that exemestane induced autophagy in both cancer and stromal cells. In addition, stromal autophagy correlated with clinical and pathological response to the endocrine treatment.

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

Effect of fertility concerns on tamoxifen use in young survivors of breast cancer.

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Background: For premenopausal patients with ER+ breast cancer, a 5-year course of tamoxifen results in a 47% reduction in annual recurrence risk and a 26% reduction in annual mortality. Despite these benefits, adherence rates for tamoxifen are low, particularly among younger women. We hypothesize that fertility concerns are causally related to the poor tamoxifen adherence rates observed among young breast cancer survivors. **Methods:** With IRB approval, a retrospective analysis of 535 women with breast cancer between 2000-2012 was undertaken. Patients were younger than age 46, premenopausal and had ER+ breast cancer. 138 patients did not complete a 5-year course. Patient and provider factors that influenced tamoxifen initiation and adherence were reviewed: (1) evidence of referral to a fertility specialist; (2) documentation of discussion about tamoxifen-related fertility concerns; (3) agreement to take tamoxifen; (4) duration of tamoxifen use. Phone interviews conducted with 27 patients focused on lack of initiation or early discontinuation. The Log-rank (Mantel-Cox) test was used to compare Kaplan-Meier curves and generate hazard ratios. **Results:** Of the 138 patients who did not complete 5 years of therapy, 38 (27.5%) failed to initiate or discontinued tamoxifen secondary to fertility concerns. Only 114 (21.3%) charts documented referral to a fertility specialist. Patients who expressed a desire to maintain fertility or to have children in the future (115 patients, 21.5%) were more likely to discontinue tamoxifen treatment (HR=2.7, p=0.001). Other critical factors included being unmarried (HR=1.9, p=0.011) and lack of college education (HR=2.5, p=0.0008). Major themes from phone interviews: (1) patients felt they were not adequately informed about fertility preservation and had to pursue information independently; (2) patients did not initiate/resume tamoxifen postpartum because of inadequate physician guidance. **Conclusions:** Concerns about fertility have a significant negative impact on the initiation and adherence to tamoxifen for young breast cancer patients. Efforts to improve tamoxifen adherence among young cancer patients should include prioritization of fertility preservation as part of the treatment plan.

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

Low HER2-expression to predict impaired activity of endocrine therapy in patients with estrogen-receptor (ER) positive metastatic breast cancer (MBC).

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Background: ER cross-activation by growth-factor signalling causes resistance to endocrine therapy (ET) in patients (pts) with Her2-positive MBC. Moreover, low levels of Her2-expression (Her2 1+; Her2 2+ without gene amplification), may result in reduced efficacy of ET in early breast cancer pts. In a recently published study, these tumours had a less favourable outcome as compared to tumours with a Her2-score of 0. Here, we investigated if low levels of Her2-expression could predict for shorter progression-free survival (PFS) in MBC pts on ET. **Methods:** PFS on first-line ET was chosen as primary endpoint and estimated with the Kaplan-Meier method. To test for differences between PFS curves, the log-rank test was used. Association of the following variables with PFS was investigated: low Her2-expression, grading, level of ER-expression, progesterone-receptor status, Ki67 (cut-off $\leq$20%), prior adjuvant ET, and presence of visceral metastases. For an estimated superiority of 40% in terms of PFS in favour of the Her2-negative group, a sample of 130 pts in two groups was needed in order to rule out the null-hypothesis with a 80% power and a two-sided α of 0.025. **Results:** A total number of 320 ER-positive MBC pts were identified from a breast cancer database; 170 pts were available for this analysis. Median PFS on first-line ET was 11 months (m) (8.56-13.44), corresponding numbers for second-line were 6 m (4.65-7.36), and third-line 4 m (1.52-6.48), respectively; median OS from diagnosis of MBC was 58 m (48.15-67.86). None of the variables investigated were significantly associated with first-line PFS. Second-line PFS, however, was significantly shorter in pts with grade 3 tumours and prior adjuvant ET; a trend towards shorter PFS was observed in high proliferating tumours. **Conclusions:** In this chart review, low levels of Her2 expression did not predict for shorter PFS in pts receiving ET; PFS in different treatment lines was well in line with data from clinical trials. High tumour grading and prior adjuvant ET were associated with accelerated onset of resistance, rendering those patients candidates for early combination of ET with targeted treatment approaches.

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

Randomized phase II placebo-controlled trial of fulvestrant plus vandetanib in postmenopausal women with bone only or bone predominant, hormone receptor-positive metastatic breast cancer (MBC): OCOG Zamboney study—NCT00811369.

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Background: Biomarkers of bone turnover, including urine N-telopeptide (uNTx) and serum C-telopeptide (sCTx) reflect tumor-related bone breakdown and have been used as surrogate measures of response to therapy in trials. Vascular endothelial growth factor (VEGF) levels correlate with extent of bone metastases (BM). We assessed whether vandetanib, an inhibitor of VEGF, epidermal growth factor receptor and RET signalling, improved uNTx response when added to fulvestrant (F) in patients with BM. **Methods:** Postmenopausal patients with bone only, or bone predominant, hormone receptor positive MBC were randomised to F (500mg IM day 1, 14, 28, then monthly) with either vandetanib (100mg PO OD) (FV) or placebo (FP) until progression. The primary objective was uNTx response (>30% reduction from baseline). uNTx was collected at baseline, weekly to wk 4, at wk 12 and then every 12 wks. Secondary objectives included PFS, OS, RECIST response, pain and toxicity. **Results:** 61 patients were allocated to FV and 68 to FP. Median age was 59. 18% had received 1 prior chemotherapy regime and 73% prior endocrine therapy for MBC. uNTx response (n=124 pts) was 64% for FV vs. 52% for FP (p=0.20). No difference was detected between groups for median PFS; 6 months for FV vs. 4.8 months for FP, HR=0.93 (95% CI: 0.64 to 1.36). 16 patients died in FV arm vs. 21 in the FP arm, HR=0.71 (95% CI: 0.37 to 1.36). For those patients with measurable disease, clinical benefit rates were 41% and 43%, respectively, p=1.00. Serious adverse events were similar, 3.3% for FV vs. 5.9% for FP. Elevated baseline uNTx (>65 nM BCE/mmol Cr) was prognostic for PFS, HR=1.62 (95% CI: 1.08 to 2.43 and for mortality, HR= 2.4 (95% CI: 1.2 to 4.6). In an exploratory analysis uNTx was predictive of responsiveness to FV for PFS, HR=0.60 when uNTx >65 vs. HR=1.37 when uNTx <65, P = 0.025 for interaction. **Conclusions:** The addition of vandetanib to F did not improve biomarker response, PFS or OS compared to F alone in patients with bone predominant disease. Exploratory analyses confirmed that baseline bone turnover markers are prognostic for PFS and OS. Clinical trial information: NCT00811369.

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

A meta-analysis of endocrine therapy trials in early breast cancer (BC) evaluating the impact of obesity: Are aromatase inhibitors (AIs) optimal therapy in obese ER+ BC?

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Background: Obesity is an adverse prognostic factor in BC. Mixed results are reported for the relative efficacy of AIs compared to tamoxifen (T) in obese ER+ BC patients. Our purpose was to conduct a meta-analysis of adjuvant randomised trials of AIs vs T assessing the impact of body mass index (BMI). **Methods:** We identified four studies evaluating BMI and endocrine therapy. Of these, 3 were randomised (non-steroidal AIs vs T) and were evaluable for the aggregation of results for DFS and OS in our meta-analysis. We extracted published data from ATAC, ABCSG-12 and BIG01-98, analyzed according to standard meta-analytic techniques. **Results:** A total of 11,383 patients were included in our study. BMI>25 is associated with reduced disease free survival (DFS) and a trend towards worse overall survival (OS) (Table 1). A significantly shorter DFS was seen for patients with BMI>25 treated with an AI while a trend was seen for OS. Reduced relative efficacy was seen for DFS for AIs compared to T for BMI<25 (HR=0.78; 95%CI 0.66- 0.91; p=0.002) and a trend for BMI>25 (HR=0.85; 95%CI 0.70- 1.02; p=0.08). The test for interaction was not significant (p=0.48), with similar results for OS for BMI<25 (HR=0.79; 95%CI 0.63-0.9; p=0.009) and BMI>25 (HR=0.98; 95%CI 0.61-1.60; p=0.95). The test for interaction was not significant (p=0.37). Notably, significant heterogeneity in patients treated with anastrozole and a BMI>25 did not allow a comparison between anastrozole and letrozole. **Conclusions:** BMI>25 has a negative prognostic effect in BC. AIs demonstrate improved outcomes in normal weight BC patients (BMI<25). Obesity was associated with observed relative reduced efficacy of AIs; however, we were not able to detect a significant interaction between BMI and treatment effect. Further analyses into the differing impact of type of AIs on BC outcomes in obese patients are warranted.

	HR	95%CI	P value
DFS DMI>25 vs <25	1.09	1.00-1.19	0.04
OS BMI>25 vs <25	1.12	0.97-1.29	0.12
DFS AI treated patients BMI>25 vs <25	1.21	1.07-1.39	0.003
OS AI treated patients BMI>25 vs <25	1.44	0.76-2.74	0.26
DFS T treated patients BMI>25 vs <25	1.01	0.90-1.14	0.84
OS T treated patients BMI>25 vs <25	1.08	0.88-1.33	0.45

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

Evaluation of microRNA-10b expression as a novel predictive marker of metastases development and patients' survival in breast cancer.

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Background: MicroRNA-10b was found highly expressed in metastatic breast cancer cell lines and able to generate metastases in mice models. The aim of this study is to evaluate the putative association between miR10b expression and disease progression. **Methods:** We selectedfrom our tumor bank 150 consecutive breast cancers with at least three years follow up. For each case frozen paired tumor and normal tissue and complete clinical data were available**.** Pathological examination was performed to ensure that each tumour sample contained more than 70% of cancer cells resulting in 114 samples suitable for RNA extraction. RNA quality was measured and only samples with RIN≥7.0 were analyzed (n=101) by a relative quantification method. **Results:** miR10b relative expression in tumor to normal samples (RERs) was significantly higher in the subgroup of patients with metastases (median 0.25 IQR 0.11-1.02) as compared with patients without metastases (median 0.09 IQR 0.04-0.29) (P=0.023 Mann Whitney Test). The association between miR-10b RERs and survival was evaluated in the group of patients without metastases at diagnosis (n=90). In univariate Cox regression model, patients with high miR-10b RERs had a higher risk of distant metastases development (HR 4.91, P=0.02) and disease related death (HR 6.02; P=0.01). In a multivariate Cox regression model adjusted for tumor size, lymph node metastases, grade, ER, PgR status, and Ki67 labeling index (n=79), higher miR-10b RERs were still associated with increased risk of distant metastases development (HR18.84; P<0.001) and disease related death (HR 13.39; P=0.003) (Table). **Conclusions:** We show that in breast cancer patients miR-10b expression is associated with worse prognosis on a short term follow up. These results suggest that miR-10b expression could be used for individual patient's risk assessment and perhaps as potential therapeutical target.

Cox regressions models evaluating the association of miR10b RERs with clinical endpoints.

	Events/total	Model	HR	95% CI	P
OS	18/90	Univariate	6.02	1.42 - 25.55	0.01
	16/79	Multivariate	13.39	2.57 - 92.33	0.003
MFS	30/90	Univariate	4.91	1.29 - 18.56	0.02
	27/79	Multivariate	18.84	3.36 -105.8	<0.001

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

Effect of nanosomal docetaxel lipid suspension (NDLS) on response rate compared to docetaxel: A randomized phase II study in patients with locally advanced or metastatic breast cancer.

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Background: Docetaxel formulated inpolysorbate 80 and ethanol (Docetaxel) is among the most active agents in the treatment of breast cancer. The primary rationale for developing nanosomal docetaxel lipid suspension (NDLS) is to improve the drug's safety profile by eliminating polysorbate 80 and ethanol from docetaxel formulation. Previously, we conducted a clinical study comparing pharmacokinetic parameters of NDLS and docetaxel at 75 mg/m^2. The log transformed NDLS/docetaxel ratio for C_{max} and $AUC_{0\text{-}t}$ was 149.3% and 119.3% respectively. The higher systemic availability of NDLS prompted us to conduct current efficacy study. **Methods:** 72 locally advanced or metastatic breast cancer patients were enrolled into the study after failure of prior chemotherapy. The mean age for the enrolled patients was 47 years and the racial make-up of the study was 100% Asian. Patients were administered NDLS or docetaxel at 75 mg/m^2 as per randomization schedule, by IV infusion for one hour in each cycle of 21 days. Each patient received maximum of 6 cycles of NDLS or docetaxel. No premedication was given to the patients in NDLS treatment group. **Results:** Safety - The total number of post-dose AEs observed in the study was 510. The breakdown by treatment groups is as follows: AEs were reported in 91.30% and 93.88% patients who received the docetaxel and NDLS respectively. There were 34 SAEs in the study, out of which 04 SAEs resulted in death of the patients (3 in docetaxel and 1 in NDLS). Efficacy - The results showed that 4.2% patients had complete response (CR) in NDLS treatment group while there was no CR in docetaxel treatment group. Further, 31.3% partial response rate (PR) was observed in NDLS treatment group and 26.3% in docetaxel treatment group. Overall response (CR+PR) rate was 35.4% in NDLS treatment group and 26.3% in docetaxel treatment group. Stable disease (SD) was observed in 45.8% patients in NDLS group and 63.2% patients in docetaxel group. **Conclusions:** Overall, the NDLS was well tolerated in the multiple doses of 75 mg/m^2 and found to increase response rate compared to docetaxel in breast cancer patients. Clinical trial information: CTRI/2010/091/000610.

578 General Poster Session (Board #6A), Sat, 1:15 PM-5:00 PM

Involvement of microRNA in the regulation of progesterone receptor in breast cancer.

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Background: The progesterone receptor (PgR) is a prognostic factor in ER positive breast cancers treated by adjuvant hormonal treatment. While PgR protein is usually assessed by immunohistochemistry (IHC), RT-PCR measurement of mRNA levels is provided by Oncotype Dx and other tests. Between 20-40% of tumors are discrepant in IHC and RT-PCR PgR expression, reflecting either technical problems or biological mechanisms. MicroRNAs regulate gene expression either at the mRNA or the protein translation level. Our hypothesis is that the latter potentially explains discrepancies between IHC and RT-PCR results. **Methods:** ER positive tumors were divided to three groups by PgR expression according to IHC and RT-PCR: (i) positive by IHC; (ii) negative by IHC and high mRNA levels by RT-PCR; (iii) negative by IHC and low mRNA levels by RT-PCR. RNA was extracted from tumors and adjacent normal tissue and the expression of PgR and microRNAs was assessed by RT-PCR. In addition, microRNAs were transfected into MCF-7 cells. The levels of PgR mRNA and protein were analyzed. **Results:** The PgR gene contains potential conserved binding sites for MicroRNAs 23a, 181a, 135a and 26b. Of these, miR- 23a and miR-181a showed inverse expression relative to the PgR expression in normal and tumor tissue, as expected. MicroRNA levels were determined in tumors of all three groups. The highest expression of microRNAs 23a, 181a and 26b was seen in IHC negative tumors with low levels of mRNA. Intermediate expression was seen in IHC negative tumors with high mRNA levels, and the lowest expression was detected in IHC positive tumors. Preliminary results suggest that over expression of microRNAs 23a, 181a and 26b in MCF7 cells decreased PgR levels. **Conclusions:** Our results suggest that microRNAs 23a , 181a and 26b regulate the level of the progesterone receptor in breast cancer and that tumors with relatively high mRNA levels may be deficient in PgR protein due to downregulation by microRNAs.

	mir181a			mir 23a			mir26b		
Tumor group	RQ	ST-err	ttest	RQ	ST-err	ttest	RQ	ST-err	ttest
IHC-, RT-PCR low	1	0.126	-	1	0.497	-	1	0.361	-
IHC-, RT-PCR high	0.75	0.555	0.578	0.722	0.655	0.646	0.699	0.128	0.505
IHC+, RT-PCR high	0.35	0.582	0.026	0.286	0.729	0.287	0.437	0.023	0.258

579 **General Poster Session (Board #6B), Sat, 1:15 PM-5:00 PM**

Collaboration of AR and ERα in conferring resistance to an aromatase inhibitor.

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Background: We have previously shown a role for AR overexpression in tamoxifen resistance in ERα-positive MCF-7 breast cancer cells; here we hypothesized that AR overexpression might similarly be involved in resistance to the aromatase inhibitor anastrazole (Anas). **Methods:** MCF-7 cells were transfected to express the aromatase gene (MCF-7 Arom), or the aromatase and AR (MCF-7 AR Arom cells). Western blot analysis was used to evaluate protein levels, MTT and soft agar assays to evaluate proliferation, luciferase reporter assays to evaluate transcriptional activities and confocal microscopy was used for localization. **Results:** Anas inhibited androstendione (AD)-stimulated growth in MCF-7 Arom cells but not in MCF-7 AR Arom cells. Similarly, Anas did not inhibit ERα transcriptional activity in MCF-7 AR Arom cells. Enhanced activation of pIGF-1R, pIRS-1, pAKT, and pMAPK were also observed in AR Arom cells, suggesting constitutive activation of nongenomic signaling in these cells. Consistent with activation of these potential treatment "escape" mechanisms, inhibitors of AKT and IGF-1R restored sensitivity to Anas. Sensitivity to Anas was also restored using the AR antagonist MDV3100, however use of Abiraterone acetate as a single agent most effectively blocked proliferation of AR-overexpressing cells. These results suggest that both AR and ERα must be blocked to restore sensitivity to hormonal therapies in AR overexpressing ERα-positive breast cancers. Unexpectedly, AR contributed to ERα transcriptional activity in MCF-7 AR Arom cells, as shown by inhibition with the AR antagonist bicalutamide. AR and ERα co-localized both in the cytoplasm and in the nucleus of AD+Anas-treated cells, suggesting potential activation of both non-genomic and nuclear-mediated effects when AR is overexpressed in ERα-positive cells. We confirmed these findings in breast cancer cells with acquired resistance to tamoxifen. **Conclusions:** These results show the necessity to block both AR and ER in patients whose tumors express elevated levels of AR. In addition, inhibitors to the AKT/IGF-1R signaling pathways or direct inhibition of androgen/estrogen synthesis provide alternative approaches to restore hormone sensitivity in resistant breast tumors.

580 General Poster Session (Board #6C), Sat, 1:15 PM-5:00 PM

Classifying circulating, mutation bearing tumor cells from breast cancer patients.

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Background: The treatment of advanced breast cancer demands systemic therapies that can address disease heterogeneity and the development of treatment resistance without a "real-time" molecular window into disease biology. New technologies have focused on increased capture and molecular analysis of circulating tumor cells (CTCs) including cells undergoing epithelial mesenchymal transition (EMT). We conducted a pilot experiment to test the efficiency of capture and cytokeratin (CK) detection and the presence of single point variants (SNV) to determine the best utility of scoring alternatives for CTC. **Methods:** EpCAM expressing CTC were recovered from breast cancer patients using CellSearch (Veridex) and LiquidBiopsy (Cynvenio Biosystems). EpCAM recovery and CK scoring were indexed in spiked samples and in 12 inflammatory breast cancer (IBC) patient samples using antibodies against CKs 7, 8 or CKs 1-8, 10, 13-16, 18, 19. Additionally, LiquidBiopsy template was analyzed using an Ampliseq 1.0 panel on the IonTorrent PGM. SNV present in the CTC but not white blood cell (WBC) negative controls were identified and where possible, compared to tissue biopsy SNV analyzed using Foundation One (Foundation Medicine). **Results:** CTCs were detected using CellSearch 10/12 (83%) (range 0-2502 CTC/7.5ml) and LiquidBiopsy 12/12 (100%) (range 6-2800 CTC/7.5mL). More CK positive events were scored using CKs 1-8, 10, 13-16, 18, 19 than CKs 7, 8 in patient samples. Upon sequencing, shared germline polymorphisms were observed in CTC and WBC. Conversely, 1 or 2 SNV were detected in the Epcam selected population but not WBC controls from 6/12 patients (frequency 1.1%-2.1% with 520-5160x coverage) with SNV observed in TP53, MPL, PIK3ca, MET and IDH1. All but one of the PIK3ca mutations were absent in evaluable tissue biopsy. **Conclusions:** CTC recovery and scoring are two separate events. Altered CK detection emphasized the need to tailor CTC classification to specific disease settings. Sequence analysis showed one correlated SNV among 6 evaluable comparisons to tissue reflecting variable analysis as well as the biologic disparity of metastatic disease. This pilot demonstrates the feasibility of using CTC for molecular analysis.

581 **General Poster Session (Board #6D), Sat, 1:15 PM-5:00 PM**

Prospective comparison of uPA/PAI-1 and EndoPredict-clin score in ER-positive, HER2-negative breast cancer: Impact on risk stratification and treatment decisions.

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Background: Adjuvant therapy decisions in breast cancer patients are based on accurate risk assessment. UPA/PAI-1 can be used for risk evaluation. Recently, the EndoPredict-clin score (EPclin), a second generation multigene test has been introduced into clinical practice. Aim of this prospective study is to compare risk assessment by uPA/PAI-1 and EPclin and to determine, how these parameters influence treatment decisions. **Methods:** 100 consecutive cases of ER-pos, HER2neg, intermediate risk breast cancer cases were enrolled in this study. EPclin and uPA/PAI-1 (for G2-tumors) were obtained by central pathology assessment of the patients´ surgical specimen. Type of adjuvant treatment was chosen after case discussion in an interdisciplinary tumor conference. **Results:** 94 Patients (pt) have been evaluated. Tumor grading within the presented cohort was as follows: G1: 15 pt (16%), G2: 66 pt (70%), G3: 13 pt (14%). 20 pt (21%) had positive axillary lymph node involvement. Tumor size was less than 1 cm in 27 pt (29%). EPclin could be assessed in 94 pt (100%). 32 pt (34%) were classified as “high risk” whereas 62 pt (66%) were classified as “low risk”. uPA/PAI was obtained from 54 pt (57%). 36 pt (67%) out of these 54 pt had high uPA/PAI-1 levels whereas 18 pt (33%) showed low uPA/PAI-1 levels. Only 2 pt (4%) with low uPA/PAI-1 levels were classified as “high risk” with EPclin, whereas 17 pt (32%) with high uPA/PAI-1 were classified as “low risk” via EPclin (p=0,003). In 29 cases (31%) treatment decision was influenced by EPclin: In 26 pt (28%) adjuvant chemotherapy (ctx) was omitted whereas in 3 pt (3%) ctx was added following the EPclin. **Conclusions:** This prospective study shows for the first time, that high risk status according to the EPclin score is strongly associated with a high risk status as defined by uPA/PAI-1. Providing analytically valid results for all patients evaluated EPclin’s clinical practicability was clearly superior to uPA/PAI-1. This finding, combined with the fact that EPclin assigns twice as many patients to the low risk group indicated that EPclin is a more versatile and powerful tool to help spare patients from chemotherapy than uPA/PAI-1.

582 General Poster Session (Board #6E), Sat, 1:15 PM-5:00 PM

Evaluation of the prognostic significance of RACGAP1, Ki67, and TOP2A mRNA expression in high-risk early breast cancer.

Kyriaki Pliarchopoulou, Helen Gogas, Christos A. Papadimitriou, Ralph M Wirtz, George Kouvatseas, Eleni Timotheadou, Flora Stavridi, Christos Christodoulou, Angelos Koutras, Nikolaos Pisanidis, George E. Pentheroudakis, Dimitris Bafaloukos, Epaminontas Samantas, Konstantine T. Kalogeras, Meletios A. Dimopoulos, Dimitrios G. Pectasides, George Fountzilas; Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece; STRATIFYER Molecular Pathology GmbH, Cologne, Germany

Background: Proliferation is a major process in carcinogenesis. RACGAP1 is a protein involved in cell growth regulation and metastasis, Ki67 is a known proliferation marker and TOP2A has a key role in DNA replication and remodeling. The aim of the present study was to explore the prognostic significance of a signature of proliferation markers, such as RACGAP1, Ki67 and TOP2A on disease-free survival (DFS) and overall survival (OS) in high-risk early breast cancer patients. **Methods:** A total of 1681high-risk breast cancer patients, enrolled in two consecutive phase III trials, were treated with anthracycline-based adjuvant chemotherapy. Formalin-fixed paraffin-embedded tumor tissue samples from 963 of these patients were extracted using a standardized fully automated isolation method for total RNA based on silica-coated magnetic beads, followed by multiplex RT-qPCR for assessing RACGAP1, Ki67 and TOP2A mRNA expression. CALM2 was included in the same reaction, as a reference gene. **Results:** After a median follow-up of 107 months, 289 patients (30.0%) demonstrated disease progression and 261 (27.1%) patients died. Univariate analysis revealed that poor OS was associated with high RACGAP1 mRNA expression ($p=0.0185$, log-rank), high Ki67 ($p=0.0219$), as well as high TOP2A ($p=0.0019$) mRNA expression, while in multivariate analysis only TOP2A retained significance (Wald's $p=0.008$). In an effort to improve prognostic significance, combinations of the expression of two or all three genes were tested, with low mRNA expression of the three genes being associated with improved DFS (HR=0.74, CI=0.56-0.98, $p=0.035$) and OS (HR=0.60, CI=0.42-0.85, $p=0.004$). However, in multivariate analysis, none of the combinations retained prognostic significance, except the combination of high RACGAP1 and TOP2A mRNA expression, which was found to be associated with decreased DFS (HR=1.26, CI=0.96-1.63, $p=0.092$) and OS (HR=1.49, CI=1.10-2.03, $p=0.009$). **Conclusions:** High RACGAP1 and TOP2A mRNA expression was found, in multivariate analysis, to be of adverse prognostic significance in high-risk early breast cancer patients treated with anthracycline-containing adjuvant chemotherapy.

583 General Poster Session (Board #6F), Sat, 1:15 PM-5:00 PM

Cardiac safety and efficacy of concomitant liposomal doxorubicin, docetaxel, and trastuzumab as neoadjuvant therapy in HER2-overexpressing breast cancer: A retrospective analysis.

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Background: Concurrent therapy of trastuzumab, anthracycline and taxane for the neoadjuvant treatment of breast cancer (BC) results in an improved rate of pathological complete response (pCR). However, there is considerable concern about the cardiac safety of this combination. The use of liposomal doxorubicin might be a valuable alternative with lower cardiotoxicity. We report cardiac safety and pCR-rate of a single arm, retrospective, multicenter analysis of neoadjuvant treatment for BC with liposomal doxorubicin, trastuzumab, and docetaxel. **Methods:** In this study 84 women with BC and HER2 overexpression were investigated in 3 oncological departments in Austria. All patients were treated with liposomal doxorubicin (50 - 60 mg/m^2), docetaxel (75 mg/m^2) and concurrent with trastuzumab for 6 cycles as neoadjuvant therapy. All patients were free of cardiovascular disease and had a left ventricular ejection fraction (LVEF) of $\geq$ 55%. Cardiac function was by LVEF and was examined at regular intervals(cycles 0-3, cycle 6, FU). Clinical response was evaluated by diagnostic breast imaging after cycles 3 and 6. All patients underwent surgery after neoadjuvant chemotherapy. The absence of any residual invasive cancer in the breast and axilla was defined as pathological complete response (pCR). Median follow up was 2.4 years. **Results:** Median age of the patients was 50 years. After 6 cycles of treatment the pCR rate was 46%. In this cohort a negative estrogen-and/or progesteron receptor was predictive for pCR ($p<0.001$). No patient progressed during treatment. None of the patients suffered symptomatic heart failure. Only one patient (1.6%) with asymptomatic LVEF of 45% was observed during follow-up. **Conclusions:** In this multicenter analysis we observed a considerably high rate of pCR in HER2-positive BC treated with liposomal doxorubicin, docetaxel and trastuzumab. The addition of liposomal doxorubicin instead of conventional doxorubicin or epirubicin entails a very favorable cardiotoxicity profile. This regimen is a safe treatment option in patients with HER-2 positive breast cancer.

584 **General Poster Session (Board #6G), Sat, 1:15 PM-5:00 PM**

The haplotype of three polymorphisms in the SATB1 promoter-region and impact on survival in breast cancer patients.

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Background: Special AT-rich sequence binding protein 1 (SATB1) has regulatory effects on gene expression and appears to play an important role in tumor progression. We screened the promoter region of the SATB1 gene for polymorphisms, evaluated the corresponding haplotypes regarding alterations in promoter activity in vitro and analyzed the impact of these haplotypes on the clinical course of breast cancer patients. **Methods:** 241 caucasian breast cancer patients who had been treated were enrolled in this retrospective analysis. The median follow up time was 93 months (4-155 months). PCR products from DNA of 10 healthy unrelated volunteers were analyzed to identify new polymorphisms within the promoter region. Genotyping was conducted using restriction length polymorphism and pyrosequencing. PCR constructs with the respective alleles from the four most frequent haplotypes were cloned into the vector pGEM-Teasy (Promega Corporation, Madison, WI, USA) and then transferred into the luc2-containing reporter vector pGl 4.10 Vector (Promega) for transfection of HEK293 cells. The pGl 4.73 Vector (Promega), containing hRluc, was used for norming the transfection rates. **Results:** Sequencing the region -3807bp to -2828 upstream from ATG of ten healthy blood donors, we found three single nucleotide polymorphisms SNPs consisting of base exchanges, -3600T>C, -3363A>G and -2984C>T.The SATB1 -3600T/-3363A/-2984C haplotype had a lower promoter activity than all other constructs in vitro and showed a significant association with the nodal status ($p=0.049$). Kaplan-Meier survival analysis revealed a significantly better survival for homozygous SATB1 -3600T/-3363A/-2984C haplotype carriers compared with heterozygous or the other haplotypes ($p=0.033$). **Conclusions:** The SATB1 -3600T/-3363A/-2984C haplotype is associated with lower promoter activity and appears to impact upon survival in breast cancer patients.

585 General Poster Session (Board #6H), Sat, 1:15 PM-5:00 PM

Predictive value of tumor infiltrating lymphocytes (TIL) for response to breast cancer neoadjuvant chemotherapy (NCT).

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Background: The association of tumor microenvironment immune response with outcome after breast cancer (BC) NCT has been suggested by several studies. However, the relevance of each TIL subpopulation is still controversial. The objective of this study was to evaluate the predictive and prognostic value of TIL before and after NCT in patients with BC. **Methods:** We analyzed TIL and CD68 cells in pre- and post-chemotherapy biopsies of BC patients treated with NCT (80.4% sequential AC-docetaxel). A tissue microarray with paired pre- and post-NCT biopsies was built, and stained with immunohistochemistry (IHC) for CD3, CD4, CD8, CD20, FOXP3 and CD68. Morphometric analysis (TIL count/mm^2) was performed after slide scanning and digitalization. **Results:** We included 121 consecutive patients with invasive BC, most of them with stages IIB (28%) or IIIA-C (56.4%). IHC phenotype: 50.4% Her2- hormone-sensitive (HS), 13.2% Her2+ HS, 10.7% Her2+ non-HS, and 21.5% triple negative. Pathologic complete response (pCR): 17.4%. Median overall survival (OS) and disease free survival (DFS) has not been reached (median follow-up: 60 months). Higher than median pre-NCT TIL infiltration was predictive of pCR to NCT: CD3 $>$ 172/mm^2 (p=0.001; Hazard Ratio [HR]: 9,61, 95% confidence interval [95%CI] 2.49–37.02); CD4 $>$ 67/mm^2 (p=0.001; HR: 8.82, 95%CI 2.43–31.96); CD20 $>$ 42/mm^2 (p=0.001; HR: 8.71, 95%CI 2.31–32.74). Logistic regression multivariate models including grade and IHC phenotype confirmed the independent predictive value of higher pre-NCT CD3, CD4, and CD20 for pCR. In the group of patients with HS Her2- BC without pCR (n=44), higher infiltration (cut-point: median value) by some TIL subpopulations and by CD68 cells in post-NCT residual tumor associated to lower DFS: CD8 $>$ 37/mm^2 (log-rank; p=0.04), CD20 $>$ 14/mm^2 (p=0.07) and CD68$>$ 39/mm^2 (p=0.06). **Conclusions:** Higher pre-treatment CD3, CD4 and CD20 TIL predicted pRC in patients with invasive BC receiving anthracyclines and taxanes NCT, while higher infiltration of residual tumor by CD8 associated to worse DFS in patients with HS Her2- BC without pCR after NCT. TIL might be useful as predictive factors in the setting of NCT for BC [Supported by GEICAM-Beca Ana Balil].

586 General Poster Session (Board #7A), Sat, 1:15 PM-5:00 PM

A study on the prevalence of HER2 genetic heterogeneity and its impact on breast cancer survival.

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Background: HER2 heterogeneity (GH) has been described in breast cancer that has conventionally been labeled as HER2 negative (FISH score <2.2). We aimed to ascertain the prevalence of GH in HER2 negative breast cancers and to investigate for any impact on survival. **Methods:** We reviewed HER2 FISH (Vysis) data for 158 primary breast cancer specimens from 2006-2010 which were 0 – 2+ on immunohistochemistry. HER2:CEP17 ratios were calculated for each of the 60 cells scored and cases were classified as HER2 GH according to the ASCO/CAP guidelines (GH = 5-50% tumor cells with a ratio >2.2). **Results:** 67% (106/158), 7% (11/158) and 26% (41/158) were HER2 negative, equivocal (FISH ratio 1.8-2.2) and positive respectively. GH was found in 43% and 100% of Her2 negative and HER2 equivocal patients respectively. Of the 117 cases (with FISH score <2.2), HER 2 GH was associated with higher histologic grade (grade 3: 81.8%, 52.3% and 33.3% in HER2 equivocal, negative with GH and negative without GH ($p = 0.007$). There were no significant associations with ER status or the presence of lymphovascular invasion. The mean overall survival was 63 months (95% CI 43-87), 118 months (95% CI 96-141) and 148 months (95% CI 148-168) for HER 2 equivocal, negative with GH and negative without GH patients respectively ($p=0.017$). In a subset analysis of HER2 negative (with FISH score <2.2), non metastatic patients, with at least a 4 year follow up period ($n=63$), mean overall survival was 79 months (95% CI 60-98), 119 months (95% CI 96-143) and 159 months (95% CI 139-180) for HER2 equivocal, negative with GH and negative without GH patients ($p=0.034$). GH remained a significant factor in the multivariate analysis irrespective of grade, stage and ER status ($p=0.046$). **Conclusions:** HER2 GH occurs in 100% of HER2 equivocal and 43% of HER2 negative breast cancers and is associated with higher histologic grade and poorer overall survival, irrespective of grade, stage or hormonal status.

587 **General Poster Session (Board #7B), Sat, 1:15 PM-5:00 PM**

Breast cancer screening: Biology of tumors detected by analog and digital mammography.

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Background: Population-based screening might be associated with a higher likelihood of a (ultra)low risk tumor assessed by the 70-gene signature (MammaPrint) (ultralow defined as indexscore >0.6, no distant metastasis observed at 5 years in the original 78 patients). The aim of this study is to determine the proportion of biologically (ultra)low risk tumors among the screen-detected tumors and to evaluate the impact of the analog versus digital screening technique. **Methods:** All Dutch breast cancer patients enrolled in the MINDACT trial (EORTC-10041), who were invited for the Dutch screening program (biennial, age 50-75), were included (n=1409). The proportions of 70-gene signature high, low and ultralow risk were calculated for patients with screen-detected (n=775), interval (n=390), and symptomatic, non-screening (n=244) carcinomas, taking into account analog vs. digital technology. Co-variants such as age, tumor size, grade, histological type, ER, HER2 and nodal status were included in the analyses. **Results:** Among the screen-detected tumors, 31.5% had a high risk, 31.2% a low risk and 37.3% an ultralow risk 70-gene signature result, compared to 47.4%, 28.5% and 24.1% among the interval carcinomas, respectively (p=0.001). Among the screen-detected carcinomas, 40.6% were detected using analog (n=315) and 59.4% using digital mammography (n=459). When using digital imaging a shift was seen among the screen-detected tumors in the proportions of high risk tumors from 27% to 35% and ultralow risk from 42% to 34%, low risk proportions remained the same (31%)(p=0.011). No such difference was seen for other tumor characteristics. **Conclusions:** Screen-detection was found to be associated with a higher likelihood of a biologically low risk tumor. The transition from analog to digital mammography resulted in a smaller proportion of ultralow risk and a larger proportion of high risk tumors among the screen-detected carcinomas.

588 General Poster Session (Board #7C), Sat, 1:15 PM-5:00 PM

Association of the canonical NF-κB pathway with clinical outcome measures in ER-negative breast cancer.

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Background: Although breast cancer morality rates have fallen, resistance to treatment remains a major problem. The NF-κB pathway regulates transcription of a wide range of genes involved in inflammation, proliferation and apoptosis and are hypothesized to play a role in tumor progression. **Methods:** Immunohistochemistry was employed to assess expression of members of the NF-κB pathway in a cohort of 544 breast cancer specimens with full clinical follow-up. Antibodies for the p65 subunit, phosphorylated p65 at the serine 536 residue (p-p65 S536), nuclear localization signal of p65 (p65 NLS), IKKα and IKKb had specificity confirmed by both a single band of appropriate size on a western blot and appropriate expression patterns in cell pellets treated with TNFα. **Results:** When the full cohort was considered patients with tumors that expressed high levels of cytoplasmic IKKα had significantly shorter disease free survival compared to those with low expression (P=0.015). Increased expression of nuclear p-p65 S536 was also associated with shorter disease free survival (P=0.005). By western blot analysis we observed that expression levels of p-p65 S536 were higher in MD-MBA-231 cells which are ER negative compared to MCF-7 cells that are ER positive, suggesting that NF-κB may have a prominent role in ER negative disease. However when the cohort was subdivided, by ER status the association observed for IKKα expression and shorter disease free survival was attenuated in ER positive tumors (p=0.008). In addition this attenuation with the ER positive cohort was also observed for nuclear p-p65 S536 (P=0.002). Other members of the pathway investigated (p65, p65 NLS and IKKb) were not associated with disease free survival. **Conclusions:** These results suggest that in the clinical setting the NF-kB canonical pathway is associated with poor prognosis in ER positive tumors and not with ER negative tumors as the cell line work would suggest. These results require validation in an independent cohort, but highlight the need to consider subtypes of breast cancer as individual diseases with increasingly different therapeutic targets.

589 **General Poster Session (Board #7D), Sat, 1:15 PM-5:00 PM**

Management of breast cancer during pregnancy: Results of a large registry from a single institution.

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Background: Given the rising trend of delaying pregnancy to later in life, more women are diagnosed with breast cancer during pregnancy. Management is still controversial and relies on expert guidelines. Thus the experience of single centres with high patients' volume remains of interest. **Methods:** All breast cancer patients (pts) diagnosed at the European Institute of Oncology (IEO) in Milan were included in a specific registry since 1995. **Results:** Out of 8340 patients < 47 y/o registered up to Dec 2012, 167 were diagnosed during pregnancy (2%). Median age was 36 years (24-47y). Median gestational age was 18 weeks (1-38 w). 73 % pts had a pT1-2 tumor, with positive nodes in 48%. 9,6% had luminal A, 38% luminal B, 26% basal like and 16% HER2+ tumors, according to St Gallen criteria. 29/167 pts (17%) opted for an induced abortion. Of the remaining 97 pts, 81 (84%) underwent definitive surgery during pregnancy; 58 (72%) and 23 pts (28%) had quadrantectomy and mastectomy, respectively. Immediate breast reconstruction was performed in 13 cases. Sentinel node procedure (SLN) was performed in 42 pts (52%), with positive axilla in 10 pts. 41 pts (51%) received chemotherapy during pregnancy. Regimens included weekly epirubicin (24 pts), EC/AC (12 pts), FAC/FEC (3 pts), q21 epirubicin (2 pts). No G3-G4 toxicities were reported. No pregnancy complications were observed, with the exception of 1 case of premature delivery at 28 weeks. Median gestational age at delivery was 36 weeks (29-40 w). No major malformations were observed. Gestational age at birth and birth-weight were similar in babies who received chemotherapy in-utero (36 w and 2555g) and in babies who did not receive gestational chemotherapy (37w and 2600g). At a median follow-up of 42 months (range: 1-178 m), all children had normal neurological and physical development with no late adverse effects observed. **Conclusions:** Managing breast cancer during pregnancy should follow standard practice as in non-pregnant pts. Surgeries like SLN and breast reconstruction were performed with no serious complications. Our results further emphasize the safety of anthracycline-based gestational chemotherapy without major effects on pregnancy course or fetal health.

590 General Poster Session (Board #7E), Sat, 1:15 PM-5:00 PM

ER as a predictor of early breast cancer (EBC) outcomes in patients.

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Background: Some ER-negative (ER-) breast cancers express low levels of estrogen receptors and approximately 12% express androgen receptors (Traina, T, et al. ASCO, 2012). Whether young premenopausal women (age <40) with ER- breast cancer (BC) who are more likely to retain ovarian function after adjuvant chemotherapy have a worse outcome than older women with ER- disease has not been widely investigated. **Methods:** We analyzed 2 adjuvant US Oncology BC studies: 99-016, 1830 BC patients randomized to doxorubicin/cyclophosphamide (AC)→Paclitaxel (P) (AC/P) vs AP→weekly P (no cyclophosphamide [C]) (AP/wP); and 01-062, 2611 patients randomized to AC→docetaxel (T) vs AC→T plus capecitabine (XT). ER+ patients received standard endocrine therapy following chemotherapy. Five-year DFS results did not show significant differences between the treatment arms on either study. The outcomes were analyzed for 5-year DFS by age ≤40yrs and >40yrs and by ER status. **Results:** In the two studies combined, ER- patients ≤40 had a superior DFS (84%) than ER- patients >40 (80%), while ER+ patients ≤40 had a worse 5-yr DFS (83%) than ER+ patients >40 (89%), although these findings were of borderline significance (see Table below). In 99-016, omitting C did not adversely affect outcomes in either age group, regardless of ER status. **Conclusions:** We did not observe worse outcomes in ER- patients ≤40 years compared to those >40 years in 2 US Oncology adjuvant chemotherapy trials, suggesting no adverse impact of assumed greater ovarian function following adjuvant chemotherapy in patients ≤40yrs. ER+ patients ≤40 had a worse DFS than ER+ patients >40. Omitting C in ER- patients ≤40 or >40 did not adversely affect outcome.

	ER negative		ER positive	
	n	5-year DFS (%) (95% CI)	n	5-year DFS (%) (95% CI)
01062 Age ≤ 40	171	88 (82 - 93)	168	86 (78 - 91)
>40	815	83 (80 - 85)	1457	91 (89 - 92)
99016 Age ≤ 40	92	75 (64 - 84)	102	79 (68 - 86)
>40	593	75 (71 - 79)	1,043	85 (83 - 88)
99016 (AC/P) Age ≤ 40	43	75 (58 - 85)	45	74 (55 - 85)
>40	301	74 (68 - 79)	526	86 (82 - 89)
99016 (AP/wP) Age ≤ 40	49	76 (56 - 88)	57	82 (68 - 91)
>40	292	77 (71 - 81)	517	85 (81 - 88)
Pooled 01062 and 99016				
Age ≤ 40	263	84 (79 - 88)	270	83 (78 – 88)
>40	1048	80 (77 - 82)	2500	89 (87 - 90)
P value		0.08		0.07

591 General Poster Session (Board #7F), Sat, 1:15 PM-5:00 PM

4EVER: Assessment of circulating tumor cells with a novel, filtration-based method, in a phase IIIb multicenter study for postmenopausal, HER2- negative, estrogen receptor-positive, advanced breast cancer patients.

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Background: The presence of circulating tumor cells (CTCs) has been shown to be of prognostic relevance for patients with early and advanced breast cancer (BC). The usefulness of CTC assessments depends on accurate cell counts and corresponding analysis of molecular targets. The aim of this sub study was to assess the feasibility of a novel, integrated CTC platform for automated cellular protein and nucleic acid analysis in a prospective multi-center study. **Methods:** The German 4EVER study included patients with postmenopausal, metastastic, ER positive, HER2 negative BC, who progressed after therapy with a non-steroidal aromatase inhibitor and were treated with exemestane and the mTOR inhibitor everolimus. Baseline blood samples (TransFix BD) were used for CTC analysis and processed on the modified Versant kPCR Sample Prep system using 8μm pore size Whatman Nuclepore track-etched membranes (GE Healthcare Piscataway, NJ). After CTC capture, immunostaining was performed for Cytokeratin 8/18/19 and CD45. CTCs were detected by image analytics after fluorescence scanning microscopy using a dedicated software solution implemented by Siemens. The data is summarized and correlated with baseline clinical characteristics. **Results:** CTC counts and clinical data were available for 111 blood samples (91.7%). CTCs were found in 75 patients (67,6%), 13 patients having 1 CTC, 38 having 2-9 CTCs and 24 patients having 10 or more CTCs. In an exploratory analysis the presence of CTCs was correlated with baseline patient and tumor characteristics. There were no associations with primary TNM stage, hormone receptor status or tumor type. **Conclusions:** CTC assessment with this novel filtration based method was feasible in a multi-center study setting. The CTC positivity rate was within the expected range. The follow-up of this study will give first insights, how the CTC measures of this platform can be used as a prognostic tool. As this CTC assessment platform was developed to perform additional automated cellular protein and nucleic acid analysis, the usefulness might derive from these analytic tools as well. Clinical trial information: NCT01626222.

592 General Poster Session (Board #7G), Sat, 1:15 PM-5:00 PM

Clinical and pathologic correlation of the activated form of the estrogen receptor (ER) in breast cancer (BC).

Jacques Bonneterre, Erard M. Gilles, Alexander A. Zukiwski, Jacques Bosq, Alexander Valent, Emilie Hutt, Suzanne A.W. Fuqua; Centre Oscar Lambret, Lille, France; Invivis Pharmaceuticals, Bridgewater, NJ; ARNO Therapeutics, Flemington, NJ; Institut Gustave Roussy, Villejuif, France; Baylor Breast Center, Houston, TX

Background: About 50% of ER positive (ER^{pos}) BC are resistant to hormone treatment. In absence of ligand, ERs are evenly distributed in nuclei in normal tissue. Upon ligand binding, ERs dimerizes and form a discrete focal subnuclear distribution pattern (FDP), which are associated with transcriptional activation of ER. This ER FDP is observed in BC. We hypothesized that in BC that the presence/absence of ER in the FDP could predict antiestrogen activity. This study describes an immunohistochemistry (IHC) method, by which a biomarker could be developed to investigate this hypothesis. **Methods:** 303 archived BC biopsies were obtained along with clinical and pathology data. Biopsies were analyzed for standard HES, ER, progesterone receptor (PR) and Ki67. PR positivity was determined with distinct antibodies to the A and B isoforms. The A-ER and D-ER nuclear patterns were analyzed at x1000 magnification. **Results:** Mean age; 58 (17 -89). Histology: ductal 85% lobular 13%, other 2%; 84% ER^{pos} and 84% either PRA^{pos} or PRB^{pos}, 7% ER^{pos} and 7% PRA^{pos} or PRB^{pos} only. All but 3 ER^{pos} cases had received AntiEs; Adj. chemotherapy 51%, Stage: I 51%, II 43%, III 6 %. Grade: I 24%, II 51%, III 25%. Median follow up 31 months (mo). Local or distant progression (PD) was 19%. ER status was D-ER in 78% and A-ER in 22% of the biopsies and PD was associated with the D-ER pattern ($p = 0.06$), e.g. the hypothetically non-functional pattern D-ER was associated with a higher rate of PD (4 vs 35). With DFS defined as time to PD or death (5 year cut off), ER^{pos} was better that ER^{neg} (HR= 0.38, $p = 0.016$). For ER^{pos} BC, A-ER was numerically better than D-ER (HR =0.3, p=0.24 two-sided). In univariate analyses, A-ER pattern was associated with higher grade (p=0.035), anisonucleosis (p=0.06), mitotic index (p=0.02), and Ki67 (=0.08). No association was found between ER pattern and age, stage or HER2 status. **Conclusions:** This study supports the hypothesis that AntiEs are mainly active in BC with A-ER pattern, which is targetable by AntiEs. A larger number of events are needed to reach significance in time-dependent analyses and confirmatory studies are warranted.

593 **General Poster Session (Board #7H), Sat, 1:15 PM-5:00 PM**

Identification of the activated form of the progesterone receptor (PR) in breast cancer (BC).

Jacques Bosq, Jean-Michel Caillaud, Carol A. Lange, Suzanne A. W. Fuqua, Joyce O'Shaughnessy, Erard M. Gilles, Alexander A. Zukiwski, Jacques Bonneterre; Institut Gustave Roussy, Villejuif, France; Biodoxis, Paris, France; University of Minnesota Masonic Cancer Center, Minneapolis, MN; Baylor College of Medicine, Houston, TX; Texas Oncology-Baylor Charles A. Sammons Cancer Center, The Woodlands, TX; Invivis Pharmaceuticals, Bridgewater, NJ; ARNO Therapeutics, Flemington, NJ; Centre Oscar Lambret, Lille, France

Background: Upon ligand binding, PRs dimerize and form a discrete focal subnuclear distribution pattern (FDP), which are associated with transcriptional activation of PR (APR). FDP and are observed in BC independently of menopausal status. The feasibility of using an IHC technique to characterize the PR functional status has previously been reported in BC and presence/absence of APR is hypothesized to predict anti-progestin activity. This study describes an immunohistochemistry (IHC) method, by which a biomarker could be developed to investigate this hypothesis. **Methods:** 303 paraffin embedded/formalin fixed archival BC samples were processed with PR-A or PR- B isotype specific antibodies. Nuclear morphology was analyzed with standard microscopy at x1000, interpretation of the IHC slides was done by an experienced pathologist. Standard PR, estrogen receptor (ER), and Ki67 testing were done. Tumor grading/stage was obtained from the patients' records. **Results:** Histology was ductal 85%, lobular 13%, other 2%. Consistent with prior research observations, tumors had two PR nuclear morphologies: 1. Diffuse pattern (D) where the PR was distributed evenly in a fine granular pattern or, 2. Aggregate pattern (A) where the PR is distributed in discrete clumps or aggregates. This defined 3 tumor phenotypes: A cells only (A), D cells only (D), and a heterogenous mix of A+D cells (AD). The APR^{pos} group is defined as the A and A+ D phenotypes. Tumors were PR positive in 76% for PRA and 80% for PRB. Tumors were APR^{pos} for PRA in 23% and independent of PR intensity score, ER, Ki67, and HER2, but associated with higher PR % positivity and higher tumor grade. Tumors were APR^{pos} for PRB in 22% and associated with lower PR intensity and higher tumor grade, independent of ER^{pos} %, PR^{pos} %, Ki67 and HER2. **Conclusions:** PR positive BC tumors can be grouped in two categories based on PR nuclear morphology: 1. a group with diffuse and homogenous nuclear staining, 2. a group with heterogeneous area of cells having a nuclear pattern consistent with a functional or activated PR (APR). The described IHC technique to identify APR has the potential to be developed as companion diagnostic as a potential predictor of anti-progestin efficacy in patients with BC.

594 General Poster Session (Board #8A), Sat, 1:15 PM-5:00 PM

Prediction of early and late distant recurrence in early-stage breast cancer with Breast Cancer Index.

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Background: Breast Cancer Index (BCI) is a continuous risk index based on the combination of HOXB13:IL17BR (H:I) and the Molecular Grade Index (MGI) that estimates the individual risk of recurrence in ER+, LN- breast cancer patients. In the current study, a modified BCI model was developed using untreated breast cancer patients in order to evaluate its pure prognostic value, and to better optimize BCI for both early and late risk assessment. **Methods:** A model was built by linearly combining H:I and MGI weighted by their corresponding Cox regression coefficients using ER+ LN- patients from the untreated arm of the prospective Stockholm trial (N=283). Validation was performed in 2 independent ER+, LN- cohorts: the TAM arm of the Stockholm trial (N=317), and a multisite cohort of TAM-treated patients (N=358). Correlation of BCI with distant metastasis was evaluated by Kaplan-Meier analysis using the log rank test, and multivariate analysis adjusting for standard prognostic factors was performed using Cox proportional hazards. **Results:** The BCI linear model was significantly associated with risk of cumulative (0-10y), early (<5y) and late (≥5y) distant metastasis. Based on pre-specified cutpoints, BCI classified 64% and 55% patients as low-, 21% and 22% as intermediate-, and 16% and 23% as high-risk, with 10-y rates of distant recurrence (95% CI) of 4.8% (1.7-7.8%) and 6.6% (2.9–10.0%), 11.7% (3.1–19.5%) and 23.3% (12.3-33.0%), 21.1% (18.5–32.0%) and 35.8% (24.5–45.5%), in the Stockholm TAM and multisite cohort, respectively. **Conclusions:** BCI demonstrated significant prognostic performance beyond clinicopathological factors to predict cumulative, early and late risk of recurrence in early stage breast cancer patients. Use of BCI at diagnosis should enable clinicians to identify patients who are at high risk of late recurrence and may benefit from an additional 5y of hormonal therapy.

	Stockholm TAM (N=317)		Multisite cohort TAM-treated (N=358)	
	HR (95% CI)	P	HR (95% CI)	P
Cumulative (0-10y)	4.2 (1.5, 11.8)	0.006	9.3 (4.2, 20.5)	<0.0001
Early (<5y)	11.0 (1.8, 67.4)	0.010	10.5(3.7, 29.9)	<0.0001
Late (≥5y)	3.59 (1.07, 12.0)	0.039	11.7 (3.1, 43.6)	0.0003

595 General Poster Session (Board #8B), Sat, 1:15 PM-5:00 PM

Effect of PK-guided tamoxifen dose escalation on endoxifen serum concentrations in CYP2D6 intermediate and poor metabolizers.

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Background: Breast cancer patients with absent or reduced CYP2D6 activity may benefit less from tamoxifen treatment because of impaired biotransformation to the active metabolite endoxifen. We investigated whether a temporary one-step dose escalation of tamoxifen in CYP2D6 poor (PM) and intermediate metabolizers (IM) could increase endoxifen serum concentration to a similar level observed in CYP2D6 extensive metabolizers (EM) without increasing toxicity. **Methods:** From a prospective study population of early breast cancer patients using tamoxifen, 12 CYP2D6 poor and 12 intermediate metabolizers were selected and included in a one-step tamoxifen dose escalation study during two months. The escalation dose (120 mg maximum) was calculated by multiplying the individual's endoxifen level divided by the median endoxifen concentration (33.7 nM) observed in CYP2D6 extensive metabolizers by 20 mg. Toxicity was assessed and all patients returned to the standard dose of 20 mg after two months. **Results:** Tamoxifen dose escalation in CYP2D6 poor and intermediate metabolizers significantly increased endoxifen concentrations (PMs: from 8.0 nM to 27.3 nM, $p<0.001$; IMs: from 17.8 nM to 30.3 nM, $p=0.002$) without increasing side effects. In intermediate but not in poor metabolizers dose escalation increased endoxifen to levels comparable with those observed in extensive metabolizers using tamoxifen 20 mg once daily (33.7 nM). **Conclusions:** CYP2D6 genotype and endoxifen guided tamoxifen dose escalation increased endoxifen concentrations without increasing short term side effects. Whether such tamoxifen dose escalation is effective and safe in view of long term toxic effects is uncertain and needs to be explored. Clinical trial information: NTR1509.

596 General Poster Session (Board #8C), Sat, 1:15 PM-5:00 PM

Independent characterization by duel staining of progesterone receptor (PR) and estrogen receptor (ER) in breast cancer (BC).

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Background: The oncology literature indicates that ER and PR are linked and in BC the presence of PR usually indicates functional ER. BCs express both ER and PR to varying degree, but little has been published on expression of ER + PR in individual cancer cells. The goal of this study is to 1. Determine the expression ER and PR at the cellular level, 2. Determine if ER and PR are expressed in the same BC cells. If ER and PR are separate, this may indicate that antiestrogens and antiprogestins may target different cells. **Methods:** Archived 1° BC specimens were processed using standard IHC techniques for ER/PR testing. The procedure consisted of sequential double staining on the same microtone section, where the PR was visualized through brown staining using HRP/DAB, and the ER was visualized through red staining using AP/Permanent Red. The initial testing on 13 tumor samples utilized a duel anti-PR-A/B antibody (Ab) and an ER Ab. The next 63 tumor samples utilized; 1. anti-ER and anti-PR-A Abs, 2. anti-ER and anti-PR-B Abs. A pathologist experienced with IHC, interpreted and enumerated the cells staining positive for ER only, for PR only and cells staining positive for both ER & PR. The number of cells expected to be stained for both ER & PR by chance can be calculated as the rate of total ER by the rate of total PR and compared with the observed rate (paired rank test). ER/PR positivity is defined as $\geq$ 5% cells positive. **Results:** In the first series, 11/13 tumors were ER^{pos}, 13/13 were PR^{pos}, 7/13 tumors had both ER & PR expressed in 5-20% (median 5%) of the same tumor cells. In the 2^{nd} series of 63 tumors; 1. 50/53 were ER^{pos}, 52/53 were PRA^{pos} and 44/53 had both ER & PRA expressed in $<$5-20% (median 5%) of the same tumor cells, 2. 44/52 were ER^{pos}, 52/52 were PRB^{pos} and 42/52 tumors had both ER & PRB expressed in $<$5-20% (median 10%) of the same tumor cells. Areas of ER or PR only predominance were frequent. A paired rank test indicates that the observed rate (median 9%) of ER/PR duel staining is less than predicted (median 18%, $p < 0.000$). **Conclusions:** ER & PR were expressed in the majority of tumors examined with a minority the tumor cells expressing both ER & PR. These data support evaluating antiprogestins as a different therapeutic target from ER.

597 **General Poster Session (Board #8D), Sat, 1:15 PM-5:00 PM**

CYP2D6 genotype related to tamoxifen efficacy: An analysis with exclusion of potential false CYP2D6 genotype assignment caused by loss of heterozygosity in tumor tissue.

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Background: The clinical importance of CYP2D6 genotype as predictor of tamoxifen efficacy is still unclear. Recent genotyping studies on CYP2D6 using DNA derived from tumor blocks have been criticized because loss of heterozygosity (LOH) in tumors may lead to false genotype assignment. **Methods:** Postmenopausal early breast cancer patients who were randomized to receive tamoxifen, followed by exemestane in the Tamoxifen Exemestane Adjuvant Multinational trial (TEAM) were genotyped for 5 CYP2D6 variant alleles. CYP2D6 genotypes and phenotypes were related to disease free survival during tamoxifen use (DFS-t) in 731 patients. By analyzing three microsatellites flanking the CYP2D6 gene, patients whose genotyping results were potentially affected by LOH were excluded. **Results:** Analysis of the CYP2D6 alleles and the microsatellite markers demonstrated heterozygosity for at least one of the CYP2D6 alleles or microsatellite markers in 97.7% of patients with a specified CYP2D6 phenotype. The 14 patients (2.3%) with a homozygous CYP2D6 genotype in which no heterozygosity could be demonstrated for the microsatellite markers were excluded from the analysis. No association was found between the CYP2D6 genotype or predicted phenotype and DFS-t. **Conclusions:** In postmenopausal early breast cancer patients treated with adjuvant tamoxifen followed by exemestane neither CYP2D6 genotype nor phenotype was associated with DFS-t. This is in accordance with two recent studies in the BIG1-98 and ATAC trials. Our study is the first CYP2D6 association study using DNA from paraffin embedded tumor tissue in which potentially false interpretation of genotyping results because of LOH was excluded.

598 **General Poster Session (Board #8E), Sat, 1:15 PM-5:00 PM**

A comparative analysis of distant recurrence risk assessments by Oncotype DX recurrence score alone and integrated with clinicopathologic factors in early-stage breast cancer.

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Background: Treatment planning for patients with node negative, ER-positive, HER-2 negative breast cancer often incorporates the use of prognostic and predictive tools like Oncotype DX. Prior to the availabilty of Oncotype DX, clinicopathologic factors such as age, nodal status, tumour size and grade were used to determine risk of recurrence (ROR). RSPC represents a validated formal integration of oncotype DX recurrence score (RS) and clinicopathologic factors that further refines prognostic accuracy. RSPC does not improve the prediction of likelihood of chemotherapy benefit. The objective of this study was to compare distant recurrence risk assessment by RS and RSPC. **Methods:** We included patients with node negative, ER-positive, HER2-negative breast cancer who had Oncotype DX testing routinely or on clinical trial. We retrospectively reviewed patient charts and extracted clinicopathological and RS data. We calculated the RSPC using the RSPC educational tool. A comparative analysis was performed looking at the statification of patients into low (LR), intermediate (IR) and high (HR) ROR groups by RS and RSPC. The cut offs for low, intermediate and high risk by the RSPC were set to less than 12%, 12-20% and more than 20% risk of distant recurrence at 10yrs, corresponding to the risks of recurrence associated with the RS categories. **Results:** We identified 658 patients from 5 academic hospitals in Ireland and the US. Oncotype DX RS classified the following proportions of patients into three risk groups for distant recurrence: LR, n=334 (50.5%), IR, n=259 (39.4%), HR, n=67 (10.1%). RSPC classified the following proportion of patients into the three risk groups for recurrence: LR, n= 455 (69.1%), IR, n=110 (16.7%), HR, n=93 (14.1%). RSPC reclassified 72.6% (n=188) of the IR group (59.1% (n=153) from IR to LR and 13.5% (n=35) from IR to HR). RPSC reclassified 10.5% (n=35) of the LR group (8.1% (n=27) from LR to IR, and 2.4% (n=8) from LR to HR). RSPC reclassified 25.3% (n=17) of the HR group (17.9% (n=12) from HR to IR, and 7.4% (n=5) from HR to LR). **Conclusions:** RSPC reclassified 240 patients (36.5%) and was most helpful reassigning the IR group.

599 **General Poster Session (Board #8F), Sat, 1:15 PM-5:00 PM**

Differential impacts of Oncotype DX and Mammostrat prognostic indices upon the management of ER+ N0 breast cancer.

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Background: Oncotype DX (Genomic Health, Redwood City CA) and Mammostrat (Clarient, Aliso Viejo CA) are two distinct prognostic measures currently marketed to facilitate adjuvant chemotherapy decision making for ER+ breast cancer patients and their physicians. Both assays define three prognostic strata—favorable, intermediate, and unfavorable. Both assays were also validated in the same retrospective cohorts, but there is significant discordance between these assays, suggesting that assay selection may affect clinical decisions. **Methods:** We have previously reported that Oncotype DX significantly reduces adjuvant chemotherapy use in 89 consecutive ER+, N0 patients for whom this assay was ordered at our institution. Mammostrat assays were performed on 46 of these cases for which tumor blocks were available. Decision analysis was applied to determine changes in management that would have been most likely if Mammostrat had been substituted for Oncotype DX. **Results:** Oncotype DX and Mammostrat were concordant for prognostic strata in just 11 (24%) cases. Oncotype DX predicted a more favorable prognosis than Mammostrat in 27 (59%) cases, while Mammostrat predicted a more favorable prognosis in the remaining 8 (17%) cases. As shown in the Table, Oncotype DX reduced chemotherapy utilization whereas Mammostrat would have increased it. **Conclusions:** Despite being validated in identical patient cohorts, Oncotype DX and Mammostrat are frequently discordant and may often affect adjuvant treatment decisions in opposite directions.

Adjuvant Rx	Conventional criteria alone	Oncotype DX	Mammostrat
Hormones alone	59%	74%	35%
Chemotherapy plus hormones	41%	26%	65%

600 General Poster Session (Board #8G), Sat, 1:15 PM-5:00 PM

Efficacy and safety of first-line (1L) pertuzumab (P), trastuzumab (T), and docetaxel (D) in HER2-positive MBC (CLEOPATRA) in patients previously exposed to trastuzumab.

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Background: CLEOPATRA is a global phase III trial of P + T + D vs placebo + T + D in HER2-positive 1L MBC. Results showed a significant improvement in PFS (Baselga NEJM 2012) and OS (Swain SABCS 2012) favoring P + T + D. CLEOPATRA started recruitment in 2008 soon after the approval of T in the adjuvant setting in 2006 and mandated a disease-free interval (DFI) of ≥12 mos from the end of adjuvant therapy to MBC diagnosis. Due to this, a low proportion of pts with prior T exposure was included. Here we present the efficacy and safety of 1L P + T + D in the subset of pts in CLEOPATRA with prior T exposure. **Methods:** Pts received P + T + D or placebo + T + D, had a DFI ≥12 mos, baseline left ventricular ejection fraction (LVEF) ≥50% and no LVEF decline to <50% during/after prior T therapy. Exploratory analyses of PFS and OS in pts with (neo)adjuvant therapy with or without T were conducted. **Results:** Of the study population, 47% had received (neo)adjuvant therapy and 11% had received (neo)adjuvant T; 82% of the prior T group came from Europe or North America. A univariate Cox regression analysis did not identify prior T therapy as a statistically significant risk factor for developing left ventricular systolic dysfunction (LVSD). However, due to the low number of LVSD events overall, this analysis has limited sensitivity. **Conclusions:** Data from CLEOPATRA show that pts with HER2-positive 1L MBC who have received prior T (DFI ≥12 mos) derive the same magnitude of benefit from the combination of P + T + D when compared with the whole study population or those who are T-naïve. This is in agreement with prior evidence of the activity of P + T in pts pretreated with T (Baselga JCO 2010). Efficacy and safety of P-T-based therapy is being explored in the PERUSE and PHEREXA trials, in a pt population with wider exposure to prior T and a shorter DFI, which may better represent current clinical practice. Clinical trial information: NCT00567190.

	Placebo + T + D	P + T + D
	Median PFS, mos	
All pts n = 808	12.4	18.5
	HR 0.62 (0.51, 0.75)	
	p < 0.0001	
(Neo)adjuvant therapy with T n = 88	10.4	16.9
	HR 0.62 (0.35, 1.07)	
(Neo)adjuvant therapy without T n = 288	12.6	21.6
	HR 0.60 (0.43, 0.83)	
Median OS		
All pts n = 808	HR 0.66 (0.52, 0.84)	
	p = 0.0008	
(Neo)adjuvant therapy with T n = 88	HR 0.68 (0.30, 1.55)	

601 General Poster Session (Board #8H), Sat, 1:15 PM-5:00 PM

Leptomeningeal disease and breast cancer: Relationship of outcome and subtype.

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Background: Breast cancer (BC) is one of the most common tumors to involve the leptomeninges. Outcome of leptomeningeal disease (LMD) across BC subtypes is not well documented. We aimed to characterize clinical features and outcomes of LMD based on BC subtypes. **Methods:** We retrospectively reviewed medical records of patients diagnosed with LMD from BC (1997 to 2012). All patients had BC. Cases of LMD were based on the presence of neoplastic cells on cerebrospinal fluid examination and/or evidence of LMD by imaging studies. Survival was estimated by the Kaplan-Meier method and significant differences in survival were determined by Cox proportional hazards or log-rank tests. **Results:** 232 patients were included, 189 of them had available tumor subtype classified as: hormone receptor positive (HR+) BC N=67 (35.5%), human epidermal growth factor receptor 2 positive (HER2+) N=55 (29%), and 67 (35.5%) triple-negative BC (TNBC). Median age at diagnosis of LMD was 49.7 years. (Range 24-89). Median overall survival (OS) from LMD diagnosis across all subtypes was 3.1 months (95% CI, 2.5 to 3.7). Median OS correlated with BC subtype: 3.7 months (95% CI: 2.4, 6.0) in HR+, 4.0 months (95% CI: 2.6, 6.9) in HER2+, and 2.2 months (95% CI: 1.5, 3.0) in TNBC, (p=0.0002). There was an 11.4% chance a patient diagnosed with LMD would survive 1 year and the chance of surviving at least 3 years was 1.3%. When age was used as a continuous variable, older age was associated with worse outcome ($p<0.0001$). Patients with HER2+ BC and LMD were more likely to have received systemic therapy (ST) (70%), compared to HR+ (41%) and TNBC (41%) (p=0.002). 38% of patients with HER2+ BC received HER2 directed therapy. There was no difference in the use of intrathecal therapy (IT) (52%) across subtypes (p=0.3). Use of IT therapy ($p<0.0001$) and ST ($p<0.0001$) were both associated with improved age-adjusted OS. After adjusting for age, ST, there was no difference in OS between patients with HR+ and HER2+ BC ($p=0.14$), but a significant difference remained between TNBC and HER2+ BC ($p < 0.0001$). **Conclusions:** LMD carries a dismal prognosis. Our data shows that OS correlates with tumor subtype. Patients with TNBC had a significantly shorter OS compared to patients with HER2+ BC. New treatment strategies are needed.

602 General Poster Session (Board #9A), Sat, 1:15 PM-5:00 PM

Efficacy of trastuzumab re-therapy in routine treatment of HER2-positive breast cancer patients who relapsed after completed (neo-)adjuvant anti-HER2 therapy.

Lars Christian Hanker, Thomas Hitschold, Tobias Hesse, Andrea Grafe, Frank Gerhard Foerster, Jan Klaus Schroeder, Jan Janssen, Dietmar Arno Reichert, Carsten Hielscher, Jasmin Greinemann, David Julian Borquez, Marcus Schmidt; Universitaetsklinikum Schleswig-Holstein, Campus Luebeck, Klinik für Frauenheilkunde und Geburtshilfe, Luebeck, Germany; Klinikum Worms gGmbH, Worms, Germany; Diakoniekrankenhaus Klinik fuer Frauenheilkunde, Rotenburg, Germany; MVZ Nordhausen gGmbH, Nordhausen, Germany; Schwerpunktpraxis fuer Gynaekologische Onkologie und Palliativmedizin, Chemnitz, Germany; Praxis fuer Haematologie und Onkologie, Muehlheim, Germany; Gemeinschaftspraxis für Hämatologie und Onkologie, Westerstede, Germany; Gynäkologie Kompetenzzentrum Stralsund, Stralsund, Germany; iOMEDICO AG, Freiburg, Germany; Onkologische Schwerpunktpraxis, Bergisch Gladbach, Germany; Department of Obstetrics and Gynecology, Johannes Gutenberg University, Mainz, Germany

Background: Addition of trastuzumab (Roche; T) to chemotherapy (CT) has improved outcomes in patients (pts) with HER2+ breast cancer at all stages, including locally advanced and metastatic disease. Anti-HER2 re-treatment with T is an increasingly used therapy option for the treatment of recurrent/metastatic breast cancer (MBC). However, limited data on T re-treatment is currently available. **Methods:** Patients with locally recurrent and/or MBC who received T re-therapy were included in this non-interventional study. Among 232 pts enrolled at 121 sites in Germany, 174 pts (33 locally recurrent disease, 141 MBC) were already sufficiently documented to be analyzed for efficacy of T re-therapy in this ongoing study. Progression-free survival (PFS) was assessed by the investigator. **Results:** The median disease-free interval (calculated from the time of resection of the primary tumor to diagnosis of local recurrence/MBC) was 3.1 years. Median duration of re-therapy with T was 9.3 months. The median PFS of all patients was 10.1 months (95% confidence interval (CI), 8.5 to 13.1). PFS for pts with only locally recurrent disease (n= 33) was 23.6 months. PFS for MBC pts (n=141) was 8.9 months (95% CI, 7.4 to 10.6). For pts with visceral metastases (n=96) a PFS of 8.0 months compared to 10.1 months in patients with only non-visceral (n=45) was recorded. 104 pts were re-treated with T + CT (>70% paclitaxel, vinorelbine, capecitabine or docetaxel alone; PFS= 9.3 months), 26 pts with T + hormonal therapy (HT) (mostly anastrozole, fulvestrant, exemestane, letrozole or tamoxifen; PFS=10.1 months), 24 pts with T+CT+HT (PFS= 19.9 months) and 20 pts with T monotherapy (PFS= 9.4 months). **Conclusions:** This study provides clinical evidence that re-application of T in combination with either CT, HT or alone is effective in the routine treatment of patients with MBC and/or locally recurrent disease. The benefit observed for pts receiving first-line treatment with T in combination with taxane in pivotal trials as well as recently published data seems comparable to the presented results of pts receiving T re-therapy.

603 General Poster Session (Board #9B), Sat, 1:15 PM-5:00 PM

Trastuzumab-based adjuvant chemotherapy for breast cancer: Early myocardial dysfunction detected by "speckle tracking" echocardiography (STE).

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Background: While anthracycline-induced type 1 cardiotoxicity is well established, type 2 trastuzumab (TZM)-induced cardiotoxicity, although less relevant and reversible, is nonetheless significant in combination with other drugs, such as taxanes (TAX). A paradigmatic clinical example of this regimen is the adjuvant setting of breast cancer patients overexpressing HER-2. In the present study we chose STE with longitudinal and circumferential Strain (S) and Strain Rate (SR), as a very sensitive tool to timely identifying left ventricular dysfunction. The biological markers of chronic inflammation/oxidative stress were also studied. **Methods:** A phase IV prospective non-randomized study was carried out to assess cardio-toxicity induced by the combination of epirubicin (EPI) + TAX followed by TZM administered with the conventional schedule in adjuvant setting of breast cancer patients (pts) overexpressing HER-2. Inclusion criteria: 18–70 y, histologically confirmed HER-2+ve breast cancer candidates for TZM-based 3 weekly regimen; LVEF ≥55%; ECOG PS score 0-1, no history of cardiac disease. STE parameters (longitudinal and circumferential S and SR) and chronic inflammation (IL-6 and TNF-a)/oxidative stress (reactive oxygen species) markers were assessed at baseline before TZM and after each of the subsequent 18 TZM administrations. **Results:** Forty pts (mean±SD age 53±10 y) were assessed up to the 8^{th} TZM administration. A progressive reduction of longitudinal SR was observed, becoming significant from the 4^{th} TZM dose (0.65±0.18 s-1 vs 0.81±0.16 s-1, $p<0.005$); a significant reduction of circumferential SR (0.60±0.15 s-1 vs 0.51 ±0.14 s-1, $p< 0.01$) and rotation index was also observed from the 2^{nd}TZM dose. These changes are all indicative of myocardial systolic dysfunction. No changes of biological parameters were observed. **Conclusions:** The sequential administration of TZM after EPI/TAX induced an early left ventricular dysfunction detected by STE which persisted at least up to the 8^{th} TZM administration. This study is in progress with close monitoring of pts and its ultimate goal is to select pts candidates for an effective cardio protective treatment.

604 General Poster Session (Board #9C), Sat, 1:15 PM-5:00 PM

Quantitative measurements of p95HER2 (p95) protein expression in tumors from patients with metastatic breast cancer (MBC) treated with trastuzumab: Independent confirmation of the p95 clinical cutoff.

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Background: Expression of p95 in HER2-positive breast cancer is potentially a major determinant of trastuzumab resistance because p95 lacks the trastuzumab binding site while retaining kinase activity. Previously, an optimal clinical cutoff for a continuous measurement of p95 expression was defined in a training set of trastuzumab-treated MBC patients (Clin Cancer Res, 16:4226, 2010). **Methods:** Quantitative H2T (HERmark HER2-total) and p95 assays (VeraTag, Monogram Biosciences) were retrospectively performed on formalin-fixed, paraffin-embedded tumors from an independent series of 240 trastuzumab-treated MBC patients. The pre-specified cutoff for p95 was tested to determine whether p95 above the cutoff in the HER2-positive subset correlated with worse progression-free survival (PFS) and overall survival (OS), as was observed in the training set. P95 expression was also assessed by immunohistochemistry (IHC) using the same antibody as the p95 VeraTag assay. **Results:** In the subset of tumors assessed as H2T-positive (N=190), p95 VeraTag values above the pre-defined cutoff correlated with shorter PFS (HR=1.41; p=0.043) and shorter OS (HR=1.72; p=0.021) where both outcomes were stratified by hormone receptor status and tumor grade. The hormone receptor positive patients (N=78) primarily drove the shorter PFS (HR=2.08, p=0.0026) and OS (HR=2.28, p=0.0099) observed in the p95-high subset. In contrast to the quantitative p95 VeraTag measurements, p95 IHC was not significantly correlated with outcomes. **Conclusions:** A clinical p95 cutoff (VeraTag assay) predictive of clinical outcomes derived from a previous training dataset was confirmed in a second independent clinical series. In contrast, p95 IHC did not correlate with outcomes. The observed consistency in the p95 VeraTag cutoff across different cohorts of MBC patients treated with trastuzumab justifies additional studies employing blinded analyses in larger series of patients. Clinical relevance of p95 protein expression remains to be established in a controlled clinical trial.

605 General Poster Session (Board #9D), Sat, 1:15 PM-5:00 PM

Phase (Ph) I/II study of investigational Aurora A kinase (AAK) inhibitor MLN8237 (alisertib): Updated ph II results in patients (pts) with small cell lung cancer (SCLC), non-SCLC (NSCLC), breast cancer (BrC), head and neck squamous cell carcinoma (HNSCC), and gastroesophageal cancer (GE).

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Background: MLN8237 is an investigational oral AAK inhibitor being evaluated in pts with hematologic (Ph III) and non-hematologic malignancies. We report here Ph II results from a, 5-arm study of single agent MLN8237 in pts with advanced, predominantly refractory, solid tumors (NCT01045421; closed for enrolment). **Methods:** Pts ≥18 years with relapsed/refractory disease measurable by RECIST, ECOG PS 0–1, and ≤2 prior (≤4 for BrC pts) cytotoxic chemotherapy regimens were enrolled. Pts with stable brain metastases were eligible. Pts were treated at the recommended Ph II dose; 50 mg BID for 7 d in 21-d cycles. For each cohort, a Simon's 2-stage design was employed for Ph II, with ≥2 responses required in the first 20 response-evaluable pts to proceed to stage 2. The primary endpoint was overall response rate (ORR) by RECIST v1.1; safety and progression-free survival (PFS) were key secondary endpoints. **Results:** As of Dec 2012, 47 SCLC, 23 NSCLC, 49 BrC, 45 HNSCC and 47 GE pts in Ph II were response-evaluable (median age, 61 yrs [range 30–88]). NSCLC did not proceed to stage 2. ORR was 9%, 6%, and 4% in HNSCC, GE, and NSCLC pts, respectively; median PFS was 2.7, 1.5 and 3.1 months. BrC and SCLC data are shown in the Table. 92% of pts had a drug-related adverse event (DRAE). 57% of pts had Gr ≥3 DRAEs; including neutropenia (38%), anemia (10%), stomatitis (8%), and thrombocytopenia (6%). 22 pts died during the study; none were study-drug related. **Conclusions:** Single-agent activity of MLN8237 was evaluated across a range of solid tumors with a manageable toxicity profile. Encouraging Ph2 data in BrC and SCLC pts suggest that MLN8237 warrants further evaluation in these tumor types. Clinical trial information: NCT01045421.

	SCLC			BrC			
	All	Chemo-refractory	Chemo-sensitive	All	Triple-negative	HER2+	HR+
Treatment cycles, median (range)	3 (1–10)	2 (2–6)	3.5 (1–10)	5 (1–20)	2 (1–14)	6 (1–19)	8 (1–20)
Response-evaluable, n	47	11	36	49	14	9	26
ORR (PR*), n (%)	10 (21)	3 (27)	7 (19)	9 (18)	1 (7)	2 (22)	6 (23)
Stable disease, n (%)	15 (32)	2 (18)	13 (36)	24 (49)	5 (36)	3 (33)	16 (62)
Median PFS, months	2.8	1.4	2.6	5.4	1.5	4.1	7.9

* Partial response.

606 General Poster Session (Board #9E), Sat, 1:15 PM-5:00 PM

Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with HER2-overexpressing metastatic breast cancer (MBC).

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Background: Pertuzumab is a monoclonal antibody which binds to extracellular domain II of HER2 distally from trastuzumab, disrupting HER2 dimerization and signaling. Pertuzumab improves progression-free survival (PFS) and overall survival when combined with docetaxel/trastuzumab. We report results of a phase II study to evaluate the efficacy and safety of pertuzumab, trastuzumab and weekly paclitaxel. **Methods:** Patients (pts) with HER2+ MBC with 0-1 prior treatment (Rx) were eligible. Rx is weekly (w) paclitaxel (80mg/m^2), q3w trastuzumab (loading dose 8mg/kg → 6mg/kg), and q3w pertuzumab (flat loading dose 840mg → 420mg). The primary endpoint is PFS at 6 months (mo). Evaluable pts are those who started study Rx and are assessed at 6 mo for PFS, including pts who progressed prior to 6mo. Secondary endpoints include response, safety (including cardiac events), and tolerability. Left ventricular ejection fraction (LVEF) is monitored by echocardiogram every 3 mo. Cardiac events are defined as symptomatic LV systolic dysfunction (LVSD), non-LVSD cardiac death, or probable cardiac death. **Results:** As of 1-18-13, 53 pts are enrolled; 36 are evaluable at 6 mo. At 6 mo, 29/36 pts (81%) are progression-free (4 CR, 14 PR and 11 SD); 7 pts progressed. The 6 mo PFS results for all patients will be updated. Median LVEF is 64% at baseline (range 50-72%), 63% at 3 mo (range 50-73%), and 62% at 6 mo (range 49-69%). There are no cardiac events to date. Of the 36 pts, grade 3/4 toxicities include fatigue (3 pts, 8%), peripheral neuropathy (2 pts, 6%), sepsis (1pt, 3%), cellulitis (1pt, 3%), neutropenia (1pt, 3%), and skin ulceration (1pt, 3%). There are no grade 3 diarrhea or febrile neutropenic events in the evaluable pts to date. **Conclusions:** The preliminary 6-month PFS is 81% (95% CI 67-91%) in evaluable patients. The study is closing to accrual. Treatment is ongoing, with few grade 3/4 toxicities and no signal of increased cardiac toxicity to date. This phase II study demonstrates efficacy and safety for pertuzumab with trastuzumab and weekly paclitaxel in HER2+ MBC. Clinical trial information: NCT01276041.

607 **General Poster Session (Board #9F), Sat, 1:15 PM-5:00 PM**

Choice of primary endpoints in first-line phase III trials of HER2-negative or HER2-unknown metastatic breast cancer (MBC).

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Background: OS is considered the most clinically relevant endpoint in cancer therapy trials, but OS can be confounded by post-trial therapy, particularly in settings with long post-progression survival (PPS). Based on statistical modelling with 50,000 simulated trials, Broglio & Berry [JCNI 2009] suggested the association between improved progression-based endpoints (eg, PFS) and OS is weak in settings with PPS $>$12 months and can only be shown in very large trials. To test this hypothesis, we analysed efficacy outcomes and choice of primary endpoints in first-line MBC trials. **Methods:** Data wereanalysed from:randomised, controlled phase III trials comparing systemic chemotherapies and/or targeted agents; enrolling $\geq$150 pts; published in peer-reviewed journals from 2000–2011. Trials that enrolled only HER2-positive MBC pts or evaluated non-EU approved agents were excluded. **Results:** Of27 trials, 1 (3.7%) had OS as the primary endpoint, while 18 (66.7%) had progression-based parameters, commonly PFS (9 trials, 33.3%). A significant increase in progression-based parameters was seen in 14 trials (51.9%). All 5 trials (18.5%) showing a significant OS benefit had a PPS $<$12 months. Mean PPS was considerably longer in trials published in 2006–2011 vs 2000–2005 (14.1 $\pm$ 4.0 vs 9.7 $\pm$ 2.3 months, respectively), as was mean PFS (8.3 $\pm$ 2.2 vs 6.6 $\pm$ 1.6 months) and mean OS (25.4 $\pm$ 5.6 vs 18.6 $\pm$ 3.0 months). A weak correlation was seen between OS and PFS (Pearson's coefficient r=0.32), but a higher correlation was seen in treatment arms with an OS benefit (r=0.59), as well as in treatment arms with a PPS $<$12 months (r=0.43) or older studies (r=0.51). Data were insufficient to allow a valid analysis of the effect of further-line therapies or cross-over on OS (16 trials reported further-line therapies; 9 cross-over therapy). **Conclusions:** In support of the hypothesis by Broglio & Berry, a significant OS advantage was shown exclusively in trials with a PPS $<$12 months. Due to the weak correlation between PFS and OS, it is difficult to determine the possible surrogacy of PFS for OS. Thus, as an OS benefit might be increasingly difficult to attain, progression-based parameters appear to be valid endpoints in MBC clinical trials.

608 General Poster Session (Board #9G), Sat, 1:15 PM-5:00 PM

The Long-HER study: Clinical and molecular analysis of advanced HER2+ breast cancer treated with trastuzumab and associated to long-term survival.

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Background: Some patients with advanced HER2+ breast cancer survive in the long-term after receiving trastuzumab-based therapy. Long-HER study was an observational, multicenter study that compared long-term survivors and a control group from the clinical and molecular point of view. **Methods:** Patients with metastatic HER2+ breast cancer that had been treated with trastuzumab-based therapy and had an objective response or stable disease for at least 3 years were included. A control group having a progression in the first year of therapy was selected for comparison (similar first-line therapy). A microarray platform was used to assess whole genome expression analysis in paraffin-embedded samples. Differential expression, ontology and analysis of metabolic pathways were performed. **Results:** 103 patients were registered, 71 of who had a long-term complete remission. Only 5 of these patients had received trastuzumab in the adjuvant setting: this was the only clinical factor associated to long-term survival. The molecular study included 35 Long-HER and 18 control samples. Gene expression ontology revealed alterations in HIF, apoptosis, and EGF, PI3K and p53 pathways. The PI3K pathway was mostly related with a poor response to therapy. **Conclusions:** trastuzumab-based therapy achieves long-term survival in a selected group of women with advanced HER2-positive breast cancer. Whole genome analysis comparing such a group with a control group found some alterations that may predict early progression to trastuzumab.

609 **General Poster Session (Board #9H), Sat, 1:15 PM-5:00 PM**

Phosphorylated ribosomal S6 (p-S6) as an indicator of HER2 signaling targeted drug resistance.

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Background: Thetargeting of HER2/neu oncoprotein with trastuzumab (Herceptin) has altered the natural history of HER2+ breast cancer, however, its clinical benefit is limited by de novo and/or acquired resistance which almost always develops in the advanced setting. While several mechanisms of resistance have been postulated, none are validated for clinical use to best select patients for treatment. Our study aims were to identify predictive biomarkers based on reproducible differences in HER2 initiated signaling pathway observed in trastuzumab-resistant, HER2-overexpressing human breast cell line models. **Methods:** Exposing HER2+ breast cancer cells BT474 and SKBR3 to 200 μg/ml of trastuzumab for 12 months, we established two trastuzumab-resistant, HER2 overexpressing breast cancer models BtRT and SkRT. MTT assay was used to characterize drug sensitivities of the cells. Immunocytochemistry and immunoblotting were used to assess the expression levels of HER2 signaling pathway proteins. The impact of trastuzumab on cell cycle process was analyzed by FACS. EdU incorporation was adapted to measure cell proliferation. **Results:** Trastuzumab-resistant cells had a higher proliferation rate and altered expression levels of HER2 signaling pathway proteins such as p-mTOR, p-S6k1, p-Akt, p-S6, and p-4EBP1, in comparison with parental cell lines. A downstream effector of HER2/Akt/mTOR pathway, phosphorylated ribosomal protein S6 (p-S6), was highly expressed and could not be suppressed by trastuzumab in the resistant cells. When the resistant cells were treated with selected HER2/Akt/mTOR pathway targeted drugs including lapatinib, erlotinib, linsitinib, AZD2014, MK-2206, everolimus and BEZ235, the level of p-S6 in these cells was found to be inversely correlated to the drug induced growth inhibition of these cells. **Conclusions:** p-S6 is a feasible and easy to measure molecular readout of HER2-targeted therapy resistance. This marker is a good candidate for further clinical validation to predict or efficiently measure a patient's response to HER2/Akt/mTOR targeted drugs and to test novel agents that would reverse resistance and improve the outcome of trastuzumab refractory, HER2 overexpressing breast cancer.

610 General Poster Session (Board #10A), Sat, 1:15 PM-5:00 PM

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

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Background: The gold standard endpoint in randomized clinical trials (RCTs) in MBC is OS, which has the disadvantage of requiring extended follow-up and being confounded by subsequent anti-cancer therapies. Although therapeutics have been approved based on PFS, its use as a primary endpoint is controversial. This study, the first IPD meta-analysis of targeted agents in MBC, aimed to collect data from RCTs of HER2-targeted agents in HER2+ MBC, assessing to what extent PFS correlates with, and may be used as, a surrogate for OS. **Methods:** A search was conducted in April 2011. Eligible RCTs accrued HER2+ MBC patients (pts) in 1992-2008. Collaboration was obtained from industrial partners (Roche, GSK) for industry-led studies. Investigator-assessed PFS was defined as the time from randomization to clinical or radiological progression, or death. A correlation approach was used: at the individual level, to estimate the association between PFS and OS using a bivariate survival model and at the trial level, to estimate the association between treatment effects on PFS and OS. Squared correlation values close to 1.0 would indicate strong surrogacy. **Results:** The search strategy resulted in 2137 eligible pts in 13 RCTs testing trastuzumab or lapatinib. We collected IPD data from 1963 pts in 9 RCTs. One phase II RCT did not have sufficient follow-up data so that 1839 pts in 8 RCTs were retained (5 evaluating trastuzumab, 3 lapatinib); 6 out of 8 RCTs were first-line. At the individual level, the Spearman rank correlation using Hougaard copula was equal to r=0.66 (95% CI 0.65 to 0.66) corresponding to an r^2 of 0.42. At the trial level, the squared correlation between treatment effects on PFS and OS was provided by R^2=0.33 (95% CI -0.22 to 0.86) using Hougaard copula and R^2=0.53 (95% CI 0.22 to 0.83) using log hazard ratios from Cox models. **Conclusions:** In RCTs of HER2-targeted agents in HER2+ MBC, PFS is moderately correlated with OS and treatment effects on PFS are modestly correlated with treatment effects on OS, similarly to first-line chemotherapy in MBC (Burzykowski et al JCO 2008). PFS does not completely substitute for OS.

611 General Poster Session (Board #10B), Sat, 1:15 PM-5:00 PM

Coexpression of HER3 as a predictor of survival in HER2-positve breast cancer patients.

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Background: Improved understanding of the pathobiology of the metastatic cascade as well as the identification of new prognostic markers may lead the path to the development of novel targeted agents in breast cancer patients (BC pts). Recently, HER3-expression was postulated as independent risk factor for metastatic spread. **Methods:** Pts of different BC subtypes (luminal, HER2-amplified, triple-negative) with metastatic disease were identified from a breast cancer data base. Tissue of the primary tumor was retrieved from the local pathology institute. Immunohistochemical staining of estrogen-receptor, progesterone-receptor, and HER2 and HER3 was performed. In HER2 equivocal cases, subsequent FISH analysis was performed. **Results:** Specimens of 110 pts (36/110 luminal, 35/110 HER2-amplified, 40/110 triple-negative) were available for this analysis. 23/110 (21%) specimens showed strong, complete, membranous staining for HER3 of at least 10% of all tumor cells. HER2/HER3 co-expression was observed in 12/110 (11%) specimens. HER3 showed a statistically significant association with HER2-expression ($p=0.02$; Chi square test). No correlation was observed for HER3-expression and overall survival (OS), incidence of brain metastases, or time to diagnosis of brain metastases in the entire patient cohort ($p>0.05$; log rank). In the HER2-amplified subgroup, however, HER3-expression was significantly associated with shorter OS (median 30 vs. 63 months; $p=0.02$; log rank test) and remained significant when entered into a multivariate model ($p=0.02$; Cox regression). **Conclusions:** HER2/HER3 co-expression is significantly associated with impaired OS in pts with HER2-positive metastatic breast cancer. Co-inhibition of HER2 and HER3 or inhibition of HER2/HER3 hetero-dimerization could improve prognosis of this patient population.

612 General Poster Session (Board #10C), Sat, 1:15 PM-5:00 PM

A phase I pharmacokinetics trial comparing PF-05280014 (a potential biosimilar) and trastuzumab in healthy volunteers (REFLECTIONS B327-01).

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Background: PF-05280014, a proposed biosimilar to trastuzumab, has an identical amino acid sequence and similar physicochemical and in vitro functional properties to trastuzumab. This study was designed to demonstrate PK similarity of PF-05280014 to trastuzumab from the US (trastuzumab-US) and EU (trastuzumab-EU), and between the licensed drugs. Safety and immunogenicity were also evaluated. **Methods:** In this double-blind trial (NCT01603264), 105 healthy male volunteers, 18-55 years old were randomized 1:1:1 to receive a single 6 mg/kg IV dose of PF-05280014, trastuzumab-US or trastuzumab-EU. All subjects provided informed consent. PK, safety, and immunogenicity assessments were conducted for 70 days. PK similarity for a given test-to-reference comparison was considered to be demonstrated if the 90% CI of the test-to-reference ratio of the AUC from time 0 to the last time point (AUC_T) and maximum concentration (C_{max}) were within 80% – 125%. **Results:** The baseline demographics for the 101 subjects evaluable for PK were similar among 3 treatment arms. The 3 study drugs exhibited similar characteristics of target-mediated disposition and similar PK parameters (Table). The 90% CI for the ratios of C_{max}, AUC_T, and $AUC_{0-\infty}$were within 80% – 125% for the comparisons of PF-05280014 to trastuzumab-EU or trastuzumab-US, and trastuzumab-EU to trastuzumab-US. Adverse events (AE) were similar for the 3 arms with treatment-related AEs reported by 71.4%, 68.6%, and 65.7% subjects in the PF-05280014, trastuzumab-EU and trastuzumab-US, respectively. No serious AEs were reported. Only 4 subjects had treatment interruptions; 2 discontinued. Only 1 subject (trastuzumab-EU) developed anti-drug antibodies after dosing. **Conclusions:** This study demonstrates PK similarity of PF-05280014 to both trastuzumab-US and trastuzumab-EU and of trastuzumab-EU to trastuzumab-US. The three study drugs also showed similar safety profiles. Clinical trial information: NCT01603264.

Mean (±SD) PK exposure estimates.

Parameters (units)	PF-05280014	Trastuzumab-EU	Trastuzumab-US
N	34	35	32
C_{max} (μg/mL)	159 ± 26	174 ± 31	164 ± 31
AUC_T (μg·hr/mL)	35700 ± 6287	38510 ± 6569	35870 ± 6878
$AUC_{0-\infty}$ (μg·hr/mL)	37130 ± 6305	40330 ± 6994	37310 ± 6728

613 General Poster Session (Board #10D), Sat, 1:15 PM-5:00 PM

Safety of trastuzumab in HER2-positive primary breast cancer in Japan: Initial safety report for the large-scale cohort study (JBCRG C-01).

Naohito Yamamoto, Hiroyasu Yamashiro, Hiroji Iwata, Norikazu Masuda, Shoichiro Ohtani, Masato Takahashi, Kosuke Yamazaki, Makoto Kato, Shinji Ohno, Katsumasa Kuroi, Kazuhiko Yamagami, Takashi Morimoto, Yoshie Hasegawa, Toshimi Takano, Takayuki Kadoya, Mitsuchika Hosoda, Hajime Abe, Satoshi Morita, Shinji Yasuno, Masakazu Toi; Chiba Cancer Center, Chiba, Japan; NHO Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan; Aichi Cancer Center Hospital, Nagoya, Japan; NHO Osaka National Hospital, Osaka, Japan; Hiroshima City Hospital, Hiroshima, Japan; NHO Hokkaido Cancer Center, Sapporo, Japan; Sapporo Kotoni Breast Clinic, Hokkaido, Japan; Kato Breast Surgery Clinic, Shiga, Japan; NHO Kyushu Cancer Center, Fukuoka, Japan; Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan; Shinko Hospital, Hyogo, Japan; Yao Municipal Hospital, Osaka, Japan; Hirosaki Municipal Hospital, Aomori, Japan; Toranomon Hospital, Tokyo, Japan; Hiroshima University, Hiroshima, Japan; Hokkaido University Hospital, Hokkaido, Japan; Department of Surgery, Shiga University of Medical Science, Otsu, Japan; Yokohama City University Medical Center, Kanagawa, Japan; EBM Research Center Kyoto University, Kyoto, Japan; Graduate School of Medicine Kyoto University, Kyoto, Japan

Background: The global randomized trials with trastuzumab (H) shows increased cardiotoxicity in patients (pts) with HER2 positive early breast cancer (BC). Safety in Japanese has not been fully evaluated. We evaluated the safety, especially focused on cardiotoxicity, of H adjuvant (adj) therapy in an observational study in Japan (UMIN000002737). **Methods:** Pts with histopathologically confirmed HER2 positive invasive BC were registered. Women with stage I-IIIC disease who received H as neo-adj and/or adj therapy were eligible. Mean LVEF at 3, 6, 9 and 18 months (M) was evaluated. The time points represent examination on day 60-120, 150-210, 240-330 and 455-635, respectively. **Results:** A total of 2024 pts were registered from 56 institutes between July 2009 and June 2011. Data of 1875 pts were collected and finalized by September 2012, and 1800 of them were analyzed for safety. The median follow-up was 35 M. The mean age was 54.5 years. Elderly pts $\geq$60 years were 32.7%. Treatments after surgery were: concurrent chemotherapy (CT) and H in 20.1%, sequential CT and H in 43.5% and H monotherapy in 35.9%. Adverse events (AEs) associated with H were reported in 350 pts (19.4%) and grade (G) 3/4 AEs in 12 pts (0.7%). G 3/4 cardiotoxicity was reported in 7 pts (dysfunction, 4pts; angina, 1 pt; myocardial infarction, 1 pt and heart failure, 1 pt). The mean LVEF at the baseline was 69.4%. Mean LVEF at 3, 6, 9 and 18M were 66.9%, 66.3%, 65.3% and 66.3%, respectively. Compared to the baseline, LVEF decreased with significant difference at all time points ($p<0.0001$). LVEF decrease $\geq$10% occurred in 177 pts (during H treatment,130 and after H treatment, 47). Follow-up data were available in 66 pts: 34 pts recovered to the baseline. Mean time to recover was 262 days. The univariate analysis showed using anthracycline (odds ratio 2.312, $p=0.003$) was the only risk factor for cardiotoxicity. However, elderly, radiation concurrent/sequential treatment with CT and H had no impact. **Conclusions:** From our study, we found the AE profiles of H were consistent with previously known AEs. We found using anthracycline was the risk factor for cardiotoxicity at the moment. We should carefully follow pts and watch long-term safety. Clinical trial information: 000002737.

614 General Poster Session (Board #10E), Sat, 1:15 PM-5:00 PM

Association of MiR-1290 and its potential targets with characteristics of estrogen receptor α-positive breast cancer.

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Background: Recent analyses have identified heterogeneity in estrogen receptor (ER) α-positive breast cancer. Subtypes called luminal A and luminal B have been identified, and the tumor characteristics, such as response to endocrine therapy and prognosis are different in these subtypes. However, little is known about how the biological characteristics of ER-positive breast cancer are determined. **Methods:** In this study, expression profiles of microRNAs (miRNAs) and mRNAs in ER-positive breast cancer tissue were compared between ER^{high} $Ki67^{low}$ tumors and ER^{low} $Ki67^{high}$tumors by miRNA and mRNA microarrays. **Results:** Unsupervised hierarchical clustering analyses revealed distinct expression patterns of miRNAs and mRNAs. We identified a down-regulation of miR-1290 and up-regulations of 6 miRNAs in ER^{high} $Ki67^{low}$tumors. We picked up 11 genes that were potential target genes of the selected miRNAs. Protein expression patterns of the selected target genes were analyzed in ER-positive breast cancer samples by immunohistochemistry: miR-1290 and its 4 putative targets, BCL2, forkhead box A1 (FOXA1), microtubule associated protein tau (MAPT) and N-acetyltransferase-1 (NAT1) were identified. Transfection experiments revealed that introduction of miR-1290 into ER-positive breast cancer cells decreased mRNA and protein expression of NAT1 and FOXA1. **Conclusions:** Our results suggest that miR-1290 and its potential targets, NAT1 and FOXA1, might be associated with characteristics of ER-positive breast cancer.

615 General Poster Session (Board #10F), Sat, 1:15 PM-5:00 PM

Prognostic significance of the chemokine CXCL13 in node-negative breast cancer.

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Background: The chemokine CXCL13 is chemotactic for B cells. We examined the prognostic significance of CXCL13 mRNA expression in node-negative breast cancer. **Methods:** Microarray based gene-expression data for CXCL13 (205242_at) were analysed in four previously published cohorts (Mainz, Rotterdam, Transbig, Yu) of node-negative breast cancer patients not treated with adjuvant therapy (n=824). A meta-analysis of previously published cohorts was performed using a random effects model. Prognostic significance of CXCL13 on metastasis-free survival (MFS) was examined in the whole cohort and in different molecular subtypes (ER+/HER2-, ER-/HER2-, HER2+). Independent prognostic relevance was analysed using multivariate Cox regression. **Results:** Higher RNA expression of CXCL13 was related to better MFS in a meta-analysis of the whole cohort (HR 0.88, 95% CI 0.83-0.94, P<0.0001). Prognostic significance was most pronounced in the HER2+ positive molecular subtype (HR 0.72, 95% CI 0.59-0.87, P=0.0009) as compared to ER+/HER2- (HR 0.86, 95% CI 0.76-0.98, P=0.0024) and ER-/HER2- (HR 0.85, 95% CI 0.75-0.98), P=0.02) carcinomas of the breast. CXCL13 showed independent prognostic significance (HR 0.81, 95% CI 0.7336 0.8982, P=0.0001) in multivariate analysis. In addition to CXCL13, only histological grade of differentiation (HR 2.20, 95% CI 1.41-3.42, P=0.0005) and tumor size (HR 1.72, 95% CI 1.13-2.61, P=0.012), but neither age nor HER2 status nor hormone receptor status retained an independent prognostic association with MFS. **Conclusions:** The chemokine CXCL13 has independent prognostic significance in node-negative breast cancer. Higher expression of CXCL13 is associated with improved outcome.

616 General Poster Session (Board #10G), Sat, 1:15 PM-5:00 PM

Completion of adjuvant trastuzumab for older patients with early-stage breast cancer (BC).

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Background: Few data are available about factors associated with completion of adjuvant trastuzumab in older women with BC. We examined rates and predictors of adjuvant trastuzumab completion for older women with early-stage BC. **Methods:** We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data to identify 1,319 patients ≥66 years with early-stage BC diagnosed between 1999-2007 who received trastuzumab. Completion of trastuzumab was defined as >270 days of therapy. We examined patient, clinical and geographic characteristics associated with trastuzumab completion using multivariable logistic regression. We also assessed rates of hospital admissions for cardiac events during treatment. **Results**: Most of the 1,319 women were aged ≤76 (70%) and had a comorbidity score=0 (88%); 37% and 23% received anthracyline-taxane-based and taxane-based therapy, respectively, and 16% received trastuzumab without chemotherapy. Overall, 982 women (74.5%) completed trastuzumab. Factors associated with completion are shown below. During treatment, 56 patients (4.2%) had 65 hospital admissions for cardiac events (3.0% in those who completed trastuzumab versus 8.0% in those who did not, p<.001). **Conclusions:** One-quarter of older patients who initiated adjuvant trastuzumab did not complete therapy. Older women, Hispanic women, those with more comorbidity, and those receiving anthracycline-taxane-based chemotherapy all had lower odds of completion. Rates of hosptializations for cardiac events were higher in those who did not complete therapy.

	Adjusted odds ratio for completion (95% confidence interval)
Age	--
66-70	1.0
71-75	.8 (.6-1.1)
76-80	.6 (.4-.8)
>80	.5(.4-.7)
Race/ethnicity	--
White	1.0
Hispanic/other/unknown	.7 (.5-.99)
Non-Hispanic black	.8 (.5-1.3)
Comorbidity	--
0	1.0
1	.1 (.3-.8)
2+	.3 (.2-1.5)
Year of diagnosis	--
≤2005	1.0
>2005	4.2 (2.5-6.9)
Hormone receptor status	--
Positive	1.0
Negative	.8 (.7-1)
Surgery	--
Mastectomy	1.0
Breast-conserving surgery	1.3 (1-1.6)
No surgery/unknown	1.1 (.5-2.4)
Chemotherapy	--
Anthracycline/taxane	1.0
Anthracycline based	1.2 (.8-1.8)
Taxane based	2.0 (1.6-2.6)
Single taxane	1.0 (.8-1.4)
Other chemotherapy	.6 (.3-1.2)
Other/no chemotherapy	1.1 (.8-1.5)

617 General Poster Session (Board #10H), Sat, 1:15 PM-5:00 PM

Adverse prognostic impact of intratumor heterogeneous HER2 gene amplification in patients with breast cancer.

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Background: There is increasing recognition of the existence of intratumoral heterogeneity of the human epidermal growth factor receptor (HER2), which affects interpretation of HER2 positivity in clinical practice and may have implications for patient prognosis and treatment. Only patients (pts) with HER2 positivity - defined as 3+ by IHC or FISH amplified defined as a HER2 gene to chromosome 17 (HER2/CEP17) ratio $\geq$ 2.0 - are eligible to receive trastuzumab treatment. Limited information is available on the prognosis of pts with HER2 2+ or FISH test with a HER2/CEP17 ratio $<$ 2.0. **Methods:** We retrospectively analyzed data from 455 consecutive early BC pts with HER 2+ and HER2/CEP17 ratio $<$ 2.0 who underwent surgery after 2007. The association between HER2/CEP17 ratio and other known prognostic factors was evaluated with multivariable linear regression models. The role of HER2/CEP17 ratio on recurrence free survival was assessed with multivariable Cox regression models. **Results:** Fifty-one percent of the evaluated pts were node negative, 51% were postmenopausal, 93% had ER positive BC and 85% had Ki-67 $\geq$14%. The mean HER2/CEP17 ratio was 1.27 (SD=0.3). A significant positive relationship between HER2/CEP17 ratio and Ki-67 was observed ($p<0.01$). During a median follow-up time of 2.7 years, 40 recurrences were observed (15 locoregional events and 25 distant metastases). Overall, the association between HER2/CEP17 and the risk of recurrence was not significant. From subgroup analysis, a significant interaction between HER2/CEP17 ratio and nodal involvement emerged ($p=0.02$). Among pts with node-negative disease, pts with HER2/CEP17 ratio $\geq$1.27 were at higher risk of recurrence with respect to pts with HER2/CEP17 ratio $<$ 1.27 (adjusted HR 4.0, 95% CI 1.01-15.9). **Conclusions:** Among pts with BC and HER2 intratumoral heterogeneity, HER2/CEP17 ratio $\geq$1.27 could have a strong prognostic role in node negative HER2 2+ BC, thus suggesting potential future therapeutic approaches in this setting of pts.

618 General Poster Session (Board #11A), Sat, 1:15 PM-5:00 PM

When less is better: Safety and efficacy of combination of trastuzumab and continuous low oral dose chemotherapy (HEX) as first-line therapy for HER2-positive advanced breast cancer (ABC)—First early results from a phase II trial on behalf of Gruppo Oncologico Italia Meridionale (GOIM).

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Background: Clinical activity of the combination of chemotherapy plus trastuzumab in HER2+ ABC has been well documented. We report the first results in terms of activity and safety of the combination of trastuzumab plus metronomic capecitabine and cyclophosphamide as first line therapy in HER-2 positive ABC. **Methods:** Patients (pts) at first relapse or with synchronous metastasis, were treated with trastuzumab (4 mg/kg, loading dose 6 mg/kg) plus oral capecitabine (1500mg/daily) and cyclophosphamide (50 mg/daily). Primary end-point was overall response rate (ORR), secondary end-points time to progression (TTP), clinical benefit rate (CBR; PR+ CR + prolonged SD for ≥ 24 weeks) and tolerability. The optimal two-stage design was applied. **Results:** A total of 31 pts with measurable ABC, tumors scored as +3 positive for HER-2 or FISH +, no pretreated with chemotherapy or trastuzumab for advanced disease have been enrolled, 28 actually valuable for response and toxicity. Median age was 59 years (range 42-87), visceral metastases were present in most patients (61%). Median number of cycles was 12 (range 1-37+). The ORR was 61 % (95% CI, 41-78%), with 1 CR (3.6 %) and 16 PR (57.1%). 9 patients had prolonged SD (32%). The CBR was 82.1% (95% CI , 63%-94%). Five progressions were observed (18%). Median TTP was 7 months (range 2- 19 + months). Ten pts received more than 20 courses. Worst toxicities were grade 2 hand-foot syndrome in 4 pts, grade 2 anemia in 4 pts, grade 2 nausea in 2 pts and diarrhea grade 3 in 1 pt. Cardiac toxicity grade 2 in 1 pts. Alopecia was not reported. **Conclusions:** Combination of trastuzumab and low dose metronomic oral chemotherapy in HER-2 + breast cancer has shown clinical activity. The tolerability was excellent and allowed the prolonged delivery of the combination. Thus, the patients accrual is ongoing to the pre-set target of 66 patients. Clinical trial information: 2009-017083-16.

619 General Poster Session (Board #11B), Sat, 1:15 PM-5:00 PM

Multicenter phase II trial of neoadjuvant carboplatin, weekly nab-paclitaxel, and trastuzumab in stage II-III HER2+ breast cancer: A BrUOG study.

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Background: Patients (pts) with human epidermal growth factor receptor-2 amplified (HER2+) breast cancers (BrCa) who achieve a pathologic complete response (pCR) with neoadjuvant chemotherapy (NAC) + trastuzumab (T) have an excellent prognosis (Cortazar, SABCS 2012). We tested a novel NAC + T regimen, designed to avoid potential cardiac and other toxicities associated with anthracyclines (A) and eliminate steroid premedication by replacing standard paclitaxel with nab-paclitaxel (nP). **Methods:** Clinical stage IIA-IIIC HER2+ BrCa pts received single agent either nP or T, with research biopsies and MRIs obtained before and after, then carboplatin (Cb) AUC 6 q3wks, nP 100 mg/m^{2}and T 2 mg/kg weekly x 18 wks. If present, residual tumor was collected at surgery. Post-op pts complete a year of T; other adjuvant treatment is at MD discretion. Endpoints include clinical + pathologic response (pCR is defined as no invasive BrCa in breast + axillary nodes), residual cancer burden (RCB), treatment delivery and toxicities. **Results:** 53 pts (of 60 planned) are evaluable for response, median age 51 (34-72). Median delivered dose intensity for nP was 89 mg/m^2/week; nP doses were omitted or reduced for neutropenia (ANC) (in 20% of pts) and neurotoxicity (Nt) (5%). Cb was reduced for thrombocytopenia (tcp) in 15%. Grade 3-4 toxicities: ANC 65%, tcp 22%, anemia 37%, Nt 7%. Serious adverse events: febrile neutropenia (5 pts), infections w/o neutropenia (4), vomiting, diarrhea or dehydration (7), thrombosis (2). LVEF fell by >10% in 3 pts with no clinical CHF. Response data are tabulated below: 28 pts (53%) achieved pCR or RCB class I; 15/21 who did not received A-based adjuvant chemotherapy. Of 38 clinically node-positive pts, 26 (68%) were node-negative at surgery. **Conclusions**: The Cb/nP/T regimen was well tolerated, with pCR rates comparable to those reported with A-containing regimens. Final treatment and response data will be presented; correlative studies will be reported separately. Clinical trial information: NCT00617942.

Cohort	N	pCR	pCR+ RCB I	Clinical CR	Clinical CR+PR
All patients	53	24 (45%)	28 (53%)	35%	76%
ER+	28	11 (39%)	13 (46%)	32%	72%
ER-	25	13 (52%)	15 (60%)	38%	79%
Stage IIA-IIIA	47	22 (47%)	26 (55%)		
Stage IIIB-C	6	2 (33%)	2 (33%)		

620 General Poster Session (Board #11C), Sat, 1:15 PM-5:00 PM

The potential of miR-630, an IGF1R regulator, as a predictive biomarker for HER2-targeted drugs.

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Background: Innate or acquired resistance to current HER-targeting drugs indicates that their use for HER2-overexpressing breast cancer (BC) treatment may be compromised. miRNAs may have potential as diagnostic, prognostic and predictive biomarkers for treatment response, as well as therapeutic targets and replacement therapies. We aimed to investigate miR-630 as a predictive biomarker for response to a range of HER-drugs and as a potential target for increasing sensitivity to the same. **Methods:** Following global miRNA profiling using taqman low density arrays, the reduced expression of miR-630 in cells and corresponding conditioned medium (CM) of HER2-positive BC cell lines with acquired/innate lapatinib (L) resistance (SKBR3-LR, HCC1954-LR, MDA-MB-453) was confirmed by qPCR. miR-630 mimics and inhibitors were used to assess cell response to current (L, trastuzumab (T)) and emerging (neratinib (N), afatinib (A)) HER-targeting drugs. Targetscan prediction software and immunoblotting were used to determine miR-630 regulated proteins. **Results:** miR-630 levels were significantly decreased in cells and CM with acquired lapatinib resistance compared to their age-matched controls. Decreased miR-630 was also observed for innately resistant MDA-MB-453 compared to innately sensitive SKBR3.Administration of miR-630 mimic significantly sensitised resistant cells to all 4 drugs tested. Specifically, miR-630 mimic increased the anti-proliferative effects of L by 31% (SKBR3-LR), 9% (HCC1954-LR) and 9% (MDA-MB-453). Similarly, miR-630 mimic improved the efficacy of T (11-35%), N (4-17%) and A (9-25%); (range for different cell lines). Inhibition of miR-630 in sensitive parent cells induced an insensitive/resistant phenotype, significantly reducing the efficacy of all 4 drugs tested. Interestingly, miR-630 also significantly regulates cell motility, invasion and *anoikis* resistance implicating this miRNA in overall cell aggressiveness. **Conclusions:** This data suggests a potential role for miR-630 as a predictive biomarker for HER-targeting drugs as well as an additional therapeutic target for HER2-overexpressing BC. Acknowledgements: MTCI SFI SRC (08/SRC/B1410), MKF and HEA's PRTLI Cycle 5 to TBSI.

621 General Poster Session (Board #11D), Sat, 1:15 PM-5:00 PM

Phase II study of lapatinib in combination with vinorelbine, as first- or second-line therapy in women with HER2-overexpressing metastatic breast cancer.

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Background: Lapatinib (L), an inhibitor of epidermal growth factor receptor and human epidermal growth factor receptor 2 (HER2) is approved in combination with capecitabine for second-line treatment of HER2+ metastatic breast cancer (MBC). Vinorelbine (V)is a semi-synthetic vinca alkaloid approved for use in patients (pts) with MBC. A previous phase I trial provided a maximum tolerated dose of L plus V. **Methods:** This was a multicenter, phase II study (LPT111110; NCT00709618) to evaluate the efficacy and safety of L plus V in women with histologically confirmed stage IV HER2+ MBC, ≤1 prior chemotherapeutic regimen (no prior L or V was allowed; prior trastuzumab was permitted) and a Zubrod performance status of 0-2. Pts received L (1500 mg daily) plus V (20 mg/m^{2}IV on Days 1, 8, 15) in a 4-week treatment cycle until disease progression or study withdrawal. Primary endpoint: overall response rate (ORR). Secondary endpoints: progression-free survival (PFS), overall survival, time to response (TTR), duration of response (DOR), time to progression, and safety assessments. **Results:** The study was terminated after three years due to slow enrollment; 60 pts were planned and 44 enrolled and were treated. The ORR was 41% (95% CI: 26.4%-55.4%; 4 complete responses, 14 partial responses). Investigator-assessed median (95% CI) PFS, TTR, and DOR were 24.1 (16.9-36.7), 7.5 (7.1–8.1), and 32.0 (18.0-42.3) weeks, respectively. Survival data are not available since data collection was terminated after discontinuation of study treatment. All pts experienced at least 1 adverse event (AE). **Conclusions:** The combination of L plus V resulted in a 41% ORR and was generally well tolerated. However, definitive conclusions could not be drawn as the study was terminated early and not powered for inference testing. Further exploration of L plus V is warranted to clearly define the role of this novel combination in the treatment of HER2+ MBC. Clinical trial information: NCT00709618.

	N (%)		
AEs of interest	**Grade 2**	**Grade 3**	**Grade 4**
Diarrhea	9 (20)	5 (11)	0
Nausea	8 (18)	2 (5)	0
Neutropenia	6 (14)	7 (16)	15 (34)*
Fatigue	8 (18)	2 (5)	0
Rash	9 (20)	1 (2)	0
Febrile neutropenia	0	1 (2)	2 (5)

622 General Poster Session (Board #11E), Sat, 1:15 PM-5:00 PM

Elevated pretreatment serum biomarkers and correlation with progression-free (PFS) and overall survival (OS) in first-line trastuzumab-treated metastatic breast cancer.

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Background: Approximately one-half of HER2-positive breast cancer patients will respond tofirst-line trastuzumab-containing therapy. However, in those patients with an initial trastuzumab response, most will progress within a year with acquired resistance. Since trastuzumab treatment is also now used in the HER2-positive adjuvant breast cancer setting, trastuzumab resistance will continue to be a recurring clinical problem, and better predictive and prognostic biomarkers are urgently needed. **Methods:** Seven serum biomarkers (carbonic anhydrase 9 (CA9), endoglin, HER2, IGF-1R, tissue inhibitor of metalloproteinase-1 (TIMP-1), urokinase-type plasminogen activator (uPA), and VEGF-A (isoform 165) were measured using ELISA assays in 81 metastatic breast cancer patients before starting first-line trastuzumab-containing therapy. The endoglin and IGF-IR ELISAs were from R&D Systems; others were from WILEX/Oncogene Science, Cambridge, MA. PFS and OS were analyzed using the Kaplan-Meier method and Cox modeling with continuous pretreatment serum biomarker variables. **Results:** For univariate PFS analysis, higher pretreatment serum biomarkers (except IGF-1R and VEGF-A) predicted reduced PFS ($p<0.05$) to first-line trastuzumab-containing therapy. In multivariate PFS analysis, only serum CA9 ($p= 0.038$) remained a significant independent covariate. In univariate OS analysis, higher pretreatment serum biomarkers (except IGF-1R and VEGF-A) were prognostic for reduced OS ($p<0.05$). In multivariate analysis for OS, TIMP-1 ($p=0.001$) and CA9 ($p=0.04$) remained significant independent prognostic factors, as well as line of chemotherapy (3 vs. 2 or 1 line)($p=0.005$), and hormone receptor status (ER and/or PR positive vs. negative)($p=0.013$). **Conclusions:** Higher pretreatment serum CA9 (a marker of hypoxia) predicted reduced PFS, and higher serum CA9 and TIMP-1 predicted reduced OS in metastatic breast cancer patients treated with first-line trastuzumab-containing therapy. These serum biomarkers deserve further study in larger trials of HER2-targeted breast cancer treatment. Supported by a grant from Komen for the Cure.

623 General Poster Session (Board #11F), Sat, 1:15 PM-5:00 PM

Correlation between poly (ADP-ribose) polymerase (PARP) and phospho-p65 expression in human breast cancer.

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Background: Despite the efficacy of targeted agents in patients with HER2+ breast cancer, resistance often develops necessitating novel treatment strategies. Poly (ADP-ribose) polymerase inhibitors (PARPi) are known to target tumors with aberrant DNA repair. We previously reported sensitivity of HER2+ breast cancer cells to PARPi independent of a DNA repair deficiency but rather due to attenuation of NF-kB signaling. In this study, we investigated the expression of PARP and the active NF-kB subunit phospho-p65, indicators of activity for these pathways, in human HER2+ breast tumors and compared to HER2- tumors. **Methods:** Patients with breast cancer treated at the University of Alabama at Birmingham between the years 1999 and 2012 were identified. Formalin-fixed, paraffin-embedded tissue blocks were stained for PARP and phospho-p65 and evaluated independently by two blinded physicians, including a board-certified pathologist. An H-score was calculated by multiplying the percent of tumor cells with staining intensity of 0, 1, 2, and 3 and subsequently adding these together for a final score of 0-300. Nuclear and cystosolic staining were scored separately for both proteins. **Results:** Forty-six HER2+ and 38 HER2- patients with available tissue were identified; however, only 41 HER2+ and 32 HER2- cases had tumoral tissue at the time of analysis. PARP and phospho-p65 were found to be almost exclusively nuclear in both groups. The mean nuclear PARP score was 122.3 in HER2+ cases compared to 61.6 in HER2- cases (p value <0.0001). Mean nuclear phospho-p65 scores were 89.0 and 59.4 in HER2+ and HER2- groups, respectively (p value 0.0008). Additionally, a significantly positive correlation was observed between PARP and phospho-p65 levels. **Conclusions:** Our study suggests that HER2+ breast cancers have elevated PARP and NF-kB activity compared to HER2- cancers. Furthermore, a direct correlation between PARP and phospho-p65 levels was found. When combined with our previously published preclinical findings, the current research supports the potential clinical utility of PARPi in patients with this aggressive form of breast cancer.

624 General Poster Session (Board #11G), Sat, 1:15 PM-5:00 PM

Cardiac toxicity in breast cancer patients treated with dual HER2 blockade: A meta-analysis of randomized evidence.

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Background: The dual antiHER2 blockade has been shown promising results in patients with HER2-positive breast cancer. Whether this treatment strategy jeopardizes the risk for cardiac adverse events is unclear. We conducted a meta-analysis of randomized trials to investigate the risk of cardiac adverse events when a combination of anti-HER2 therapies is used. **Methods:** We searched Medline, the Cochrane library, as long as the electronic abstract databases of the major international congresses' proceedings to identify randomized trials that evaluated the administration of anti-HER2 monotherapy (lapatinib or trastuzumab or pertuzumab) versus anti-HER2 combination therapy with or without chemotherapy in breast cancer. Study outcomes were the congestive heart failure (CHF) grade >/= 3 and left ventricular ejection fraction (LVEF) decline < 50% or more than 10% from baseline. We calculated pooled odds ratios (ORs) and 95% Confidence Intervals (CI) with the Peto method. **Results:** Six trials were considered eligible. Overall incidence results for CHF in the combined antiHER2 therapy and the antiHER2 monotherapy were 0.88 % (95% CI: 0.47% - 1.64%) and 1.49 % (95% CI: 0.98% - 2.23%). The incidence of LVEF decline was 3.1 % (95% CI: 2.2% – 4.4%) and 2.9% (95% CI: 2.1% - 4.1%) respectively. The OR of CHF was 0.58 (95% CI: 0.26-1.27, p-value= 0.17) while the OR of LVEF decline was 0.88 (95% CI: 0.53-1.48, p-value= 0.64). In subgroup analyses, there were no significant differences in CHF or LVEF decline among different treatment settings or types of antiHER2 therapy. **Conclusions:** This meta-analysis offers substantial randomized evidence from trials with well-defined cardiac evaluations that a dual anti-HER2 therapeutic approach does not increase the risk for cardiac toxicity.

625 General Poster Session (Board #11H), Sat, 1:15 PM-5:00 PM

Estimated life years saved with trastuzumab in first-line HER2+ metastatic breast cancer from 1999 to 2013.

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Background: Trastuzumab was approved in the United States (US) in September 1998 for the treatment of HER2+ metastatic breast cancer (MBC). This model estimates the total number of life years saved (LYS) in US women treated with trastuzumab over a 15-year period (1999-2013). **Methods:** Using US population estimates and cancer registry-based incidence data, we estimated the number of women with recurrent stage I-III or de novo stage IV HER2+ MBC by year, age, hormone receptor, and nodal status. Trastuzumab utilization was based on published studies of HER2 testing rates, true positive rates in the community, and treatment initiation rates. Survival was estimated by extrapolating survival data pooled across 5 trials and 2 observational studies separately for women treated with trastuzumab and with chemotherapy alone. Few studies reported survival in women with HER2+ MBC without trastuzumab (N=3). Sensitivity analyses were conducted by estimating overall survival from the initial phase 3 trial (67% of placebo patients crossed over to trastuzumab after progression; HR=0.80), and assuming a higher risk reduction to account for crossover effects in clinical trials (HR=0.60). **Results:** In the base case, approximately 83,462 women with HER2+ MBC were estimated to receive 1st line trastuzumab over a 15-year period. The pooled median overall survival across studies without and with trastuzumab was 21.2 and 35.5 months, respectively. Patients were projected to live a total of 216,290 life years if trastuzumab had not been available and if they received chemotherapy only. These same patients were estimated to live a total of 294,877 life years with first-line trastuzumab, for an incremental benefit of 78,587 LYS. In sensitivity analysis, total LYS ranged from 48,334-96,360. **Conclusions:** Real-world evidence supports a median overall survival of approximately 36 months in women with HER2+ MBC receiving 1st line trastuzumab. Using a population-based, conservative model, we found that trastuzumab use has resulted in $>$ 75,000 life years over 15 years in women with HER2+ MBC. Future research is warranted to examine the characteristics, experiences, and outcomes among women living longer with HER2+ MBC.

626 General Poster Session (Board #12A), Sat, 1:15 PM-5:00 PM

What are NCI-designated cancer centers using for breast cancer HER2 testing?

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Background: After 15 years of HER2 testing in breast cancer, various testing methods are used in practice. Studies comparing methods are published but no consensus exists on which method is best. Our study provides a benchmark on the use of breast HER2 testing methods in leading U.S. cancer centers. **Methods:** We conducted an IRB-approved web survey of 58 NCI cancer centers (pathologists and oncologists) providing adult breast cancer care. The survey included 14 questions on breast HER2 testing methods, and reflex and retest practices. We analyzed results using simple frequencies and Fisher's exact test. **Results:** We achieved a response rate of 98% (57/58 sites). In this cohort, 42% (24/57) of sites conduct HER2 testing for breast cancer using an IHC method with reflex to FISH. Of these, all sites reflex IHC 2+ results and 54% (13/24) automatically reflex IHC results beyond 2+ (see table, results are not mutually exclusive). Concurrent primary FISH and IHC testing is conducted at 32% (18/57) of sites; FISH only testing at 18% (10/57); concurrent primary SISH and IHC testing at 5% (3/57); concurrent primary CISH and IHC testing at 2% (1/57), and CISH only testing at 2% (1/57) of sites. The choice of testing protocol had no correlation with the size of institution, metro vs rural location, NCCN membership, or whether the site acts as a reference lab. However, sites where oncologists always or often request a specific test method were more likely (75%, 21/28) to use FISH as a primary method vs as a reflex method (38%, 9/24), p=.0108. Repeat HER2 testing on surgical tumor samples, after the core biopsy, was reported by 47% of sites (27/57); retesting of relapsed patients by 63% (36/57); and retesting for progressive metastatic disease by 56% (32/57). **Conclusions:** For HER2 breast biomarker testing, concurrent FISH and IHC testing and expanded reflex testing, beyond IHC 2+ results, have become a common practice at the NCI designated cancer centers.

Primary HER2 test result	Automatically reflex based on primary test result	Reflex based on order from medical oncologist
IHC 0	13% (3/24)	21% (5/24)
IHC 1+	21% (5/24)	25% (6/24)
IHC 2+	100% (24/24)	0
IHC 3+	25% (6/24)	21% (5/24)
Triple positive (ER+, PgR+, HER2+)	8% (2/24)	4% (1/24)
Triple negative (ER-, PgR-, HER2-)	17% (4/24)	13% (3/24)

627 General Poster Session (Board #12B), Sat, 1:15 PM-5:00 PM

Prognostic and predictive value of a low estrogen receptor expression in breast cancer: A retrospective study from a reference center.

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Background: Threshold of estrogen receptors positivity in breast cancer has been lowered to ≥1% of stained cells by immunohistochemistry testing. This change was based on experts' recommendations from the 2009 St Gallen International Expert Consensus and from the 2010 guidelines of the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP). However few studies support these guidelines and the benefit of treating weakly positive estrogen receptor tumors (1-9%) is unknown. **Methods:** We identified 2221 breast cancer patients with estrogen receptors tested by ligand-based assay, treated and followed in our institution between 1976 and 2008. Date and cause of death were identified through linkage to Quebec Mortality File. A multivariate Cox proportional-hazards model was used to assess the effect of estrogen receptor levels on breast cancer mortality in patients who received hormonal therapy (tamoxifen). **Results:** In patients with low estrogen receptors, 17% (383 patients) were within 0-3 fmol/mg of cytosol and 12% (266 patients) were within 4-9 fmol/mg of cytosol. Patients with estrogen receptor levels of 0-3, 4-9, 10-19, 20-49, and ≥50 fmol/mg of cytosol had a 20-year breast cancer survival rate of 56%, 56%, 63%, 71% and 60% respectively. From the 2221 patients, 661 (29.8%) received hormonal therapy. In these patients, estrogen receptor levels of 0-3, 4-9, 10-19, 20-49 and ≥50 fmol/mg of cytosol were associated with lower breast cancer mortality (HR (p-value) of 1.00 (reference), 0.59 (0.09), 0.19 (<0.0001), 0.26 (<0.0001) and 0.31 (<0.0001) respectively); with significant mortality reduction only for estrogen receptor levels ≥10 fmol/mg of cytosol. **Conclusions:** A weak expression of estrogen receptors (<10 fmol/mg) in breast cancer is associated with increase breast cancer mortality. Our results did not show a significant benefit to treat these patients with hormonal therapy as oppose to those with estrogen receptor levels ≥10 fmol/mg of cytosol. To further support these findings, a similar study should be repeated in patients with estrogen receptors tested by immunohistochemistry.

628 General Poster Session (Board #12C), Sat, 1:15 PM-5:00 PM

Lack of efficacy of adjuvant lapatinib in HER2-negative breast cancer (HER2–ve BC): Analysis of patients in the TEACH trial.

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Background: Benefit from trastuzumab (T) in patients (pts) with HER2–ve tumors by central laboratory FISH testing was shown in an exploratory analysis of the NSABP B-31trial and confirmed by levels of expression of HER2 mRNA. DNA sequencing studies demonstrate that undetected HER2 mutations may drive tumor growth. It is hypothesized that pts with BC deemed as HER2–ve based on amplification may still benefit from anti-HER2 therapy. We undertook an exploratory analysis of disease free survival (DFS) in pts in TEACH whose tumors were HER2–ve or borderline by central FISH testing. **Methods:** TEACH, a randomized, double-blind, placebo (P)-controlled trial in 33 countries, evaluated lapatinib (L) in reducing relapse risk in T-naive pts pretreated with chemotherapy for HER2+ BC. L showed a hazard ratio (HR) for DFS compared with P of 0.83 (95% confidence interval [CI] 0.70-1.00); $P=.053$ in the ITT population (n=3147) and in pts with HER2+ BC by central FISH [HR: 0.82 (0.67-1.00); $P=.04$]. We conducted an exploratory analysis of DFS in pts with borderline or HER2–ve tumors by central FISH. Estimated DFS times were calculated using a stratified log-rank test. HR was estimated by a stratified Cox regression model. **Results:** 657 pts (21%) did not have centrally confirmed HER2+ BC (L: 341 and P: 316) in the ITT population: 425 had negative (HER2:CEP-17 ratio <1.8) or borderline ($\geq 1.8 - <2.0$) FISH testing (L: 218 and P: 207), 216 were unevaluable due to insufficient tissue or sample failed to hybridize (L: 114 and P: 102) and 16 were not centrally tested. In the 425 pts with centrally confirmed HER2–ve or borderline FISH results with 27 events in L and 34 in P, the HR for DFS in L compared with P was 0.94 (0.56-1.57). The percentage of pts with DFS at 4 yrs was 85.0% (79.5%-90.4%) in L and 81% (75.1%-87.1%) in P. **Conclusions:** Although L showed efficacy in pts with centrally confirmed HER2+ BC in the TEACH trial, our analysis did not show benefit in pts whose tumors were HER2–ve or borderline by central FISH. The TEACH trial shows once again that quality control of HER2 testing is crucial and central laboratory testing should be considered for non-specialized centers worldwide. Clinical trial information: NCT00374322.

629 General Poster Session (Board #12D), Sat, 1:15 PM-5:00 PM

Double-blind, randomized, parallel group, phase III study to demonstrate equivalent efficacy and comparable safety of CT-P6 and trastuzumab, both in combination with paclitaxel, in patients with metastatic breast cancer (MBC) as first-line treatment.

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Background: CT-P6(C) is an anti-HER2 MoAb, a biosimilar to trastuzumab (T). This trial is a global phase III study to compare C with T, both in combination with paclitaxel (P) as first-line treatment in women with HER2+ MBC. **Methods:** 475 patients with centrally confirmed HER2+ MBC were randomized to receive either C+P (n=244) or T+P (n=231). Patients had to have a baseline LVEF ≥50% and no history of serious cardiac disease. Study medication was as follows: C or T 8 mg/kg i.v. (day 1), followed by 3-weekly C or T 6 mg/kg. P (175 mg/m^{2}3-weekly) was co-administered. The primary endpoint was overall response rate (ORR) as determined by independent review. Pooled analysis with data from phase I/IIb (NCT01084863) and III studies (NCT01084876) was predefined and endorsed by the EMA. Patient safety was monitored throughout the study by an independent data monitoring committee. Treatment was continued until disease progression, death or patient's withdrawal. **Results:** In the pooled ITT population, ORR was 57% for C+P and 62% for T+P (difference: 5%; 95% CI: -0.14, 0.04) during the first 8 cycles of treatment. The limits of the 95% CIs for the difference in the proportions of responders were contained within the pre-defined range [-0.15, 0.15] required for equivalence. Median time to progression and median time to response were 11.07 vs. 12.52 months (P =0.10), and 1.38 vs. 1.38 months (P =0.37) for C+P and T+P, respectively. Frequency of treatment-related AEs is shown in the Table. **Conclusions:** Equivalence of C and T was observed for ORR in patients with HER2+ MBC in combination with P as first-line therapy. Secondary efficacy endpoints also supported the comparability between C and T. C was well tolerated with a safety profile comparable to that of T. Clinical trial information: NCT01084876.

	C + P (N=244)	T + P (N=231)	Total (N=475)
Serious AEs	33 (13.5%)	28 (12.1%)	61 (12.8%)
All AEs#	87 (35.7%)	95 (41.1%)	182 (38.3%)
Infusion reaction/hypersensitivity#	38 (15.6%)	60 (26.0%)	98 (20.6%)
Cardiotoxicity#	8 (3.3%)	10 (4.3%)	18 (3.8%)
Infection#	3 (1.2%)	0 (0.0%)	3 (0.6%)

Treatment related with C or T.

630 General Poster Session (Board #12E), Sat, 1:15 PM-5:00 PM

Longer-term cardiac safety and outcomes of dose dense (dd) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) and trastuzumab (H) with and without lapatinib (L) in patients (pts) with early breast cancer (BC).

Patrick Glyn Morris, Neil M. Iyengar, Sujata Patil, Carol Chen, Alyson Abbruzzi, Robert James Lehman, Richard Steingart, Kevin C. Oeffinger, Nancy Lin, Beverly Moy, Steven E. Come, Eric P. Winer, Larry Norton, Clifford Hudis, Chau T. Dang; Memorial Sloan-Kettering Cancer Center, New York, NY; Dana-Farber Cancer Insitute, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA

Background: The addition of H to chemotherapy has improved outcomes in HER2-positive early BC. This approach is associated with (w/) an increased risk (<4%) of congestive heart failure (CHF). At a median f/u of 36 months, the addition of anti-HER2 Rx to dose-dense (every 2 weeks) anthracycline-taxane therapy (Rx) was not associated with excess cardiotoxicity. Here we report the incidence of NYHA Class III/IV CHF in 2 phase II studies with longer follow-up. **Methods:** We conducted a retrospective review of pts w/ HER2 + early stage BC treated at MSKCC and DF/HCC on two trials: In trial A - pts received dd AC (60/600 mg/m^2) x 4 → T (175mg/m^2) x 4 (w/ pegfilgrastim) w/ H x 1 year. Trial B differed w/ use of weekly T (80mg/m^2) x 12 and the addition of L (1000mg orally daily) x 1 year. In both trials, H was begun after completion of AC and concurrent with T. Left ventricular ejection fraction (LVEF) was prospectively assessed by multi-gated acquisition scan serially throughout Rx. **Results:** Trial A enrolled 70 pts and Trial B enrolled 95 pts w/ the median age of 46 years (range 27-73 years). Overall, the 5-year distant disease-free survival (DDFS) for trials A and B is 92% (95%Cl; 83-97%) and 89% (95%CI; 81-94%), respectively. The baseline median LVEF was 68% (range 52-81%). In total, 28 of 165 (17%) pts had pre-existing hypertension. Now at a median follow-up of 84 and 57 months respectively, only one (1.4%, 95%CI; 1.36-7.7%) and 4 (4.2%, 95%CI; 4.2-10.4%) pts developed CHF. Since our earlier report, 1 additional CHF event occurred (Trial B) at month 44. **Conclusions:** Longer follow-up of these 2 studies demonstrate that dd AC → TH with or without L is associated w/ a low risk of CHF. This is consistent w/ the long-term cardiac toxicity reported from the randomized phase III studies of H w/ conventionally scheduled anthracycline-based regimens (with or without taxanes). DDFS outcomes are also encouraging. Clinical trial information: NCT00482391.

631 General Poster Session (Board #12F), Sat, 1:15 PM-5:00 PM

Utility of 2D-speckle tracking echocardiography in early identification of left ventricular dysfunction in antineoplastic therapy-induced cardiotoxicity.

Carmela Coppola, Carlo G. Tocchetti, Giovanna Piscopo, Clemente Cipresso, Carlo Maurea, Maria Cristina Lombari, Domenica Rea, Piera Maiolino, Maria Gaia Monti, Luigi Tarantini, Giulia Russo, Giovanni Cioffi, Francesco Giotta, Stefano Oliva, Immacolata Capasso, Rosario Vincenz Iaffaioli, Claudio Arra, Nicola Maurea; National Cancer Institute, Pascale Foundation, Naples, Italy; National Cancer Institute, G. Pascale Foundation, Naples, Italy; NCI of Naples, Naples, Italy; Federico II University, Naples, Italy; Cardiology Unit, San Martino Hospital, Belluno, Italy; Centro Cardiovascolare ASS1 Triestina, Trieste, Italy; Villa Bianca Hospital, Trento, Italy; National Cancer Institute, Bari, Italy; Cardiology Unit, National Cancer Institute of Bari, Bari, Italy; Abdominal Oncology Department, National Cancer Institute, Napoli, Italy

Background: ErbB2 is overexpressed in about 25% of breast cancers; in the heart, it modulates myocardial development and function. Trastuzumab (T), an anti-ErbB2 inhibitor, has improved the prognosis of patients with breast cancer, but is related to an increased risk of asymptomatic left ventricular (LV) dysfunction (3-34%) and heart failure (2-4%). Conventional measures of ventricular function, such as fractional shortening (FS) and ejection fraction (FE) are insensitive in detecting early cardiomyopathy induced by antineoplastic therapy. Aim of this study is to evaluate whether myocardial strain by 2D-speckle tracking (ST) is able to identify early LV dysfunction in mice treated with doxorubicin (D) and T, alone or in combination (D+T) and to relate data of cardiac function with tissue alterations. **Methods:** Cardiac function was measured with FS, by M-mode echocardiography, and with radial myocardial strain with ST in sedated C57BL/6 mice (8-10 wk old) at time 0, 2 and 6 days of daily administration of D, T, D+T and in a control group. In excised hearts, we evaluated TNFα and CD68 by immunohistochemistry; interstizial fibrosis was analyzed with picrosirius red staining. **Results:** FS was reduced in group D and D+T at 2 days (52+0.2% and 49+2% respectively), both $p<0.001$ vs 60+0.4% (sham), while in group T it decreased only at 6 days (49+1.5% vs 60+0.5%, $p=.002$). In contrast, after 2 days, myocardial strain was already reduced not only in D and D+T, but also in T alone: 43+3%, 49+1%, and 44+7%, respectively, all $p<0.05$ vs sham (66+0.6%). Cardiotoxicity was associated with significant alterations in extracellular matrix remodeling as confirmed by an increase of interstizial collagen with D (4.56%), T (2.17%) and D+T (3.77%)at 6 days $p<0.05$ vs sham (1.17%) and by increased cardiac inflammation in fact the myocytes were positive for TNFα and CD68 cells/mm^{2}at 6 days in group D (16.46% and 155 respectively), in group T+D (12.35% and 74.16) and in group T (5.65% and 72.32) $p<0.01$ vs sham (0.56% and 2.3). **Conclusions:** Myocardial strain identifies LV systolic dysfunction earlier than conventional echocardiography and can be a useful tool to predict cardiotoxicity in this setting.

632 General Poster Session (Board #12G), Sat, 1:15 PM-5:00 PM

Effect of afatinib alone and in combination with trastuzumab in HER2-positive breast cancer cell lines.

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Background: Trastuzumab and lapatinib have been shown to significantly improve the prognosis for HER2 positive breast cancer patients. However, resistance is a significant clinical problem. The aim of this study is to assess the activity of afatinib, an irreversible pan-HER tyrosine kinase inhibitor, in HER2 overexpressing breast cancer cell lines, including trastuzumab and/or lapatinib resistant cells. **Methods:** Using proliferation assays, the effect of afatinib was assessed alone and in combination with trastuzumab in HER2 positive cell lines. The effect of afatinib on HER2, Erk and Akt was determined by immunoblotting. **Results:** The eight HER2 positive breast cancer cell lines tested, including trastuzumab and/or lapatinib resistant cells, responded to afatinib with IC_{50}values ranging from 5 to 80 nM. The combination of afatinib and trastuzumab was additive in four trastuzumab sensitive cell lines and one model of acquired trastuzumab resistant HER2 positive breast cancer. In the remaining three trastuzumab and/or lapatinib resistant cell lines, combined treatment with trastuzumab and afatinib showed no enhancement compared to afatinib alone. Finally, afatinib decreased the phosphorylation of HER2 and Erk in all cell lines tested. **Conclusions:** Our results suggest that afatinib has activity in HER2 positive breast cancer, including trastuzumab and/or lapatinib resistant breast cancer. We also demonstrate that afatinib in combination with trastuzumab may be more effective than either agent alone in trastuzumab sensitive breast cancer.

Effect of afatinib alone, and in combination with trastuzumab, in HER2-positive breast cancer cell lines.

	Sensitive/resistant			% Growth inhibition		
	Trastuzumab	Lapatinib	Afatinib IC_{50} (nM)	Trastuzumab (1 μg/ml)	Afatinib	Trastuzumab + afatinib
BT474	S	S	4.7 ± 0.9	60.4 ± 3.4	2 nM - 29.7 ± 3.1	80.2 ± 3.7
SKBR3	S	S	5.9 ± 2.4	44.5 ± 3.1	10 nM - 59.7 ± 1.1	79.3 ± 2.1
MDA-MB-361	S	S	6.0 ± 1.0	41.6 ± 6.1	10 nM - 49.8 ± 4.9	65.1 ± 6.6
SKBR3-L	R	R	6.3 ± 2.1	23.3 ± 8.7	20 nM - 54.2 ± 7.5	58.6 ± 7.9
SKBR3-T	R	S	9.3 ± 3.2	1.9 ± 3.3	5 nM - 7.7 ± 4.0	29.0 ± 4.8
HCC1419	R	S	10.5 ± 0.3	0.5 ± 8.6	5 nM - 41.0 ± 7.4	49.4 ± 9.4
EFM-192A	S	S	12.6 ± 2.1	31.7 ± 10	5 nM - 25.1 ± 7.9	65.3 ± 2.7
SKBR3-TL	R	R	80.4 ± 5.2	17.5 ± 7	20 nM - 56.1 ± 6.5	60.9 ± 5.9

633 General Poster Session (Board #12H), Sat, 1:15 PM-5:00 PM

Identification of patients at high risk of recurrent disease development by detection of HER2-positive disseminated tumor cells in bone marrow of patients with HER2-negative tumors.

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Background: A subpopulation of patients with HER2-negative tumors benefit from HER2 therapy. HER2 expression can be discordant between primary tumors and metastases. We have examined the bone marrow (BM) of early stage breast cancer patients for HER2-expression by disseminated tumor cells (DTCs) and the association with disease recurrence. **Methods:** BM was collected from clinical stage II-III breast cancer prior to treatment between 2007-2011. Gene expression of *ERBB2* was determined by multiplex PCR (Fluidigm Biomark [FB]). Positive expression was defined as at least 1.4 fold above a pool of normal BM. Expression was confirmed by single gene PCR and Nanostring nCounter (NC) assays. Cox proportional model was used to estimate hazard ratios (HR). **Results:** BM from 74 patients was analyzed. Median follow-up was 3.4 years (range 8 months-84 months)**.** 24% of the patients developed metastatic disease. For *ERBB2* detection, there was excellent correlation between NC and the FB assays (kappa=0.87, 95% CI [0.62, 1.00]). Nine patients expressed *ERBB2* in their BM. Five of the 9 patients had Her2-positive tumors and were treated with trastuzumab. One of 5 (20%) of these patients relapsed whereas 75% (3 of 4) of the patients with HER2-negative tumors but *ERBB2*-positive DTCs relapsed. Patients with HER2-negative tumors/*ERBB2*-positive BM were found to have a greater hazard of recurrence than patients with HER2-negative tumors/*ERBB2*-negative BM or *ERBB2*-positive DTCs treated with trastuzumab (p=.0069; Table). Those patients with *ERBB2*-positive BM who did not receive trastuzumab had a decreased disease free survival (p=.016). **Conclusions:** We have found discordant expression of HER2/*ERBB2* in tumors and BM of stage II-III breast cancer patients. The presence of *ERBB2* expressing DTCs in patients with HER2-negative tumors identifies a subset of patients at increased risk of recurrence who may benefit from targeted HER2-therapy.

HER2 status of tumor and DTCs and risk of recurrence.

Tumor	DTCs	No. of patients	P value	Hazard ratio	95% CI
HER2-	*ERBB2-*	50		1	
HER2+	*ERBB2-*	15	0.44	1.58	(0.495, 5.06)
HER2+	*ERBB2+*	5	0.60	0.57	(0.072, 4.56)
HER2-	*ERBB2+*	4	.0069	6.24	(1.65, 23.6)

634 General Poster Session (Board #13A), Sat, 1:15 PM-5:00 PM

Predictive factors for pathologic complete response (pCR) to trastuzumab (T)-based neoadjuvant chemotherapy in HER2+ breast cancer (BC) women treated in the National Cancer Institute (NCI) of Mexico.

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Background: Neoadjuvant treatment identifies subgroups of patients (pts) with different prognosis. In HER2+ BC, some tumors have been reported to be more sensitive to anti-HER2 therapy than others. We conducted an exploratory analysis in HER2+ BC women who received T-based neoadjuvant chemotherapy. **Methods:** Clinico-pathologic data from HER2+ BC pts who received neoadjuvant chemotherapy and T between January 2007 and May 2012 at the NCI were identified. Estrogen receptor (ER), progesterone receptor (PR) and HER2 expression were determined by immunohistochemistry and/or FISH. pCR was defined as complete absence of invasive tumor in breast and axillary nodes. Proportion differences were tested using the Chi-square test. A generalized linear model was used for multivariate analysis. **Results:** 243 pts received T-based neoadjuvant chemotherapy for localized HER2+ BC tumors. Median age was 49 (26-72) years. 96% had positive axillary nodes at diagnosis and median tumor size was 5.5 (1.5-20) cm. 49.4% had hormone receptor (HR) + (ER+ and/or PR+) and 50.6% HR negative (ER- and PR-) tumors. 63.4% pts achieved pCR. HR negative tumors reached significantly higher pCR rates than HR + tumors (69.9% vs. 56.7%, p=0.034). Pts with inflammatory BC (n=27) had a trend to achieve pCR less frequently than the non-inflammatory tumors (48.1% vs. 65.3%). Those who received taxane-anthracyline sequence chemotherapy (n=20) achieved pCR in 70% of the cases vs. 62.8% with anthracycline-taxane sequence. Differences among other variables (age, tumor size, nodes and HER2 positivity ++/+++) were not significant. Variables that positively influenced pCR were HR negative status (p=0.015), non-inflammatory BC (p=0.082) and chemotherapy sequence (p=0.086). **Conclusions:** HR negative HER2+ BC tumors were associated with higher pCR, consistent with neoadjuvant trial reports. Preclinical data suggest bi-directional crosstalk between HER2 and ER pathways, which might influence anti-HER2 agents and chemotherapy sensitivity for tumors co-expressing both receptors. New strategies are needed to overcome resistance for HER2+ HR+ BC tumors.

635 General Poster Session (Board #13B), Sat, 1:15 PM-5:00 PM

Brain and tumor penetration of carbon-11–labeled lapatinib ([^{11}C]Lap) in patients (pts) with HER2-overexpressing metastatic breast cancer (MBC).

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Background: About a third of HER2-overexpressing (HER2+) breast cancer pts will develop brain metastases in the course of their disease. Drug access to normal brain and brain metastases is therefore key to prevention and treatment of cerebral metastases. To provide direct evidence of Lap drug access and evaluate whether therapeutic doses of Lap act as a substrate for efflux transporters, thereby increasing Lap concentrations, we performed positron emission tomography (PET) studies with [^{11}C]Lap. **Methods:** Pts with HER2+ MBC with an ECOG of <3 were grouped into 2 cohorts: with at least one 1-cm diameter brain metastasis or without brain metastases and underwent 90-minute dynamic cranial PET-CT scans after IV administration of a microdose (<1 mg) of [^{11}C]Lap before and after 8 days of oral Lap (1500 mg once daily). Arterial blood samples were performed to assess [^{11}C]Lap radioactivity contribution in blood and plasma, and the fraction of plasma [^{11}C] radioactivity corresponding to metabolites. Tissue time-radioactivity curves (TACs) were generated and [^{11}C]Lap exposure (AUC; area under TAC) derived for normal brain and brain metastases. Signal dissection of the total image activity was performed to remove the contribution of blood volume to the image and the actual tissue contribution due to [^{11}C]Lap obtained. **Results:** 6 pts (3 with brain metastasis) were recruited. Arterial plasma analysis revealed that [^{11}C]Lap contributed to >80% of activity in plasma at 60 minutes. Tissue data revealed [^{11}C]Lap signal in normal brain was low with no appreciable uptake observed when corrected for blood volume contribution. [^{11}C]Lap uptake was higher in brain metastases compared with normal brain and appreciable, even after correction for tissue blood volume contribution. Uptake was also observed in extra-cranial normal tissue. There was no difference in [^{11}C]Lap uptake in normal brain and metastases between treatment-naïve and post-treatment scans. **Conclusions:** [^{11}C]Lap uptake in brain metastases was higher than in normal brain. [^{11}C]Lap drug access to brain metastases might therefore indicate possible efficacy against HER2+ brain metastases. Clinical trial information: NCT01290354.

636 General Poster Session (Board #13C), Sat, 1:15 PM-5:00 PM

The importance of adjusting for treatment crossover bias in oncology clinical trials: An analysis of the EGF104900 trial in metastatic breast cancer (mBC).

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Background: EGF104900 is a phase III trial in mBC that compared lapatinib + trastuzumab (LAPTRZ, n=146) with LAP monotherapy (LAP, n=145). The trial allowed LAP subjects to switch to LAPTRZ on documented disease progression (following ≥4 weeks of LAP). Conventional intent-to-treat (ITT) analysis does not control for potential bias due to treatment crossover. The Rank Preserving Structural Failure Time Model (RPSFTM) estimates event times had patients not switched, and performs re-censoring. The approach preserves randomization and ordering of patients' observed survival times, assuming that patients switching benefit from the treatment effect seen in those initially randomized to the treatment arm. The method is recognized by NICE, UK, as an appropriate method for adjusting for crossover bias. **Methods:** 53% of LAP subjects crossed over to LAPTRZ. Analyses were stratified by hormone receptor status and visceral/non-visceral disease. RPSFTM was implemented in Stata (using White's strbee procedure). Absolute overall survival (OS) was estimated using a parametric survival distribution fitted to the trial data with/without crossover adjustment. The unadjusted ITT Cox hazard ratio (HR) was compared with the crossover adjusted RPSFTM estimate, and the absolute gain in OS evaluated. **Results:** Median OS in the LAPTRZ and LAP arms was 61 and 41 weeks, respectively (ITT HR 0.74, 95% CI: 0.56, 0.96); RPSFTM crossover-adjusted median OS for LAP was 32 weeks (RPSFTM HR 0.52; 95% CI: 0.29, 0.92). Mean OS for LAPTRZ was estimated under a Weibull distribution as 74 weeks, compared with 57 (ITT) and 44 (RPSFTM) weeks for LAP. Treatment with LAPTRZ was estimated to extend mean OS by 30 weeks controlling for treatment crossover using RPSFTM compared with 17 weeks by ITT. **Conclusions:** Oncology trials are often subject to treatment crossover. Controlling for potential treatment crossover bias can result in greater estimates of gain in OS compared with ITT analysis. In the context of mBC such differences are of great importance to patients, clinicians, and healthcare payers. Treatment crossover-analyses are therefore also important for estimating cost-effectiveness in oncology.

637 General Poster Session (Board #13D), Sat, 1:15 PM-5:00 PM

Role of HER3 expression and PTEN loss in patients with HER2-overexpressing metastatic breast cancer (MBC) patients who received taxane plus trastuzumab treatment.

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Background: The HER3 receptor is a key member of ErbB family and preferentially signals through the PI3K pathway. Formation of dimers between HER3 and HER2 seems to be crucial for HER2-driven signals in HER2 overexpressing tumors. Given the fact that HER2-HER3 is considered the most active signalling dimer of the ErbB system, HER3 activity may contribute to the resistance of trastuzumab. PTEN plays a well-established role in the negative regulation of the PI3K pathway. Our aim of this study was to investigate the role of HER3 and PTEN expression in patients with HER2 overexpressed MBC. **Methods:** One-hundred twenty-five MBC patients who were treated with taxane plus trastuzumab chemotherapy as the first line therapy were included in this analysis. Immunohistochemical stainings (IHC) with HER3 and PTEN antibody were conducted retrospectively. **Results:** Median age was 48 years. HER3 IHC was graded from 0 to 3. PTEN IHC was scored as multiplication of intensity and proportion from 0 to 300. The patients who had negative HER3 stain showed better progression free survival (PFS) to taxane plus trastuzumab chemotherapy than those positive HER3 stain ($p=0.001$, median PFS 21 vs. 11 mo.). The patients who had PTEN score of more than 20 showed longer PFS than those PTEN score of 20 or less than 20 ($p=0.006$, median PFS 13 *vs.* 9 mo.). The patients who had PTEN score of more than 20 showed longer overall survival (OS) than those PTEN score of 20 or less than 20 ($p=0.005$, median OS 48 *vs.* 25 mo.). HER3 negativity and PTEN loss were identified as independent risk factors for PFS [Hazard Ratio (HR) 0.4 (95% CI 0.3-0.8 for HER3 negativity; HR 2.1 (95% CI 1.2-3.7) for PTEN loss]. However, PTEN loss (HR 3.1 [95% CI 1.6-6.3]) was identified as an independent risk factor for OS. **Conclusions:** HER3 and PTEN expression may be predictive markers for trastuzumab treatment in HER2-positive MBCs. PTEN expression may have a potential predictive and prognostic biomarker for trastuzumab treatment.

638 General Poster Session (Board #13E), Sat, 1:15 PM-5:00 PM

Biomarq: A novel approach to automated HER2-analysis of circulating tumor cells (CTCs).

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Background: Targeted treatment approaches directed against CTCs might improve the outcome of metastatic breast cancer patients. Accurate and reproducible assessment of the CTC phenotype is a requirement to use CTCs as treatment targets. The aim of this study was to test the suitability of the automated BioMarQ System (Veridex, USA) – an enhancement of the FDA-approved CellSearch System (Veridex USA) for CTC detection– for assessing the Her2-status of CTCs based on fluorescence and cell-morphology data. **Methods:** Data on classification of the Her2-status into four groups (0, +, ++, +++) obtained by visual inspection of CTCs after immunocytochemical staining with the CellSearch System, and of BioMarQ-generated automatic measures on fluorescence and cell morphology via image clips generated from raw images were available for 329 CTCs from 17 metastatic breast cancer patients. A discriminant analysis was performed to test whether linear combinations of the fluorescence and/or cell morphology measures allow a separation of CTCs into four groups according to the visual classification of their Her2-status. **Results:** The highest concordance with the visual classification was obtained by a set of three discriminant functions based on the five variables mean-, maximum- and integrated fluorescence intensity, cell area (μm^2), and coefficient of variation for the pixel fluorescence values within a cell. All five variables differed significantly among the 17 patients (Kruskal-Wallis-test, all $p < 0.001$). Based on the three discriminant functions, 74.5% of all cases were correctly assigned to the four visually obtained categories (6 out of 8 CTCs classified as +++; 57 out of 80 as ++; 17 out of 65 as +, 165 out of 176 classified as 0). **Conclusions:** Our preliminary analysis shows that discriminant functions derived from measures on fluorescence and cell morphology generated by BioMarQ correctly assigned the Her2-status of CTCs to the four visually obtained categories in 75% of all cases. Further analysis based on a larger number of Her2-positive CTCs, and cross validation by FISH-analysis will provide deeper insight into the suitability of BioMarQ for objectively assessing the Her2-status of CTCs.

639 General Poster Session (Board #13F), Sat, 1:15 PM-5:00 PM

Second-line treatment of HER2+ metastatic breast cancer (MBC): Trastuzumab (T) beyond progression or lapatinib (L)? A retrospective database study.

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Background: L and T "beyond progression" (TBP) for MBC pts who progressed on 1st line therapy with T, are both reimbursed in Israel since 1/2010. The relative efficacy of L vs. T when combined with chemotherapy in 2nd line therapy for HER2+ MBC is unknown. In this retrospective database study we compared outcomes of 2ndline L or TBP, in the daily practice (″real life″) in Israel. **Methods:** Using the computerized databases of Clalit Health Services' (CHS), Israel's largest health care provider, we identified all MBC pts that received 2nd line anti HER2 therapy, with either L or TBP after a 1stline protocol containing T, between 1/1/2010 and 31/12/2011. Pts characteristics and treatments were retrieved. The primary end point was overall survival (OS) defined as the time interval between date of initiation of 2nd line anti HER2 therapy and death or last day of follow-up. Secondary endpoint was progression free survival (PFS), defined as duration of 2nd line therapy. **Results:** The study population included 83 pts (28 L and 55 TBP). Mean age (59.9 vs. 61.4) and average Charlson co-morbidity index score (6.54 vs. 6.13) were similar between the cohorts. The groups differed in rates of prior adjuvant T (32.1% vs. 10.9%, p=0.017). The interim cutoff date for analysis was 31/12/2012 (allowing at least 12 months of follow-up). Median OS was 10.0 months for L pts (95% CI: 7.41–12.59) and was not reached for TBP, with a total of 31 deaths: 19 [67.9%] in the L group and 22 [40.0%] in the TBP group. A Cox regression showed an adjusted hazard ratio (HR) of 1.44 (95% CI 0.74-2.81), not significant (p=0.28).Prior adjuvant therapy with T was found to be a significant cofounder; HR=3.16 (95% CI 1.52-6.56). Median PFS was 6.0 months (95% CI: 4.31–7.69) for L and 7.0 months (95% CI: 4.30-9.70) for TBP, with a Cox regression adjusted HR of 0.87 (95% CI: 0.50-1.52), not statistically significant (p=0.87). **Conclusions:** In this retrospective database analysis, our interim results suggest no statistically significant difference in OS and PFS between L and TBP, as 2nd line therapy for HER2+ MBC, however the data showed a strong trend toward a survival benefit with TBP. A longer follow-up is required.

640 General Poster Session (Board #13G), Sat, 1:15 PM-5:00 PM

Prognostic value of HER2 on breast cancer survival.

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Background: HER2 overexpression and overamplification have originally been described as a prognostic factor indicating a poor prognosis. However the highly effective anti-HER2 treatment was approved in 2006 after several large randomized trials showing that the prognosis in HER2 positive women could be improved. Few data has been generated comparing HER2 positive patients treated with trastuzumab with comparable HER2 negative patients. Aim of this analysis was to investigate the prognostic relevance of HER2 status in a post trastuzumab approval study. **Methods:** The SUCCESS trial is an open-label, multicenter, randomized controlled, phase III study comparing FEC-docetaxel (Doc) vs. FEC-Doc-gemcitabine (Doc-G) regime and 2 vs. 5 year treatment with zoledronat in 3754 patients with primary breast cancer (N+ or high risk). All patients were treated per protocol with trastuzumab, if HER2 status was shown to be positive by local pathology. Furthermore HER2 status was a stratification factor. The prognostic value of HER2 status with respect to overall survival (OS) and progression-free survival (PFS), disregarding the above stated treatment arms, was studied with Cox proportional hazards regression models in univariate as well as multivariate analyses adjusted for age, BMI, tumor size, nodal status, grading, estrogen receptor status and progesterone receptor status. **Results:** 2628 patients were included into this analysis. Median Follow up time was 4.8 years, 221 deaths and 412 recurrences were recorded until data base closure. HER2 was not a prognostic factor in the univariate analysis (OS: HR= 0.86, 95% CI: 0.63 to 1.19; PFS: HR = 0.95, 95% CI: 0.76 to 1.19). In the multivariate analysis all of the above stated prognostic factors were of prognostic relevance. HER2 was of prognostic relevance with a HR of 0.67 (OS, 95% CI: 0.48 to 0.92) and 0.79 (PFS, 95% CI: 0.62 to 0.99) indicating that patients with a positive HER2 status had a better prognosis. **Conclusions:** Patients treated with trastuzumab showed a more favourable prognosis compared to HER2 negative patients in this prospectively randomized trial, possibly due to the therapeutic effect of HER2-targeted treatment.

641 General Poster Session (Board #13H), Sat, 1:15 PM-5:00 PM

Liposome-encapsulated doxorubicin plus cyclophosphamide followed by trastuzumab plus docetaxel as neoadjuvant therapy for HER2-positive breast cancer (BC): A multicenter single-arm phase II study.

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Background: Trastuzumab combined to sequential chemotherapy with taxanes and anthracyclines as primary treatment achieved high rates of pathologic complete response (pCR) in HER2 positive BC. Liposome-encapsulated doxorubicin (DLNP) shown equal efficacy but minor cardiotoxicity compared to doxorubicin. This phase II study aimed to evaluate the activity and safety of trastuzumab associated with chemotherapy for early or locally advanced HER2 positive BC. **Methods:** Primary objective of the study was pCR defined as the absence of residual invasive cancer both in the breast and regional nodes. Preoperative treatment included DLNP (60 mg/mq iv) plus cyclophosphamide (600 mg/mq iv) every 3 weeks for 4 cycles followed by docetaxel (35 mg/mq iv) plus trastuzumab (4 mg/mq loading dose iv, then 2 mg/mq iv) weekly for 16 weeks. Patients (pts) were scheduled to receive adjuvant trastuzumab (8 mg/mq loading dose, then 6 mg/mq iv) every 3 weeks for 12 cycles and radiation and hormonal therapy according to guidelines. **Results:** From December 2005 to September 2011, 43 pts were treated at 3 centers in Italy. 39 out of 43 pts were evaluable for the purpose of the study. Median age was 53 years (range: 31-78). The majority of pts had cT2 (63%), grade 3 (93%), N+ (77%) ER positive (56%) and MIB-1 $\geq$20% (77%). pCR was reported in 19 (49%) of 39 pts. The histological regression score (Von Minckwitz G, J Clin Oncol 2012) is shown in the Table. A significant correlation between MIB-1 $\geq$20% at baseline and pCR was observed ($p=0.018$). Pts with pCR had a time to response (29.4 weeks, 95% CI 28-31) lower than pts without pCR (32.9 weeks, 95% CI 27-39). No cardiac toxicity or discontinuation of trastuzumab was reported. After a median follow-up of 30 months only 2 pts relapsed, both with pCR. **Conclusions:** This study confirms the high activity of trastuzumab combined with chemotherapy based on anthracyclines and taxanes as primary treatment for HER2 positive BC. DLNP is an active and safe option to minimize cardiotoxicity.

Regression grade (RG)	n (total= 39)	%
No or minimal (RG 0-1)	8	20%
Focal invasive (RG 2)	12	31%
Only noninvasive (RG 3)	9	23%
No residual tumor (RG 4)	10	26%

642 General Poster Session (Board #14A), Sat, 1:15 PM-5:00 PM

Comparison of discontinuation, health care resource utilization (HRU), and costs between metastatic breast cancer (mBC) patients (pts) who received trastuzumab (T) in an office clinic versus outpatient hospital setting.

Melissa Brammer, Deepa Lalla, Geneviève Gauthier, Annie Guérin, Philippe Giguere-Duval, Eric Q. Wu, Eduardo Santos; Genentech, Inc., South San Francisco, CA; Genentech Inc., South San Francisco, CA; Analysis Group, Inc., Boston, MA; Analysis Group, inc., Boston, MA

Background: T treatment for mBC may be administered in an office clinic or outpatient hospital setting. This study assesses the impact of the site of care on T discontinuation risk, HRU, and costs. **Methods:** Adult women with mBC who received ≥2 T infusions in an outpatient hospital or office clinic setting were selected from the US-based Humana database (2007-2012). Pts were required to be continuous eligible in their healthcare plan for ≥6 months prior and ≥2 months following the first T infusion (index date). Pts were classified, based on their index site of care, into one of the following cohorts: 1) office clinic, or 2) outpatient hospital. Outcomes were measured from the index date up to the end of continuous eligibility/data availability, a change in the site of care, or 12 months after the index date, whichever occurred first. Treatment discontinuation (gap ≥45 consecutive days) was compared between cohorts using multivariate Cox-proportional hazards model. Monthly healthcare costs (2012 USD) and HRU were compared between cohorts using multivariate generalized linear/two-part models, and multivariate negative binomial regression models, respectively. **Results:** A total of 280 pts met the inclusion criteria; 64% and 36% in the office clinic and outpatient hospital cohort, respectively. Baseline characteristics were similar between cohorts. However, differences were found in terms of insurance plan type, year of index date and comorbid conditions (chronic pulmonary disease and peripheral vascular disorder). After adjusting for confounding factors, the outpatient hospital cohort had a 1.5 time higher risk of treatment discontinuation (p=.043) and incurred an incremental monthly cost of $1,954 (p=<.001), mainly driven by higher office clinic and outpatient hospital costs ($1,483 *p*=.016). No differences were observed in HRU. **Conclusions:** Pts in the office clinics cohort were less likely to discontinue T and were associated with lower monthly total healthcare costs. Future research should examine the impact early discontinuation may have on clinical outcomes.

643 General Poster Session (Board #14B), Sat, 1:15 PM-5:00 PM

A Bayesian meta-analysis of the prognostic value of circulating HER2/neu levels in breast cancer (BC) patients.

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Background: Many reports have shown the prognostic value of HER-2 measured in tumor tissue or in blood. In 2009, Finn et.al. showed that in a study of 579 MBC patients whose serum HER-2 levels (sHER-2) were constantly below normal had a longer PFS than patients with a sHER-2 level constantly above normal. Patients who converted from above normal to less than normal during therapy had a longer PFS than the opposite change. **Methods:** We performed a Bayesian meta-analysis of 12 studies where all sHER-2 levels were measured using an FDA cleared sHER-2 test with a standard cutoff of 15ng/ml. We chose a Bayesian approach because a "meta-analysis" is a natural extension of the Bayesian view that current knowledge is the result of prior knowledge modified by the data. After an in depth literature search, we selected 12 publications based on the following criteria. Baseline levels were available from either early stage or late stage patients who had at least a 2 year disease free or progression free survival as indicated by a Kaplan-Meier (K-M) curve. **Results:** The analysis included 4030 BC patients of which 1106 patients had baseline levels $<$ 15ng/ml and 2924 patients had baseline values $>$15ng/ml. From the K-M curves, we estimated the number of recurrences up to 24 months in each group and prepared a 2x2 table for each study. We determined the odds ratio (OR) for the 12 studies which ranged from 0.57 to 74. A posterior distribution for the aggregated 12 studies can be represented by a Dirichlet distribution. 10,000 estimates of the aggregated OR indicated that there is a 95% credibility that the odds of a woman with baseline sHER-2 $>$15ng/ml recurring at or before two years is between 3.39 and 4.57 times higher than the odds of a woman whose baseline sHER-2 was $<$ 15ng/ml recurring at or before two years. **Conclusions:** This meta-analysis agrees with previous studies that serum HER-2 levels $>$ 15ng/ml can be a strong prognostic indicator for women with Breast Cancer and that managing therapy regimens to maximize the decrease in serum HER-2 levels could be important target in treating patients.

644 General Poster Session (Board #14C), Sat, 1:15 PM-5:00 PM

Exposure–efficacy relationship of trastuzumab emtansine (T-DM1) in EMILIA, a phase III study of T-DM1 versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC).

Bei Wang, Jin Jin, Russell Wada, Liang Fang, Dan Lu, Ellie Guardino, Sandra M. Swain, Michael Untch, Sandhya Girish; Genentech, Inc., South San Francisco, CA; Quantitative Solutions, Menlo Park, CA; Medstar Washington Hospital Center, Washington, DC; HELIOS Hospital Berlin-Buch, Berlin, Germany

Background: T-DM1 is an antibody–drug conjugate composed of trastuzumab (T), a stable thioether linker, and the potent cytotoxic agent DM1. In the phase III study EMILIA, median PFS and OS were significantly prolonged with T-DM1 vs XL in patients (pts) with HER2-positive locally advanced or MBC previously treated with T and a taxane; (PFS hazard ratio [HR]=0.65, p<0.001; OS HR=0.68, p<0.001). We report the effects of T-DM1 exposure on efficacy outcomes in EMILIA. **Methods:** In EMILIA, pts were randomized 1:1 to receive T-DM1 3.6 mg/kg q3w (n=495) or XL (n=496) in 21-day cycles. Pharmacokinetic (PK) samples were from cycle 1 (n=350, T-DM1 arm only). Exposure variables were T-DM1 AUC, T-DM1 C_{min}, total T AUC, and DM1 C_{max}calculated by noncompartmental analysis. A logistic regression model was used to evaluate the relationship between T-DM1 exposure and objective response rates (ORR) in the T-DM1 arm. Multivariate Cox proportional hazards models were used to calculate HRs of OS and PFS for each T-DM1 exposure quartile vs all randomized pts in the XL arm, adjusting for baseline covariates. **Results:** For ORR, mean T-DM1 AUC was 536 day*ug/mL for responders and 502 day*ug/mL for non-responders (P=0.09); mean DM1 C_{max} was 4.55 ng/mL and 4.64 ng/mL, respectively (P=0.64). OS and PFS HRs (and 95% CIs) of T-DM1 vs XL stratified by T-DM1 exposure quartiles are shown (Table). **Conclusions:** In EMILIA, no clear trends were observed between T-DM1 exposure and PFS, OS, or ORR, following administration of T-DM1 3.6 mg/kg q3w. However, there was a suggestion of improved OS HR by stratified T-DM1 C_{min} quartiles, albeit with mostly overlapping 95% CIs. Ongoing T-DM1 clinical trials will further evaluate this potential relationship.

	T-DM1 exposure quartiles			
	Q1 (lowest)	Q2	Q3	Q4 (highest)
OS HRs (95% CI)				
AUC	0.94 (0.76, 1.17)	0.68 (0.51, 0.89)	0.61 (0.43, 0.86)	0.83 (0.66, 1.06)
C_{min}	0.91 (0.74, 1.12)	0.78 (0.61, 0.99)	0.76 (0.57, 1.00)	0.56 (0.39, 0.81)
PFS HRs (95% CI)				
AUC	0.94 (0.78, 1.12)	0.75 (0.62, 0.91)	0.69 (0.55, 0.87)	0.70 (0.58, 0.85)
C_{min}	0.78 (0.65, 0.93)	0.88 (0.73, 1.05)	0.72 (0.58, 0.89)	0.67 (0.55, 0.83)

<1.0 favors T-DM1; >1.0 favors XL

645 General Poster Session (Board #14D), Sat, 1:15 PM-5:00 PM

Differential expression of microRNAs induced by trastuzumab emtansine (T-DM1) during megakaryocytopoiesis.

Hirdesh Uppal, Kaushiki Mahapatra, Sock-Cheng Lewin-Koh, Steven Olsen, Mark X. Sliwkowski, Sandhya Girish, Dylan Hartley, Donna Dambach, Vanitha Ramakrishnan; Genentech, Inc., South San Francisco, CA; Array Biopharma (formerly of Genentech, Inc), Boulder, CO

Background: Treatment with the HER2-targeted antibody–drug conjugate T-DM1 resulted in significantly longer PFS and OS vs lapatinib + capecitabine in patients previously treated with trastuzumab and a taxane in the phase 3 study EMILIA. Thrombocytopenia (TCP) was the dose-limiting toxicity for patients treated with T-DM1, although platelets do not express HER2. In EMILIA, grade 3/4 TCP was observed in 12.9% of T-DM1-treated patients. We have previously shown that T-DM1 inhibits megakaryocyte (Mk) production and differentiation. Here, we investigated the effect of T-DM1 on microRNAs (miRNAs) associated with megakaryocytopoiesis. **Methods:** Human stem cells (HSCs; CD133+/CD34+) from 8 donors were differentiated into Mks in the presence of T-DM1, trastuzumab, or vehicle. Total RNA was extracted using the miRNeasy MiniKit. cDNA was prepared using the Taqman miRNA RT Kit, FAM-MGB probes, and stem-loop RT primer pool set. miRNA expression was measured using the 96.96 Dynamic Array Chip on the Biomark HD Reader. Data were analyzed using Fluidigm real-time analysis software Spotfire 5, and SAS 9.2. hsa−let−7g and hsa−miR−671−3p were chosen as reference miRNAs due to their low variation between treatments and time points. Median normalization was also applied. **Results:** A total of 526 miRNA RT-qPCR assays were used to map miRNA expression during differentiation of HSCs from 8 separate donors to Mks in vitro over 30 days. Several miRNAs demonstrated temporal changes in their expression profiles during maturation, suggesting these miRNAs are potential drivers of Mk differentiation. T-DM1 treatment inhibited Mk production and differentiation. Concomitant modifications in the expression of specific miRNAs were observed. These modifications were not present in trastuzumab- or vehicle-treated cells, suggesting these miRNAs may be involved in the development of T-DM1–induced TCP. **Conclusions:** These results suggest that the miRNAs have the potential to be used as biomarkers for TCP in patients treated with T-DM1 and possibly other DM1 conjugates. Specific miRNA alterations related to T-DM1 treatment will be discussed following investigations using clinical samples to validate these preliminary data.

646 General Poster Session (Board #14E), Sat, 1:15 PM-5:00 PM

Exposure–safety relationship of trastuzumab emtansine (T-DM1) in patients with HER2-positive locally advanced or metastatic breast cancer (MBC).

Jin Jin, Bei Wang, Yuying Gao, Meghna Samant, Chunze Li, Chunyan Song, Sandra M. Swain, Michael Untch, Sandhya Girish; Genentech, Inc., South San Francisco, CA; Genentech Inc., South San Francisco, CA; Quantitative Solutions, Menlo Park, CA; Medstar Washington Hospital Center, Washington, DC; HELIOS Hospital Berlin-Buch, Berlin, Germany

Background: Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate composed of trastuzumab, the cytotoxic agent DM1, and a stable thioether linker. The effects of T-DM1 exposure on safety in patients with HER2-positive locally advanced or MBC are reported. **Methods:** The exposure–safety analysis included 618 patients with pharmacokinetic (PK) data who received single-agent T-DM1 3.6 mg/kg q3w from five phase 2 or 3 studies: TDM4258g, TDM4374g, TDM4450g/BO21976, TDM4688g, and EMILIA. Exposure parameters observed in cycle 1 were T-DM1 conjugate AUC, T-DM1 conjugate C_{max}, and DM1 C_{max}, (no PK accumulation). Safety endpoints were worst grade of thrombocytopenia (TCP) or hepatotoxicity (HPT) by protocol definitions. A multivariate logistic regression analysis was conducted to evaluate the association of exposure and clinically relevant covariates with the probability of experiencing TCP or HPT. Platelet counts (PLT), alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin (TBL) versus time profiles were also evaluated by exposure quartiles to further test exposure effect on lab values. A secondary analysis for patients in the EMILIA study alone (n=307) was also conducted. **Results:** Grade ≥3 TCP and grade≥ 3 HPT were observed in 72 patients and 45 patients in the exposure–safety data set, respectively. Data from the pooled studies showed no statistically significant association between exposure and the incidence of grade ≥3 TCP (T-DM1 AUC $P=0.99$, T-DM1 C_{max} $P=0.97$, DM1 C_{max} $P=0.72$), or grade ≥3 HPT (T-DM1 AUC $P=0.25$, T-DM1 C_{max} $P=0.93$, DM1 C_{max} $P=0.95$). Additionally, no obvious difference was observed for longitudinal PLT, ALT, AST, or TBL profiles across exposure quartiles, with no exposure–safety relationship for the probability that PLT, ALT, AST, or TBL exceeded grade 3 thresholds. Similar results were observed for the EMILIA analysis. **Conclusions:** For patients with HER2-positive locally advanced or MBC treated with T-DM1 3.6 mg/kg q3w, no exposure–safety relationship was observed for TCP, HPT, PLT, or liver function based on T-DM1 or DM1 exposure.

647 **General Poster Session (Board #14F), Sat, 1:15 PM-5:00 PM**

Impact of single and dual neoadjuvant HER2-directed therapy on clinical outcomes among patients with HER2-positive breast cancer (BC).

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Background: While the addition of trastuzumab to neoadjuvant chemotherapy (CTX) is well established for HER2+ BC, the use of dual agent HER2 blockade in the preoperative setting is not considered standard of care. We conducted a comprehensive systematic review and meta-analysis to evaluate the impact of neoadjuvant dual and single agent HER2 blockade on breast conserving surgery (BCS), pathological complete response (pCR) for estrogen receptor (ER)+ and ER- tumors, and impact of pCR on disease-free survival (DFS) and overall survival (OS) for HER2+ BC. **Methods:** Based on QUORUM guidelines, MEDLINE and Cochrane Controlled Clinical Trials Register databases were queried to identify eligible trials. Inclusion criteria were prospective, neoadjuvant trials that had at least one arm with HER2 directed therapy, and reported pCR. Pooled relative risk ratios (RRs) and 95% confidence intervals (CIs) were estimated for endpoints using the random effects model. **Results:** We identified 34 trials (N = 4064). High pCR rates (> 40%) were seen with anthracycline-based CTX and trastuzumab, as well as taxane based CTX alone with dual HER2 blockade. The addition of trastuzumab to CTX did not improve BCS rate (RR 1.40, CI: 0.89-2.22, p=.15), but significantly increased rates of pCR (RR 1.91, CI: 1.38-2.64, p=.0001). Similarly, dual HER2 blockade compared to trastuzumab alone did not improve BCS rate (RR 1.03, CI: 0.77-1.38, p=.84), but significantly increased rates of pCR overall (RR 1.38, CI: 1.24-1.53, p<0.00001), in both ER+ (RR 1.72, CI: 1.14-2.61, p=.01) and ER- subsets (RR 1.91, CI: 1.38-2.64, p=.0001). Higher pCR was associated with improved DFS (RR 2.29, CI: 1.27-4.12, p=.006) and OS (RR 4.61, CI: 1.46-14.56, p=.009). **Conclusions:** Neither the addition of trastuzumab to CTX, nor the dual-HER2 blockade compared to trastuzumab, improves rates of BCS, but both significantly improve rates of pCR, which is associated with improved DFS and OS. A subgroup of HER2+ BC patients can achieve pCR with dual HER2 blockade without dependence on anthracycline-based therapy. Predictive biomarkers are needed to improve patient selection and personalize the optimal regimen for HER2+ BC.

TPS648 **General Poster Session (Board #14G), Sat, 1:15 PM-5:00 PM**

Antiemetic efficacy of transcutaneous electrical nerve stimulation (TENS) at pericardium 6 acupuncture point (P6) in the treatment of chemotherapy-induced delayed nausea and vomiting (CINV) in stage I to III breast cancer patients during adjuvant/neoadjuvant chemotherapy (Ad/nAd).

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Background: CINV remain major adverse effects of highly emetic chemotherapy for breast cancer patients (BC). Patients (PT) rate nausea & vomiting as the most feared chemotherapy-related symptoms. There is substantial evidence that P6 (located in the region in the middle of the wrist 3 finger breaths from the juncture of the hand & wrist) acupuncture is an effective antiemetic treatment in a variety of PT including the post-anesthesia, obstetrical, and motion sickness PT. We hypothesized that application of TENS at P6 point will reduce:1) the overall incidence of CINV episodes in stage 1-3 BC PT, 2) the severity & duration of CINV, 3) the requirement for rescue antiemetics 4) & that TENS is well tolerated & feasible. Maxima III Transcutaneous Electrical Nerve Stimulation unit is utilized in this study & is self-administered by PT. Patients and **Methods:** We are conducting a prospective, randomized, double-blinded, controlled trial to determine if self-stimulating P6 may decrease the incidence and severity of delayed CINV in stage 1-3 BC treated with the initial dose of highly emetic Ad/nAd (AC, AC-T, TAC, TC, TCH) and reduce PT' need for rescue oral antiemetic medications. PT will be randomized in a 1:1 ratio to the active treatment group (TENS self-stimulation at P6) & the control group (TENS self-stimulation at a point on the lateral side of the elbow that does not conform to any known acupuncture points). The assignments are blinded to the PT & the investigators. Subjects self-administer TENS at home q4 hours for 20 minutes during day*s* 2-5 postchemotherapy. The use of conventional antiemetic therapy (corticosteroids, setrons, aprepitant, phenergan & prochlorperazine) is similar for both treatment groups. The severity of nausea symptoms, episodes of emesis, use of rescue antiemetics, and compliance are recorded daily by the PT in diaries. A brief questionnaire is also administered to evaluate PT tolerability of TENS & their ability to comply with the treatment regimen. Twenty six out of 70 planned PT have been enrolled. Recruitment is ongoing.

TPS649 **General Poster Session (Board #14H), Sat, 1:15 PM-5:00 PM**

Early prediction of efficacy of endocrine therapy in breast cancer (BC): Pilot study and validation with 18F fluoroestradiol (18F-FES) PET/CT.

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Background: Almost 70% of early BC are endocrine responsive, as defined by estrogen receptor (ER) expression; however roughly 30% of ER+ BC patients will relapse despite adjuvant ET. Moreover, 10 to 20% of BC metastases lose ER expression. The upfront administration of ET in ER+ women with MBC is recommended by major guidelines. However, the early identification of endocrine resistance might improve systemic treatment options, sparing unnecessary toxicities and inactive drugs. 18F-FES, an oestradiol analogue labeled with 18F, may allow to test the performance of ERs, by testing their in vivo linkage ability. In MBC, 18F-FES uptake has been proposed to be a better predictor of response to ET than ER expression itself. The aim of the ET-FES study is to validate the predictive value of 18F-FES uptake at PET/CT scan in metastatic ER+ patients. **Methods:** This is aphase II, multicentric european comparative study of first line ET vs CT in ER+ MBC with low 18F- FES uptake. The primary endpoint is disease control rate (DCR). Correlative studies include: 1. Optimization of 18F-FES production; 2. Association between gene alterations in ESR1/ESR2 genes and 18F- FES uptake; 3. Development of a predictive score of endocrine responsiveness based on 18F-FES SUV value and clinical and biological information. All patients with ER+ MBC candidate to first line ET will receive a 18F-FES CT/PET at baseline, in addition to standard staging. Patients with 18F-FES uptake (SUV) $>$ 2 will receive ET. Patients with 18F-FES SUV $<$ 2 will be randomized to ET until disease progression (control arm) or CT (single agents) until PD. A total of 220 patients with ER+ MBC will be enrolled. Of these, approximately 50% (n=110) will show a 18F-FES SUV $<$ 2 and will be randomized to ET or CT. The study will have 85% power to detect an absolute 20% difference in the DCR between arms after 3 months of therapy, assuming a 5% two-sided alpha level and a 10% drop-out rate. Current status: The ET-FES study was approved for funding by the ist Join TRANSCAN European call. 18F-FES production is currently on final development (GMP), and the clinical protocol is being finalized for EC approval in the different EU countries. Clinical trial information: 2013-000287-29.

TPS650^ **General Poster Session (Board #15A), Sat, 1:15 PM-5:00 PM**

Ph III randomized studies of the oral pan-PI3K inhibitor buparlisib (BKM120) with fulvestrant in postmenopausal women with HR+/HER2– locally advanced or metastatic breast cancer (BC) after aromatase inhibitor (AI; BELLE-2) or AI and mTOR inhibitor (BELLE-3) treatment.

Hiroji Iwata, José Baselga, Mario Campone, Carlos L. Arteaga, Javier Cortes, Walter Jonat, Michelino De Laurentiis, Eva Ciruelos, Wolfgang Janni, Thomas Bachelot, Per Eystein Lonning, Cynthia Ma, Ruth O'Regan, Emmanuelle Di Tomaso, Bharani Bharani-Dharan, Vincent Duval, Helen Lau, Caroline Germa, Patrick Urban, Angelo Di Leo; Aichi Cancer Center Hospital, Nagoya, Japan; Memorial Sloan-Kettering Cancer Center, New York, NY; Institut de Cancérologie de l'Ouest/René Gauducheau, Saint-Herblain, France; Vanderbilt-Ingram Cancer Center, Nashville, TN; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Christian-Albrechts-Universität zu Kiel, Kiel, Germany; National Cancer Institute "Fondazione Pascale", Naples, Italy; University Hospital 12 de Octubre, Madrid, Spain; Universitaetsklinikum Ulm, Ulm, Germany; Centre Léon Bérard, Lyon, France; Haukeland University Hospital, Bergen, Norway; Washington University School of Medicine in St. Louis, St. Louis, MO; Emory University School of Medicine, Atlanta, GA; Novartis Institutes for Biomedical Research, Inc., Cambridge, MA; Novartis Pharmaceuticals Corp, East Hanover, NJ; Novartis Pharma AG, Basel, Switzerland; Novartis Oncology, Paris, France; Sandro Pitigliani Hospital of Prato, Prato, Italy

Background: The PI3K/Akt/mTOR pathway is commonly dysregulated in BC and linked to resistance to endocrine therapy, including AIs. Buparlisib is an oral inhibitor of class I PI3K isoforms (α, β, γ, δ), showing near complete tumor regression in an in vivo model of ER+ BC in combination with fulvestrant. Preliminary clinical activity in BC pts has been observed with buparlisib as a single agent and in combination with letrozole (Mayer et al. ASCO 2012). **Methods:** BELLE-2 (NCT01610284) and BELLE-3 (NCT01633060) are 2 Ph III randomized, double-blind, placebo-controlled trials of oral buparlisib (100 mg/d) in combination with fulvestrant (500 mg) given on D1 and 15 of Cycle 1 and D1 of each 28-day cycle thereafter in postmenopausal women with HR+/HER2– locally advanced/metastatic BC. Additional eligibility criteria: disease progression on/after AI treatment for BELLE-2; prior treatment with AI and progression on mTOR inhibitor in combination with endocrine therapy (as last therapy prior to study entry) for BELLE-3; $\leq$1 previous line of chemotherapy for advanced disease; available archival tumor tissue for PI3K-related biomarker analysis. Randomization to either arm (1:1 for BELLE-2 and 2:1 for BELLE-3) is stratified according to PI3K pathway activation status (activated *vs* non-activated *vs* unknown) and visceral disease status (present *vs*absent). Study treatment is given until disease progression or discontinuation for any reason. Co-primary endpoints in both trials: PFS in full and PI3K pathway-activated populations based on local investigator assessment (RECIST 1.1). Key secondary endpoints: overall survival (OS) in full and PI3K pathway-activated populations; other secondary endpoints: PFS and OS in PI3K non-activated/unknown population, overall response rate, clinical benefit rate, safety (CTCAE 4.03), PK, and patient-reported outcomes (EORTC QLQ-C30 and QLQ-BR23). Estimated enrollment is 842 pts for BELLE-2 and 615 for BELLE-3. As of January 2013, 96 pts were randomized to BELLE-2 and 1 pt to BELLE-3. Recruitment is ongoing globally. Clinical trial information: NCT01610284 and NCT01633060.

TPS651 **General Poster Session (Board #15B), Sat, 1:15 PM-5:00 PM**

Dovitinib plus fulvestrant in postmenopausal endocrine resistant HER2-/ HR+ breast cancer: A phase II, randomized, placebo-controlled study.

Fabrice Andre, Patrick Neven, Antonino Musolino, Luciano Latini, Mario Campone, Javier Cortes, Carlos H. Barrios, Matthew Squires, Yong Zhang, Stephanie Deudon, Alejandro Javier Yovine, Kimberly L. Blackwell; Institut Gustave Roussy, Villejuif, France; Hospital Gasthuisberg, Leuven, Belgium; University Hospital of Parma, Parma, Italy; Department of Oncology, Ospedale di Macerata, Macerata, Italy; Institut de Cancérologie de l'Ouest/René Gauducheau, Saint-Herblain, France; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Pontifícia Universidade Católica do Rio Grande do Sul School of Medicine, Porto Alegre, Brazil; Novartis Pharma AG, Basel, Switzerland; Novartis Pharmaceuticals Corp, East Hanover, NJ; Duke Cancer Institute, Durham, NC

Background: Overcoming endocrine resistance (ER) is a critical goal in the treatment of hormone receptor−positive (HR+) breast cancer (BC). Emerging in vitro evidence suggests that amplification and overexpression of fibroblast growth factor receptor 1 (FGFR1) is associated with ER. Up to 8% pts with HR+/ human epidermal growth factor receptor 2 negative (HER2–) BC have amplification of the FGFR1 gene. Dovitinib (DOV), a potent inhibitor of FGFR, vascular endothelial growth factor receptor, and platelet-derived growth factor receptor demonstrated antitumor activity in heavily pretreated BC pts with FGF-pathway amplification (FGFR1, FGFR2, or FGF3). The objective of this study is to determine if DOV plus fulvestrant (FUL) can improve outcomes in postmenopausal pts with endocrine resistant HER2-/HR+ BC. **Methods:** This multicenter, randomized, double-blind, placebo-controlled, ph II trial (NCT01528345) will enroll postmenopausal pts with HER2–/HR+ locally advanced or metastatic BC (N=150) progressing within 12 months of completion of adjuvant endocrine therapy or after ≤ 1 prior endocrine therapy in the advanced setting. Pts will be randomized 1:1 (stratified by FGF amplification and presence of visceral disease) to receive intramuscular FUL (500 mg q4w [with an additional dose 2 weeks after the initial dose]) plus oral DOV (500 mg, 5 days on/2 days off) or matching placebo until disease progression, unacceptable toxicity, death, or discontinuation (any reason). Crossover is not permitted. Primary endpoint is progression free survival (investigator's assessment; RECIST v1.1). Secondary endpoints include overall response rate (investigator's assessment; RECIST v1.1), duration of response, overall survival, time to deterioration of ECOG performance status, pt-reported outcome scores over time, safety, and assessment of plasma pharmacokinetic concentrations of FUL and DOV. Additionally, the pharmacodynamic effect of DOV on FGFR-associated angiogenic pathways in tumor specimens and potential predictive biomarkers of response to DOV will be explored. As of 21 Jan 2013, 128 pts had molecular screening; 73 pts are enrolled (of these 9 pts are FGF amplified). Clinical trial information: NCT01528345.

TPS652 **General Poster Session (Board #15C), Sat, 1:15 PM-5:00 PM**

A randomized, multicenter, double-blind phase III study of palbociclib (PD-0332991), an oral CDK 4/6 inhibitor, plus letrozole versus placebo plus letrozole for the treatment of postmenopausal women with ER(+), HER2(–) breast cancer who have not received any prior systemic anticancer treatment for advanced disease.

Richard S. Finn, Veronique Dieras, Karen A. Gelmon, Nadia Harbeck, Stephen E. Jones, Maria Koehler, Miguel Martin, Hope S. Rugo, Seock-Ah Im, Masakazu Toi, Eric Roland Gauthier, Xin Huang, Sophia Randolph, Dennis J. Slamon; University of California, Los Angeles, Geffen School of Medicine, Los Angeles, CA; Institut Curie, Paris, France; British Columbia Cancer Agency, Vancouver, BC, Canada; Breast Center, Deptartment of Obstetrics and Gynecology, University of Munich, Munich, Germany; US Oncology Research; McKesson Specialty Health, The Woodlands, TX; Pfizer Oncology, New York, NY; Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañon, Universidad Complutense, Madrid, Spain; University of California, San Francisco, San Francisco, CA; Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, South Korea; Graduate School of Medicine Kyoto University, Kyoto, Japan; Pfizer, Cambridge, MA; Pfizer Oncology, La Jolla, CA; Pfizer Oncology, San Diego, CA; University of California, Los Angeles, School of Medicine/Translational Oncology Research Laboratory, Los Angeles, CA

Background: Palbociclib (PD-0332991) is an orally bioavailable selective inhibitor of CDK4/6 that prevents DNA synthesis by prohibiting progression of the cell cycle from G1 to S phase. In a randomized phase II trial comparing palbociclib (PD-0332991) plus letrozole (P + L) to letrozole (L) in postmenopausal women with ER(+), HER2(–) advanced breast cancer (ABC) who had not received any prior systemic anticancer therapy for their advanced disease, P + L demonstrated significantly longer progression-free survival (PFS) vs L (26.1 vs 7.5 mo; HR = 0.37, $P < .001$) and was generally well tolerated, with uncomplicated neutropenia as the most frequent adverse event (Finn et al SABCS 2012). **Methods:** Based on phase II data, a global, randomized, double-blind, phase III clinical trial was designed to demonstrate that P + L provides superior clinical benefit compared with L + placebo in postmenopausal women with ER(+), HER2(–) ABC who have not received any prior systemic therapy for their advanced disease. The study aims to assess whether P + L improves median PFS over L at HR of at least 0.7. Approximately 450 eligible patients with locoregionally recurrent or metastatic, pathologically confirmed ABC who are candidates to receive L as first-line treatment for their advanced disease will be randomized 2:1 to receive either P (125 mg QD 3 wk on, 1 wk off) + L (2.5 mg QD) or L (2.5 mg QD) + placebo. Patients who received anastrozole or letrozole as part of their (neo)adjuvant regimen are eligible if their disease progressed more than 12 months from completion of adjuvant therapy. Tumor tissue is required for participation. Secondary endpoints include overall survival, objective response, duration of response, clinical benefit, safety and tolerability, and patient-reported outcomes of health-related quality of life and disease- or treatment-related symptoms. Clinical trial information: NCT01740427.

TPS653 **General Poster Session (Board #15D), Sat, 1:15 PM-5:00 PM**

UNIRAD: Multicenter, double-blind, phase III study of everolimus plus ongoing adjuvant therapy in ER^+, $HER2^-$ breast cancer.

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Background: Advances in adjuvant treatment and highly effective endocrine therapies have resulted in better prognosis and survival among patients (pts) with hormone-receptor-positive (HR^+; ER^+ and/or PgR^+) breast cancer (BC). Despite this, high risk pts ($>3N^+$ and/or T3/4) are likely to relapse during/after adjuvant therapy. In a pivotal phase 3 trial (BOLERO-2), everolimus (EVE, an oral mammalian target of rapamycin [mTOR] inhibitor), plus exemestane demonstrated clinical efficacy in postmenopausal pts with HR^+, human epidermal growth factor receptor-2–negative ($HER2^-$) advanced BC progressing on non-steroidal aromatase inhibitors. Administering EVE earlier, concurrent with adjuvant endocrine therapy (ET) may lower relapse rates, especially in pts with high and/or persistent nodal involvement after neoadjuvant therapy. This study (UNIRAD) will evaluate the safety and effectiveness of adding EVE to adjuvant ET in pts with ER^+, $HER2^-$non-metastatic BC, who are disease-free following 3y of adjuvant ET. **Methods:** This multi-center, double-blind, phase 3 study will randomize adult ($\geq$18y) women with non-metastatic ER^+, $HER2^-$ BC, any T, pN^+($\geq$4 if initial therapy and $\geq$1 after neoadjuvant therapy), who are disease-free following 3y of adjuvant ET to EVE (10mg/d) plus ongoing ET versus placebo (PBO) plus ongoing ET for a total adjuvant therapy duration of 5y. Stratification is by country, ET (tamoxifen or aromatase inhibitors), previous adjuvant versus neoadjuvant therapy, and age ($\leq$70 versus $>$70y). Follow-up will continue for 5y after treatment. The primary endpoint is disease-free survival (DFS) with EVE versus PBO. Secondary endpoints include overall survival (OS), event-free survival, distant metastasis-free survival, DFS and OS in selected subgroups, safety, incidence of secondary cancers, quality of life, and predictive value of mTOR activation markers on DFS. **Results:** Accrual to the UNIRAD study will begin in March 2013 (planned N = 1984). Updated information will be presented. Clinical trial information: 2012-003187-44.

TPS654 **General Poster Session (Board #15E), Sat, 1:15 PM-5:00 PM**

N-SAS BC06: A phase III study of adjuvant endocrine therapy with or without chemotherapy for postmenopausal breast cancer patients who responded to neoadjuvant letrozole (LET): The New Primary Endocrine-Therapy Origination Study (NEOS).

Hiroji Iwata, Shoichiro Ohtani, Tomomi Fujisawa, Naruto Taira, Norikazu Masuda, Masahiro Kashiwaba, Yutaka Yamamoto, Tatsuya Toyama, Takuhiro Yamaguchi; Aichi Cancer Center Hospital, Nagoya, Japan; Hiroshima City Hospital, Hiroshima, Japan; Gunma Prefectural Cancer Center, Gunma, Japan; Okayama University Hospital, Okayama, Japan; NHO Osaka National Hospital, Osaka, Japan; Iwate Medical University, Morioka, Japan; Kumamoto University Hospital, Kumamoto, Japan; Nagoya City University, Nagoya, Japan; Tohoku University, Sendai, Japan

Background: It is uncertain whether adjuvant chemotherapy is required in the treatment of postmenopausal women with hormone-responsive and intermediate risk breast cancer. The TAILORx and MINDACT trials are ongoing and utilize gene expression profiling in order to answer this question. We have initiated a new study to address this matter by using response to initial neoadjuvant endocrine therapy. The primary aim of this phase III study is to evaluate the necessity of using adjuvant chemotherapy for the treatment of postmenopausal breast cancer patients with node-negative, ER-positive and HER2-negative tumors who responded to neoadjuvant LET. **Methods:** Inclusion criteria are T1c-T2N0M0, ER-positive by IHC ($<$10%), HER2-negative, postmenopausal women under 75 years old and written informed consent. Lymph node positive patients as assessed by SLNB are excluded. Neoadjuvant LET is administered for 24-28 weeks before surgery. CR, PR or SD patients are then randomized into two arms receiving either chemotherapy plus LET for 4.5-5 years or LET alone for 4.5-5 years after surgery. If the primary tumor response is defined as PD before surgery, the treatment will be changed at the investigator's discretion (surgery, chemotherapy or other endocrine therapy, but these patients will be followed up). The primary endpoint is disease-free survival (DFS), and secondary endpoints are overall survival (OS), response rate of LET, pathological response, breast conserving surgery rate, DFS/OS by response rate of LET, safety, QOL and cost-effectiveness. This study utilizes a randomized selection design. The objective of this design is to select the arm with the better outcome. We also conduct an additional translational research and central pathological review of ER, PgR, HER2, and Ki67.Patient recruitment commenced in May 2008 and 803 patients were enrolled at the end of 2012. A total of 850 patients will be enrolled at the end of May 2013. This study is supported by Public Health Research Foundation. Clinical trial information: UMIN000001090.

TPS655^ **General Poster Session (Board #15F), Sat, 1:15 PM-5:00 PM**

ADAPT: Adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer.

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Background: Indication of (neo-)adjuvant therapy is based on risk profile, hormone receptor and HER2 status at time of primary diagnosis. Data indicate dynamic proliferation changes after short-term induction therapy are superior to static initial biopsy results in predicting outcome and tumor response following neoadjuvant CTx in distinct BC subtypes. First generation trials such as TAILORx, MINDACT, NNBC-3, WSG planB utilize information of new prognostic/predictive tests to reduce overtreatment by CTx. Results still pending. ADAPT is a second generation trial addressing individualization of adjuvant decision-making in early BC by utilizing optimized pre-therapeutic biomarker information and early biomarker changes in a second core biopsy after 3-week subtype specific induction therapy. It aims at reducing over-/undertreatment in luminal tumors and optimizing therapy in HER2+ (T-DM1, pertuzumab) / TNBC (nab-paclitaxel + platinum/gemcitabine). **Methods:** Design: ADAPT combines static prognosis assessment by conventional markers (nodal status) and Recurrence Score (HR+) with dynamic measurement of proliferation changes after a short 3-week induction therapy, using the baseline diagnostic and repeat core biopsy following induction. ADAPT is a prospective, multi-center, controlled, non-blinded, randomized phase II/III trial, comprising an umbrella trial and 4 sub-trials (HR+/HER2-, HR+/HER2+, HR-/HER2+, TNBC). Eligibility criteria: Pre-/postmenopausal women with histologically confirmed unilateral primary invasive BC. Pts requiring CTx/targeted therapy with no contraindications. Statistics: Assumption across sub-protocols: CTx spared in 1120 HR+/HER2-, pCR achieved in 170 HER2+/TNBC pts. Outcome of good-proliferation responders/pCR pts will be compared to reference group (n=640 HR+/HER2- pts: low RS, no CTx, 94% 5yr survival). One-sided test of non-inferiority (3.2% margin, 90.8%) with alpha=0.05 will have 80% power. Present/target accrual:By 01/2013: 16/35 sites initiated. ADAPT HR+/HER2-: 161/4000 pts recruited. ADAPT HER2+/HR+: 9/380 pts recruited. ADAPT HER2+/HR- or TNBC: start of recruitment planned for Q2 2013. Clinical trial information: NCT01781338.

TPS656 **General Poster Session (Board #15G), Sat, 1:15 PM-5:00 PM**

OPTIMA prelim: Optimal personalized treatment of early breast cancer using multiparameter tests.

Rob Stein, Andreas Makris, Luke Hughes-Davies, Amy Frances Campbell, Andrea Marshall, John M. S. Bartlett, Jenny Donovan, Christopher McCabe, David A. Cameron, Peter Canney, Adele Francis, Adrienne Morgan, Sarah Pinder, Daniel Rea, Peter Hall, Nigel Stallard, Helen B Higgins, Claire Hulme, Victoria Harmer, Janet A. Dunn; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Mount Vernon Cancer Centre, Middlesex, United Kingdom; Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom; Ontario Institute for Cancer Research, Toronto, ON, Canada; University of Bristol, Bristol, United Kingdom; University of Alberta, Edmonton, AB, Canada; University of Edinburgh, Edinburgh, Scotland; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; University Hospital Birmingham NHS Foundation Trust, Birmingham, United Kingdom; Independent Cancer Patients Voice, London, United Kingdom; Division of Cancer Studies, King's College London, London, United Kingdom; University of Birmingham, Birmingham, United Kingdom; Leeds Institute of Health Sciences, Leeds, United Kingdom; Warwick Medical School, University of Warwick, Coventry, United Kingdom; Imperial College NHS Healthcare Trust, London, United Kingdom

Background: Chemotherapy may have little effect on some subtypes of early breast cancer, identified as being hormonally responsive tumours without HER2 gene amplification and with a low or intermediate grade. Multi-parameter genomic tests such as Oncotype DX are increasingly used to identify patients for whom the addition of chemotherapy may confer little additional benefit. OPTIMA has an adaptive design seeking to advance development of personalised medicine in breast cancer by assessing the value of multi-parameter tests in a UK population of intermediate risk. **Methods:** OPTIMA *prelim*, the feasibility phase, has 3 objectives: (1) To evaluate performance and health-economics of multi-parameter tests to determine which test(s) will be used in the main trial; (2) To establish efficient and timely sample collection and analysis essential to deliver multi-parameter test driven treatment; (3) To establish the acceptability to patients and clinicians of randomisation to test-directed treatment assignment. OPTIMA prelim aims to recruit 300 patients with ER+ve HER2-ve tumours with involved nodes (pN1-2). Patients are randomized to the standard arm of chemotherapy with endocrine therapy, or to the "test-directed treatment" arm assigned to either the same chemotherapy with endocrine therapy or endocrine therapy only according to the result of an Oncotype DX test. The decision to continue to a main trial will be determined by concordance, cost and willingness of patients to be randomized to test guided treatment. Cost-effectiveness models will be based on the model developed in preparation for the OPTIMA trial, updated with contemporary evidence from the feasibility study and appropriate external data, e.g. the Ontario prospective cohort study. Results: Optima opened in Sept 2012 with 25 centres involved. To date 22 patients are registered, of which 17 have been randomised. Patient focus groups show the trial design is acceptable and has potential to reduce need for chemotherapy. TSC and DMEC agree that this is an important trial testing the feasibility within this patient population. Decision rules are challenging for this study but employment of adaptive designs gives the flexibility needed for the main trial. Clinical trial information: ISRCTN42400492.

TPS657 **General Poster Session (Board #15H), Sat, 1:15 PM-5:00 PM**

Phase III randomized, placebo-controlled clinical trial evaluating the use of adjuvant endocrine therapy with or without one year of everolimus in patients with high-risk, hormone receptor- (HR) positive and HER2-neu-negative breast cancer: SWOG/ NSABP S1207.

Mariana Chavez-Mac Gregor, William E. Barlow, Ana M. Gonzalez-Angulo, Priya Rastogi, Eleftherios P Mamounas, Patricia A. Ganz, Anne Schott, Soonmyung Paik, Danika Lew, Hanna Bandos, Gabriel N. Hortobagyi; Breast Medical Oncology Department, The University of Texas MD Anderson Cancer Center, Houston, TX; Cancer Research and Biostatistics, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX; National Surgical Adjuvant Breast and Bowel Project and University of Pittsburgh Cancer Institute, Pittsburgh, PA; National Surgical Breast and Bowel Project and MD Anderson Cancer Center Orlando, Orlando, FL; UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, CA; SWOG; The University of Michigan, Ann Arbor, MI; National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA; Southwest Oncology Group Statistical Center, Seattle, WA; NSABP Biostatistical Center, University of Pittsburgh, Graduate School of Public Health, Department of Biostatistics, Pittsburgh, PA

Background: Abnormalities of the PI3kinase/AKT/mTOR signaling pathway are common in breast cancer. This pathway has been associated with endocrine resistance. Everolimus, an mTOR-inhibitor, has been shown to increase the biological activity endocrine therapies. S1207 proposes to evaluate the role of everolimus in combination with endocrine therapy in the adjuvant setting. **Methods:** S1207 is randomized phase III double-blinded, placebo-controlled clinical trial. The primary objective is to assess whether the addition of one year of everolimus to standard adjuvant endocrine therapy improves DFS. Secondary objectives include OS, DRFS, safety, adherence, and quality of life. Submission of tissue specimens/blood samples is required. Patients will be randomly assigned to receive standard adjuvant endocrine therapy in combination with one year of everolimus (10 mg PO daily) or in combination with one year of matched placebo. Eligibility Criteria: Patients with histologically confirmed invasive breast cancer HR-positive and HER2-negative with a) node-negative disease with tumors >2cm and a recurrence score (RS) >25; b) 1-3 positive lymph nodes RS >25; c) >4 positive lymph nodes are eligible after they have completed adjuvant chemotherapy; d) Patients with >4 positive lymph nodes after neoadjuvant chemotherapy are also eligible. Patients must have completed surgery, chemotherapy, and radiation therapy (if indicated) before registration. Statistical methods/ target accrual: Parallel randomization design with equal allocation to the two treatment groups with stratification by 4 risk groups. All analyses are intent-to-treat. The study plans to randomize 3,500 patients over a 3.5-year accrual period. All patients will be followed for 10 years to assess survival and late adverse events. The first interim analysis would be after 39% of the expected events (n=295) have been observed or approximately 3.5 years after initiation of the study. Support: NCI U10-CA-37377, -12027, -69651; Breast Cancer Research Foundation; Novartis. Clinical trial information: NCT01674140.

TPS658 **General Poster Session (Board #16A), Sat, 1:15 PM-5:00 PM**

MotHER: A registry for women with breast cancer who received trastuzumab (T) with or without pertuzumab (P) during pregnancy or within 6 months prior to conception.

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Background: T and P are monoclonal antibodies that target different HER2 epitopes. T is approved for treatment of early and metastatic HER2+ BC while P is approved in combination with T for previously untreated HER2+ MBC. Oligohydramnios has been reported in patients (pts) who received T during pregnancy, and also in P-treated pregnant monkeys. Although both antibodies are FDA Pregnancy Category D, indicating evidence of fetal harm, some physicians and pts accept this risk and continue treatment. The MotHER registry was established in 2008 as an FDA postmarketing commitment to evaluate the effects of T therapy on pregnancy outcome; P was included in the study following its approval in 2012. MotHER is the first prospective study of the effects of a targeted cancer therapy on pregnancy outcome. **Methods:** MotHER is a US registry study of women exposed to T±P during pregnancy or within 6 months prior to conception. Women enroll voluntarily and are followed until pregnancy outcome; infants are followed through the first year of life. Medical information is primarily collected from healthcare providers. Information on potential birth defects noted at birth or during the pediatric follow-up is classified by a birth defect evaluator/clinical geneticist. Enrollment must be initiated before pregnancy outcome. Pts with known prenatal testing results may enroll, but to reduce the potential for bias these pts will be analyzed as a subset. Primary outcomes: number and nature of pregnancy complications, including oligohydramnios, pregnancy outcomes, fetal/infant outcomes and fetal/infant functional deficits. Secondary outcomes: preterm births, elective/therapeutic abortions, miscarriages, fetal growth abnormalities and delivery complications. The study is descriptive and not for formal hypothesis testing; event proportions with CIs will be calculated. The registry will accrue in the US from 2009 to 2019 for T-treated pts and from 2012 to 2022 for P+T-treated pts. The number of potential pts is small therefore physicians are encouraged to refer any eligible pt to increase knowledge about the safety of T±P in pregnancy. herceptinpregnancyregistry.com. Clinical trial information: NCT00833963.

TPS659 **General Poster Session (Board #16B), Sat, 1:15 PM-5:00 PM**

Phase I/II study of neoadjuvant carboplatin, eribulin mesylate, and trastuzumab (ECH) for operable HER2 positive (HER2+) breast cancer.

Lee Steven Schwartzberg, Kurt W. Tauer, Robert C. Hermann, Petros G. Nikolinakos, Arthur C. Houts; ACORN Research and The West Clinic, Memphis, TN; The West Clinic, Memphis, TN; Northwest Georgia Oncology Centers, Marietta, GA; Northeast Georgia Cancer Care, Athens, GA; ACORN Research, LLC, Memphis, TN

Background: Carboplatin, docetaxel and trastuzumab (TCH) regimen yields substantial pathologic complete response (pCR) in operable HER2+ breast cancer. Eribulin mesylate (E) is a tubulin inhibitor recently shown to improve overall survival compared to taxanes and other agents in heavily pretreated metastatic breast cancer patients. This trial was designed to determine the maximum tolerated dose (MTD) of E in combination with CH (Phase I) and to determine efficacy and safety of the ECH regimen (Phase II) given as neoadjuvant therapy to early stage HER2+ breast cancer with pathologic complete response the primary endpoint. **Methods:** This is a multicenter prospective open label single arm trial. Eligible patients were operable stage IIA – IIIB HER2+ breast cancer, ECOG 0-1, normal LVEF, QTc $<$ 480 msec, $<$ grade 1 neuropathy and no history of invasive cancer within the past 3 years. Phase I planned up to 12 patients from 4 centers to 1 of 3 E dose cohorts, with pts treated at the MTD also evaluable for Phase II. Starting dose level 0 was 1.1 mg/m^2 with escalation to dose level +1 at 1.4 mg/m^2 and de-escalation to dose level -1 at 0.9 mg/m^2 if necessary. ECH was given IV for six 3-week cycles with E d1 and d8; C AUC 6 d1; and H 8 mg/kg loading dose d1C1 and 6 mg/kg d1C2-C6. H is scheduled to continue after surgery to complete 1 year of treatment. C1 dose limiting toxicities (DLTs) were defined as: grade 4 thrombocytopenia, anemia, or neutropenia lasting $>$ 5 days; any grade 3-4 non-hematologic toxicity attributable to E, C, H, or the combination; inability to deliver all three agents at assigned dose and schedule. Standard 3+3 dose escalation design was used. At present, 6 patients have been enrolled at dose 0 and 6 have been enrolled at dose +1. The MTD for E has not yet been determined. Phase II has planned enrollment of 44 additional patients from 8 centers with primary endpoint rate of pCR at surgery to be performed 4-8 weeks after completion of ECH and secondary endpoints of safety to include peripheral neuropathy and cardiac toxicity at treatment completion and 1 year follow up. Clinical trial information: NCT101388647.

TPS660 **General Poster Session (Board #16C), Sat, 1:15 PM-5:00 PM**

BOLERO-6: Phase II study of everolimus plus exemestane versus everolimus or capecitabine monotherapy in HR^+, $HER2^-$ advanced breast cancer.

Bent Ejlertsen, Guy Heinrich Maria Jerusalem, Sara A. Hurvitz, Richard H. De Boer, Tanya Taran, Tarek Sahmoud, Howard A. Burris; Danish Breast Cancer Cooperative Group Statistical Center Department of Oncology, Copenhagen University Hospital, Copenhagen, Denmark; Centre Hospitalier Universitaire Sart Tilman Liege and University of Liege, Liège, Belgium; University of California, Los Angeles, Los Angeles, CA; Royal Melbourne Hospital, Melbourne, Australia; Novartis Pharmaceuticals, Florham Park, NJ; Global Oncology Development, Novartis Pharmaceuticals Corporation, Florham Park, NJ; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN

Background: Everolimus (EVE), an orally bioavailable inhibitor of the mammalian target of rapamycin (mTOR), has shown clinical activity as monotherapy and in combination with endocrine therapy (ET) in hormone-receptor–positive (HR^+; estrogen and/or progesterone receptors) advanced breast cancer (ABC). In a pivotal phase 3 trial in patients with HR^+ ABC progressing on ET, EVE + exemestane (EXE) significantly prolonged median progression-free survival (PFS) vs EXE alone per local (7.8 vs 3.2 months; log-rank $P<.0001$) or central (11.0 months for EVE+EXE vs 4.1 months for EXE alone; log-rank $P<.0001$) assessment. Capecitabine, an orally administered fluoropyrimidine carbamate indicated as monotherapy in paclitaxel and/or anthracycline-refractory ABC, has shown clinical benefit in patients with HR^+, human epidermal growth factor receptor 2-negative ($HER2^-$) ABC. The BOLERO-6 study in patients with HR^+, $HER2^-$ ABC progressing on prior anastrozole or letrozole will compare PFS following EVE+EXE combination therapy vs EVE or capecitabine monotherapy. **Methods:** In this multicenter, open-label, randomized, 3-arm, phase 2 study, 300 patients will be randomized to receive either EVE (10 mg/d) + EXE (25 mg/d) combination therapy, or EVE (10 mg/d) alone, or capecitabine (1,250 mg/m^2twice daily for 14 d/3-wk cycle) alone, until disease progression. Patients will be stratified based on the presence of visceral disease. Key eligibility criteria include age ≥18 years, postmenopausal status; histologic or cytologic confirmation of estrogen-receptor–positive, $HER2^-$ ABC; radiologic or objective evidence of recurrence or progression on prior aromatase inhibitors; Eastern Cooperative Oncology Group (ECOG) performance status ≤2. The primary endpoint is PFS with EVE+EXE vs EVE, based on local radiologic assessment (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1). The key secondary endpoint is PFS with EVE+EXE vs capecitabine. Other secondary endpoints include overall survival, objective response rate, clinical benefit rate, safety, quality of life, and patient satisfaction with treatment. Enrollment will start in Q1 2013. Estimated study completion in Q1 2015. Clinical trial information: NCT01783444.

TPS661 **General Poster Session (Board #16D), Sat, 1:15 PM-5:00 PM**

BOLERO-4: Multicenter, open-label, phase II study of everolimus plus letrozole as first-line therapy in ER^+, $HER2^-$ metastatic breast cancer.

William John Gradishar, Thomas Denis Bachelot, Stephen Saletan, Anne Marie Graham, Pedro Emanuel Rubini Liedke, Sergio Jobim Azevedo, Virote Sriuranpong, Fatima Cardoso; Northwestern University, Chicago, IL; Centre Léon Bérard, Lyon, France; Novartis Pharmaceuticals Corp, Florham Park, NJ; Novartis Pharmaceuticals Corp, East Hanover, NJ; Unidade de Pesquisa Clinica em Oncologia UPCO Hospital de Clinicas de Porto Alegre, Porto Alegre, MA, Brazil; Hospital Das Clinicas De Porto Alegre, Porto Alegre, Brazil; Division of Medical Oncology, Department of Medicine, Chulalongkorn University, Bangkok, Thailand; Champalimaud Cancer Center, Lisbon, Portugal

Background: Endocrine therapy (ET) is the standard of care for postmenopausal women with hormone receptor positive (HR^+; typically, estrogen receptor [ER] positive) advanced breast cancer (ABC). However, women with HR^+ ABC can progress while on ET. Crosstalk between ER signaling and the mammalian target of rapamycin (mTOR) pathway enhances tumor progression. Co-targeting these signaling pathways with the combination of everolimus (EVE), an orally bioavailable mTOR inhibitor, and ET (letrozole [LET] or tamoxifen) has been shown to significantly improve clinical outcomes in the neoadjuvant setting and in patients with HR^+ ABC progressing on/after nonsteroidal aromatase inhibitors. In a pivotal phase 3 trial in women with HR^+ ABC progressing on ET, EVE + exemestane (EXE) prolonged progression-free survival (PFS; local/central assessment: 7.8/11.0 mo [$P < .0001$]) compared with EXE alone (3.2/4.1 mo [$P < .0001$]). This study (BOLERO-4) will extend previous investigations to evaluate the safety and effectiveness of EVE+LET as first-line therapy in ER^+ $HER2^-$ metastatic BC (mBC), and the potential benefits of continuing EVE+ET beyond initial progression. **Methods:** In this multicenter, open-label, international, single-arm, phase 2 study, 200 postmenopausal women age ≥18 y with ER^+ $HER2^-$ mBC or locally ABC without prior therapy for advanced disease will receive EVE (10 mg/d) + LET (2.5 mg/d) until first disease progression. Upon disease progression, patients continuing in the trial will receive EVE+EXE (25 mg/d) until further disease progression. Patients who discontinue therapy in the first-line metastatic setting because of unacceptable toxicity will not be offered second-line therapy. The primary endpoint is PFS with EVE+LET in the first-line setting. Secondary endpoints include PFS in the second-line setting, overall survival, objective response rate, clinical benefit rate, safety, and the efficacy of oral dexamethasone solution to reduce the severity and/or duration of stomatitis using Oral Stomatitis Daily Questionnaire (OSDQ). Accrual across Europe, Asia, and the Americas begins Q1 2013. Estimated study completion is Q4 2015. Clinical trial information: NCT01698918.

TPS662 **General Poster Session (Board #16E), Sat, 1:15 PM-5:00 PM**

Denosumab versus placebo as adjuvant treatment for women with early-stage breast cancer at high risk of disease recurrence (D-CARE): An international, placebo-controlled, randomized, double-blind phase III clinical trial.

Paul E. Goss, Carlos H. Barrios, Arlene Chan, Dianne M. Finkelstein, Hiroji Iwata, Miguel Martin, Ada Braun, Beiying Ding, Tapan Maniar, Robert E. Coleman; Massachusetts General Hospital Cancer Center, Boston, MA; PUCRS School of Medicine, Porto Alegre, Brazil; Mount Hospital, Curtin University, Perth, Australia; Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañon, Universidad Complutense, Madrid, Spain; Amgen, Inc., Thousand Oaks, CA; Cancer Research UK Institute for Cancer Studies/YCR Sheffield Cancer Research Centre, Sheffield, United Kingdom

Background: In women with early-stage breast cancer, bone is a common site of distant recurrence and represents approximately 40% of all first recurrences. Preclinical studies demonstrated that inhibition of RANKL significantly delays skeletal tumor formation, reduces skeletal tumor burden, and prolongs survival of tumor-bearing mice. Denosumab is approved for the prevention of skeletal-related events (SREs) in patients with established bone metastases from solid tumors. The D-CARE trial is designed to assess if denosumab treatment prolongs bone metastasis-free survival (BMFS) and disease-free survival (DFS) in the adjuvant breast cancer setting. The primary endpoint of this event-driven trial is BMFS. Secondary endpoints include DFS and overall survival. Additional endpoints include safety, breast density, time to first on-study SRE (following the development of bone metastasis), patient reported outcomes, and biomarkers. **Methods:** In this international, randomized, double-blind, and placebo-controlled phase 3 trial, 4509 women with stage II or III breast cancer at high risk for recurrence and with known hormone and HERE2 receptor status were randomized. High risk was defined as biopsy evidence of breast cancer in regional lymph nodes, tumor size $>$ 5 cm (T3), or locally advanced disease (T4). Standard-of-care adjuvant or neoadjuvant chemo-, endocrine, or HER-2 targeted therapy, alone or in combination, must be planned. Patients with a prior history of breast cancer (except DCIS or LCIS) or distant metastasis, oral bisphosphonate (BP) use within 1 year of randomization, or any intravenous BP use, were not eligible. Patients were randomized 1:1 to receive denosumab 120 mg or placebo subcutaneously monthly for 6 months, then every 3 months for a total of 5 years of treatment. Supplemental vitamin D ($\geq$ 400 IU) and calcium ($\geq$ 500 mg) were required. The trial, sponsored by Amgen Inc., began enrolling patients in June 2010 and completed enrollment in late 2012. Clinical trial information: NCT01077154.

TPS663 **General Poster Session (Board #16F), Sat, 1:15 PM-5:00 PM**

PIKHER2: A phase Ib/II study evaluating safety and efficacy of oral BKM120 in combination with lapatinib in HER2-positive, PI3K-activated, trastuzumab-resistant advanced breast cancer.

Anthony Goncalves, Nicolas Isambert, Mario Campone, Veronique Dieras, Jean Marie Boher, Agnes Boyer-Chamard, Benjamin Esterni, Magali Provansal, Jean-Marc Extra, Patrice Viens; Institut Paoli Calmettes, Marseille, France; Centre Georges François Leclerc, Dijon, France; Institut de Cancérologie de l'Ouest/René Gauducheau, Saint-Herblain, France; Institut Curie, Paris, France

Background: Phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR)-pathway is frequently activated in HER2-positive breast cancer and may play a major role in resistance to trastuzumab. BKM120 is an oral pan-class I PI3K inhibitor with potent and selective activity against wild-type and mutant PI3K p110α. PIKHER2 study will evaluate safety and efficacy of oral, daily lapatinib-BKM120 combination in HER2-positive, trastuzumab-resistant advanced breast cancer (ABC) with activated PI3K/AKT/mTOR pathway. **Methods:** This open label, single arm, multi-center study includes a phase Ib dose-escalation part and a phase II expansion part at the recommended dose (RP2D). Primary objectives include determination of the maximum-tolerated dose (MTD) of BKM120 in combination with lapatinib in trastumuzab-resistant HER2-positive ABC (phase Ib part) and evaluation of the activity of BKM120-lapatinib combination at RP2D as measured by objective response rate (ORR) in patients with activated PI3K/AKT/mTOR pathway, as defined by PTEN-negative by IHC and/or somatic mutations (exons 9 and 20) of *PIK3CA* and/or overexpression of phospho-AKT by IHC (phase II part). Secondary objectives include safety and tolerability of the combination, clinical benefit and progression-free survival, pharmacokinetic profiles, biological and pharmacodynamic correlates. Main eligibility criteria are PS $\leq$ 1, HER2-positive ABC resistant to trastuzumab, documented activated PI3K/AKT/mTOR pathway (phase II part only). A modified CRM using an adaptive Bayesian model guides the dose escalation of both agents with a maximum of 24 patients planned to be enrolled in phase Ib part. Efficacy will be tested according to a standard 2-stage Simon design under the following unacceptable and desirable hypotheses: H0, ORR $<=$ 10% (unacceptable rate) vs. H1, ORR $>=$30% (desirable rate). A maximum of 35 patients with activated PI3K/AKT/mTOR pathway is planned to be enrolled in phase II part with an interim look after 18 evaluable patients will have been recruited. Clinical trial information: NCT01589861.

TPS664 **General Poster Session (Board #16G), Sat, 1:15 PM-5:00 PM**

Human epidermal growth factor receptor 2 (HER2) suppression with the addition of lapatinib to trastuzumab in HER2-positive metastatic breast cancer (HALT: LPT112515).

Nancy U. Lin, Michael A. Danso, Alice K. David, Joseph J. Muscato, Daniel Rayson, William A. Houck, Catherine Elizabeth Ellis, Michelle DeSilvio, Amanda Garofalo, Jeremy Levin, Eric P. Winer; Dana-Farber Cancer Institute, Boston, MA; Virginia Oncology Associates/US Oncology, Norfolk, VA; Augusta Oncology Associates, Augusta, GA; Missouri Cancer Associates, Columbia, MO; Department of Medicine, Dalhousie University, Halifax, NS, Canada; Virginia Cancer Specialists, PC, Winchester, VA; GlaxoSmithKline, Oncology, Collegeville, PA

Background: Evidence supports the concept of dual HER2 blockade as a treatment strategy for HER2+ breast cancer (BC). In patients with prior trastuzumab (T)-treated HER2+ metastatic BC (MBC), treatment with T plus lapatinib (L) was associated with longer progression-free survival (PFS) and overall survival (OS) compared with L alone, and had an acceptable safety and tolerability profile. In patients with stage II/III BC, preoperative treatment with T plus L plus paclitaxel (P) resulted in significantly higher pathologic complete response rates compared with P combined with either agent alone. This study is designed to evaluate whether the addition of L improves PFS among women with HER2+ MBC receiving T as maintenance therapy. **Methods:** In this open-label, Phase III study, 280 patients will be stratified by line of treatment (first/second) and hormone receptor status (positive/negative), then randomized 1:1 to receive maintenance treatment with either L (1000 mg qd, continuously) in combination with T (6 mg/kg once every 3 weeks [q3w]), or T (6 mg/kg q3w) alone until disease progression, death, discontinuation due to adverse events, or other reasons. The primary endpoint is PFS; secondary endpoints are OS, clinical benefit rate, and safety. Eligible patients are females, aged ≥18 years with HER2+ MBC who have completed 12-24 weeks of first-/second-line treatment with T plus chemotherapy with an objective response or stable disease at chemotherapy discontinuation. Patients with stable brain metastases are eligible if entering the study on second-line treatment. Efficacy endpoints will be analyzed in the intent-to-treat population. A total of 193 PFS events is required to detect a 50% increase in median PFS from 18 weeks (T alone) to 27 weeks (L+T) with an associated hazard ratio of 0.667, an 80% power and a 1-sided type I error of 0.025. One interim analysis is planned for futility when ~97 PFS events (50% of required events) have been observed. Safety endpoints will be analyzed in all randomized patients who receive ≥1 dose of study medication. The trial is currently open for accrual in the United States and Canada. Clinical trial information: NCT00968968.

TPS665 General Poster Session (Board #17A), Sat, 1:15 PM-5:00 PM

PAM50 HER2-enriched (HER2E) phenotype as a predictor of early-response to neoadjuvant lapatinib plus trastuzumab in stage I to IIIA HER2-positive breast cancer.

Maria Vidal, Lorena De La Pena, Mafalda Oliveira, Javier Cortes, Antonio Llombart, Aleix Prat, SOLTI Breast Cancer Research Group; Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; SOLTI, Barcelona, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; Hospital Arnau de Vilanova de Valencia, Valencia, Spain; The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Combinations of two different anti-HER2 therapies without chemotherapy have generated great expectations. However, it is unclear which group of patients benefits the most from this strategy. Within HER2-positive breast cancer, the PAM50 assay identifies a HER2-Enriched HER2-E intrinsic subtype characterized by high activation of the EGFR/HER2 pathway. Trial Design: This non-randomized, open label multi-centre translational research study will evaluate the ability of the HER2-E subtype to predict pathological complete response (pCR) to dual HER2 blockade with lapatinib and trastuzumab for a total of 18 weeks. Patients with hormone receptor (HR)-positive disease will also receive endocrine therapy. Eligibility Criteria: Operable primary Stage I-IIIa HER2+ breast cancer. Specific Aims: The primary objective is to evaluate the ability of the PAM50 assay to predict pCR in the breast at the time of surgery.Secondary objectives are to (1) assess the correlation of HER2-E with pCR in the breast and axilla, (2) assess the correlation of HER2-E with Residual Cancer Burden (RCB) (3) evaluate the gene expression changes from Day 0 to Day 14 and the correlations with Ki67-IHC at Day 14, (4), identify additional gene expression signatures predictive of pCR, and (5) evaluate safety and tolerability. **Methods:** The statistical plan is based on the assumption that breast pCR rate will be 35.0% for HER2-E tumors and 8.0% for non-HER2E. The study will have a 95% power with a significance level of 5% (two-sided) and an assumed drop-out rate of 15%. Biomarker Analyses: Baseline, 14-day treated and post-treatment (surgical) formalin–fixed, paraffin–embedded tissues will be obtained. The expression of 547 genes will be explored with the nCounter platform. Subtype will be identified using the PAM50 predictor (Parker et al. J Clin Oncol 2009). Ki-67-IHC will also be evaluated on pre-treatment and Day-14 samples. Target Accrual: 150 patients with a maximum of 75 HR-positive patients across Spain and Portugal. Patient enrollment will begin in May 2013.

TPS666 **General Poster Session (Board #17B), Sat, 1:15 PM-5:00 PM**

NSABP B-43: A phase III clinical trial to compare trastuzumab (T) given concurrently with radiation therapy (RT) to RT alone for women with HER2+ DCIS resected by lumpectomy (Lx).

Melody A. Cobleigh, Stewart J. Anderson, Thomas B. Julian, Kalliopi P. Siziopikou, Douglas W. Arthur, Rachel Rabinovitch, Ping Zheng, Eleftherios P. Mamounas, Norman Wolmark; Rush University Medical Center, Chicago, IL; 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; The Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA; National Surgical Breast and Bowel Program; Northwestern University Feinberg School of Medicine, Chicago, IL; Virginia Commonwealth University, Richmond, VA; National Surgical Breast and Bowel Project; University of Colorado, Aurora, CO; NSABP Biostatistical Center and University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA; MD Anderson Cancer Center Orlando, Orlando, FL

Background: A significant amount of DCIS is ER-negative and/or overexpresses HER2. This study will test HER2-targeted therapy in DCIS. Among T-treated HER2+ patients (pts) with DCIS treated with a single dose of T, T is found in ductal aspirates and antibody-dependent cell-mediated cytotoxicity activity for HER2 is increased. T boosts the effectiveness of RT in breast cancer xenograft models and cell lines. T given during whole breast irradiation (WBI) may improve results for HER2+ DCIS treated with lumpectomy (Lx). A trial to examine this question will enhance the understanding of breast tumor biology, the prevention of such tumors, and could possibly extend breast-conserving surgery benefits for women with DCIS. **Methods:** After Lx for pure DCIS, each pt's DCIS lesion is centrally tested for HER2 using ASCO/CAP guidelines. HER2+ pts are randomly assigned to receive 2 doses of T, 3 weeks apart during WBI or to WBI alone. Women ≥18 yrs with a margin-clear Lx for pure DCIS, with ECOG status 0/1 who are clinically or pathologically node negative are eligible. ER and/or PR status must be known before random assignment. Primary aims are to determine if T decreases ipsilateral breast cancer (IBC) recurrence, ipsilateral skin cancer recurrence, or ipsilateral DCIS. Secondary aims are to determine the benefit of T in preventing regional or distant recurrence and contralateral invasive breast cancer or DCIS. B-43 will determine if DFS, recurrence-free interval, and/or overall survival can be improved with the use of T. 2000 pts will be accrued over 7.9 yrs, with a definitive analysis of primary endpoints performed at163 IBC events (7.5 - 8 yrs after protocol initiation) with an 80% power to detect a hazard reduction of 36%, from 1.73 IBC events per 100 pt-yrs to 1.11 events per 100 pt-yrs. The 36% observed reduction in the hazard of IIBCR-SCR-DCIS on the T arm is based on a projection of 40% hazard reduction if the compliance were perfect, with a 10% noncompliance rate. As of 1-1-13, 1,127 pts have been randomized into the study. Support: PHS NCI-U10-CA-69651, -12027, and -P30-CA-14599 from the US NCI, and Genentech, Inc. Clinical trial information: NCT00769379.

TPS667 **General Poster Session (Board #17C), Sat, 1:15 PM-5:00 PM**

PERSEPHONE: Duration of trastuzumab with chemotherapy in women with HER2-positive early breast cancer—Six versus twelve months.

Helena Margaret Earl, David A. Cameron, David Miles, Andrew M. Wardley, Emma Ogburn, A-L Vallier, Shrushma Loi, Helen B Higgins, Louise Hiller, Janet A. Dunn, PERSEPHONE Trial Group; University of Cambridge, Department of Oncology, Cambridge, United Kingdom; University of Edinburgh, Edinburgh, Scotland; Mount Vernon Cancer Centre, Northwood, United Kingdom; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom; Cambridge Cancer Trials Centre, University of Cambridge, Cambridge, United Kingdom

Background: PERSEPHONE is a randomised controlled trial comparing six months of trastuzumab to the standard 12 months in patients with HER2 positive early breast cancer. **Methods:** 4000 patients (pts) will be randomised into the two arms (1:1). The power calculations assume that the disease-free survival (DFS) of the standard treatment (12 months trastuzumab) is 80% at 4 years. Randomisation of 4000 pts will allow the trial to prove non-inferiority of six months trastuzumab (5% 1-sided significance and 85% power). Non-inferiority is defined as 'no worse than 3%' below the control arm (12 month) 4 year DFS. Primary outcome is DFS, and secondary outcomes are overall survival (OS) non-inferiority; cost effectiveness; cardiac function and quality of life. Tumour blocks are collected to research molecular predictors of survival with respect to duration of trastuzumab treatment. Blood samples are analysed for single nucleotide polymorphisms (SNPs) as pharmaco-genetic determinants of prognosis, toxicity and treatment outcome. PHARE, a similar trial from the Institut National du Cancer in France, closed to recruitment in 2010 and presented early data at ESMO 2012. Following this an unplanned interim analysis of PERSEPHONE was presented to the Data Monitoring and Safety Committee (DMSC). PERSEPHONE is funded by the NIHR HTA programme in the UK. Results: PERSEPHONE commenced recruitment in October 2007. At abstract submission, 2593 pts (65%) had been randomised from 144 UK sites. Recruitment is due to complete in September 2014 with the first planned interim analysis of the primary outcome mid-2016. The iDMSC reviewed all data available on HERA and PHARE as well as a PERSEPHONE interim analysis. There were no safety findings or signals that would warrant a change of the study plan and the high quality of data returns was noted. Conclusion: PERSEPHONE continues the active recruitment phase as planned. Preliminary but inconclusive PHARE data have reinforced interest in the PERSEPHONE trial both nationally and internationally. There has been full support from the Breast International Group (BIG) and the international breast cancer community to answer this important shorter duration question. Clinical trial information: 52968807.