breast cancer, early stage

2460
DOSE-DENSE SEQUENTIAL ADJUVANT CHEMOTHERAPY WITH EPIRUBICIN, PACLITAXEL AND CMF VERSUS EPIRUBICIN, PACLITAXEL AND CMF FOLLOWED BY TRASTUZUMAB FOLLOWED BY TRASTUZUMAB FOR ONE YEAR IN PATIENTS WITH EARLY BREAST CANCER


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Background: Dose-dense sequential chemotherapy including anthracyclines and taxanes has been well established in the adjuvant setting of high-risk operable breast cancer. However, the preferable taxane and optimal schedule of administration have not been defined as yet.

Patients and methods: From July 2005 until November 2008, 1,001 patients (990 eligible) were randomized to receive 3 cycles of epirubicin 110 mg/m² followed by 3 cycles of paclitaxel 80 mg/m² weekly in the concurrent arm or to 3 cycles of epirubicin followed by 3 cycles of CMF (cyclotaxane 50 mg/m²; methotrexate 57 mg/m²; fluorouracil 840 mg/m²) with G-CSF support (Group A; 333 patients) or to 3 cycles of epirubicin followed by 3 cycles of CMF, as in Group A, followed 3 weeks later by 9 weekly cycles of docetaxel 35 mg/m² (Group B; 331 patients) or 9 weekly cycles of paclitaxel 80 mg/m² (Group C; 328 patients). Radiation and hormonal therapy were given after the completion of chemotherapy.

Trastuzumab was administered for 1 year to all HER2-positive patients post radiation.

Results: At a median follow up of 60 months, 123 patients had documented disease relapse (51 in Group A, 37 in Group B and 35 in Group C) and 81 deaths (30 in group A, 22 in group B and 29 in group C) had been observed. The 3-year disease-free survival (DFS) rate was 86%, 91% and 89%, with overall survival (OS) rates of 96%, 97% and 96%, respectively. No differences were found in DFS or OS between the three treatment groups (log-rank, p = 0.38 and p = 0.48, respectively). The most frequently reported severe adverse events were neutropenia (29% vs 27% vs 24%, p = 0.31) and leucopenia (12% vs 13% vs 10%, p = 0.66). Febrile neutropenia occurred in fifty patients (6%, vs 5% vs 5%, p = 0.81). Severe mucositis was more frequent in Group B (3% vs 6% vs 1%, p = 0.001), while severe neuropathy was more frequent in Group A (4% vs 0% vs 1%, p < 0.001).

Conclusions: No significant differences in DFS and OS between the three regimens were identified. Taxane regimen and schedule of administration preferentially influenced the type of severe toxicities. HER2-positive patients demonstrated comparable 3-year DFS and OS rates with those reported in other similar studies.

Disclosure: All authors have declared no conflicts of interest.

2470_PR
THE DISCREPANCY BETWEEN HIGH PATHOLOGICAL COMPLETE RESPONSE (pCR) RATE AND LOW BREAST CONSERVING SURGERY (BCS) FOLLOWING NEOADJUVANT THERAPY: ANALYSIS FROM THE NEOALTTO TRIAL (BIG 1-06)

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Background: The NeoALTTO trial showed that taxalixed plus lapatinib and trastuzumab nearly doubles the rate of pCR compared to paclitaxel combined with either drug alone (51.3% vs 29.5% vs 24.7%). However, this high pCR rate did not translate into a higher rate of BCS, which was around 40% across the 3 arms. We investigated different factors that may have a effect on the choice of surgery.

Patients and methods: In the NeoALTTO trial, patients (pts) with HER2+ breast cancer were randomized to either trastuzumab, lapatinib or their combination concomitantly with paclitaxel prior to surgery. The 1st endpoint was pCR, defined as the absence of invasive cancer in the breast at the time of surgery. Here, we investigated the association between achieving pCR, and type of surgery, age, histology, grade, tumor size, ER status, multi-centricity, response to therapy and the country where the treatment was given.

Results: 429 pts were eligible for the analysis (26 have been excluded as they did not undergo breast surgery), of whom 160 (37%) achieved a pCR. 242 (57%) and 187 (43%) pts had mastectomy and BCS, respectively. Mastectomy was more frequent if the patient was < 50, if treated in developing country, if the tumor was multicientric, >5 cm, or ER. All pts diagnosed with lobular cancer (n = 17) underwent mastectomy regardless of pCR. 68 pts had a radiological complete response, yet 36 of those (53%) were subjected to mastectomy (25 pts (70%) achieved a pCR). Of the 128 pts considered for BCS at screening, only 95 (74%) had a conservative surgery and rates were similar according to pCR status (79% in pCR vs. 72% in no pCR). Conversely, 36% of pts initially evaluated as inoperable or requiring mastectomy had a BCS.

Conclusion: Tumor characteristics prior to neoadjuvant therapy appeared to play a main role in deciding the type of surgery irrespective of response. This may delay a large fraction of women the chance of preserving their breast. These results should be taken into account in addressing the criteria for BCS after neoadjuvant therapy; GSK distributed the study drugs and provided financial support to the NeoALTTO trial, but imposed no restriction to the current analysis.

Disclosure: E. De Azambuja: advisory board from GSK; honoraria from Roche. M. Piccart: Consulting/advisory role/honoraria from SanofiAventis, Amgen, Bayer, Bristol Myers Squibb, Roche, Glaxo Smith Kline, Boehringer, Pharmar. S. Di Cosimo: Speaker for GSK. All other authors have declared no conflicts of interest.

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ANALYSIS OF CORRELATION BETWEEN WEIGHT AT DIAGNOSIS, WEIGHT GAIN AFTER BREAST CANCER TREATMENT AND RECURRENCE IN WOMEN WITH EARLY STAGE BREAST CANCER (EBC)

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Background: Overweight at the time of EBC diagnosis has been linked frequently to poorer survival in most studies and some evidence suggests that women who gain weight after breast cancer diagnosis are at increased risk of cancer recurrence and death. Most previous studies on this topic have relied on retrospective chart reviews. The aim of this prospective, observational, single-center study is to determine whether weight at diagnosis and weight gain after EBC treatment are predictive of BC recurrence.

Methods: From August 1997 to March 2012, the study included a total of 320 EBC patients (stage I-IIA). We assessed weight and body mass index (BMI = kg/m²) at baseline (≤ 1 month after surgery) and 24 months after completion of treatment (chemotherapy ± radiotherapy). The chi square test (X²) was conducted to determine if a significant correlation exists between BC recurrence and 3 categories of BMI at diagnosis (lean weight: BMI <25; overweight: BMI 25-30; obese: BMI >25) and BC recurrence and weight changes after EBC treatment (loss of <1 kg/m²; loss of ≥ 1 kg/m²; gain of <2 kg/m²; gain of ≥2 kg/m²).

Results: Median age was 55 years (range 28-81); 58% of patients were postmenopausal, stage I-II in 89%; ER+/HER2- in 69%; ER-/HER2+ in 20%; 72% underwent conservative surgery + radiotherapy; 57% received chemotherapy (CT) and 78% received endocrine therapy alone or after CT. Median BMI at diagnosis was 26.8, after treatment 27.7. After a median follow up of 13 years 194 patients recurred. Statistical analysis is reported in table 1.

Conclusions: Our findings show that EBC patients gain weight after treatment. A significant correlation was found between weight gain after EBC treatment and recurrence, suggesting that women who gain weight after breast cancer diagnosis may be at increased risk of poor outcomes.

Disclosure: All authors have declared no conflicts of interest.
| Purpose: This study aimed to identify predictive proteomic biomarkers of outcome in women with estrogen and/or progesterone receptor-positive (ER/PR-positive) breast cancer after adjuvant tamoxifen, with sufficient power to alter patient management.

**Methods:** Using reverse phase protein arrays (RPAs), 140 antibodies were applied to a training set of 197 ER/PR-positive breast cancers to identify predictors. An algorithm was developed that predicted patient outcomes using a subset of antibodies. Since RPFA is a useful exploratory tool but does not lend itself as a practical clinical tool to assay validated biomarkers, quantitative immunochemistry for selected proteins was applied to 313 ER/PR-positive breast cancers (test set) for validation. Seventy-seven other ER/PR-positive cancers with transcriptional profiling data were used to compare the performance of the proteomic biomarkers and established genomic predictors. All patients were treated with adjuvant tamoxifen after loco-regional therapy.

**Results:** Two different combinations (4-protein/3-protein models) of four proteins (CCNB1/PAI1/PR/CIB1), subdivided lymph node-negative breast cancer patients into low-, medium- and high-risk groups with significantly different 10-year recurrence-free survival. The proteomic markers predicted 10-year distant metastasis-free survival in lymph node-negative patients in the test set (log-rank test) for validation. Seventy-seven other ER/PR-positive cancers with transcriptional profiling data were used to compare the performance of the proteomic biomarkers and established genomic predictors. All patients were treated with adjuvant tamoxifen after loco-regional therapy.

**Conclusion:** This study validates proteomic biomarkers that can be assayed in a practical inexpensive manner using immunochemistry, to identify lymph node-negative ER/PR-positive patients with excellent outcomes after adjuvant tamoxifen.

**Disclosure:** All authors have declared no conflicts of interest.

| **Conclusion:** This study suggests that miRNA expression could contribute to assess molecular prognosis of breast cancer and identifies clusters of miRNAs that could improve outcome prediction. A validation study in node-negative and triple negative disease is planned.

**Disclosure:** All authors have declared no conflicts of interest.

| **Purpose:** This study aimed to identify proteomic predictors of outcome after adjuvant anti-hormonal therapy for hormone receptor-positive breast cancer.

**Methods:** Seventy-seven other ER/PR-positive cancers with transcriptional profiling data were used to compare the performance of the proteomic biomarkers and established genomic predictors. All patients were treated with adjuvant tamoxifen after loco-regional therapy.

**Results:** Two different combinations (4-protein/3-protein models) of four proteins (CCNB1/PAI1/PR/CIB1), subdivided lymph node-negative breast cancer patients into low-, medium- and high-risk groups with significantly different 10-year recurrence-free survival. The proteomic markers predicted 10-year distant metastasis-free survival in lymph node-negative patients in the test set (log-rank test) for validation. Seventy-seven other ER/PR-positive cancers with transcriptional profiling data were used to compare the performance of the proteomic biomarkers and established genomic predictors. All patients were treated with adjuvant tamoxifen after loco-regional therapy.

**Conclusion:** This study validates proteomic biomarkers that can be assayed in a practical inexpensive manner using immunochemistry, to identify lymph node-negative ER/PR-positive patients with excellent outcomes after adjuvant tamoxifen.

**Disclosure:** All authors have declared no conflicts of interest.

| **Conclusion:** This study demonstrates high variability in adjuvant chemotherapy treatment advice between multidisciplinary teams from 4 different European hospitals based on traditional patient and tumor related parameters. MammaPrint disclosure) and increased to 79% after disclosing MammaPrint and in 22% of patients by the Belgian team. The inter-institutional agreement for treatment advice was assessed again. Discordance in treatment advise between the 4 multidisciplinary teams was determined and the impact of MammaPrint was measured. Discordance in treatment advise between the 4 multidisciplinary teams was determined and the impact of MammaPrint was measured.

**Disclosure:** All authors have declared no conflicts of interest.
META-ANALYSIS OF PROSPECTIVE EUROPEAN STUDIES ASSESSING THE IMPACT OF USING THE 21-GENE RECURRENCE SCORE ASSAY ON CLINICAL DECISION MAKING IN WOMEN WITH ER-POSITIVE, HER2-NEGATIVE EARLY STAGE BREAST CANCER

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Background: The Oncotype DX Recurrence Score is a validated assay to help inform the appropriate treatment of estrogen receptor-positive (ER+), early stage breast cancer. Adjuvant treatment traditions vary significantly among different countries. Prospective studies assessing the impact of the Oncotype DX test on adjuvant treatment decisions have been performed in several European countries. This is a meta-analysis of these studies.

Methods: Four prospective studies assessing the impact of using the Recurrence Score result on clinical decision making in patients with node negative and pN1 (mi) disease were identified. Node positive patients were excluded. The identified studies had a similar study design with consecutive patients and treatment recommendations before and after having the Recurrence Score results were recorded. In three of the studies, medical oncologists completed questionnaires regarding their confidence in their recommendation before and after knowing the patient’s Recurrence Score result. The final results of the studies in Germany, Spain and the UK have been presented and final data from the French study will be presented at ASCO 2012.

Results: A total of 589 patients with node negative or pN1 (mi) ER pos HER2 negative early breast cancer were included in the four identified studies. Overall, 45% (range 36-52%) of patients in these studies were recommended chemo-endocrine and 55% endocrine treatment alone. After having the Recurrence Score result, 47% (range 38-68%) of patients recommended chemotherapy was changed to endocrine treatment alone and 17% (range 11-22%) of those recommended endocrine treatment alone were recommended chemo-endocrine treatment. There was a significant improvement in physician confidence in treatment recommendations when using the assay.

Conclusion: Using Oncotype DX’ is associated with a significant change in treatment decisions and a reduction in chemotherapy use in studied European countries despite differences in therapeutic traditions. The consistency of the results from different countries underlines the tests utility.


SECRAB (SEQUENCING OF CHEMOTHERAPY AND RADIOTHERAPY IN ADJUVANT BREAST CANCER) COSMESIS RESULTS

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Background: SECRAB, a randomised trial comparing sequential (Seq) to synchronous (Syn) chemoradiotherapy using a CMF or Anthracycline-CMF regimen, demonstrates reduces local recurrence rates after Syn treatment for early breast cancer (EBC) (Fernando 2011 EJC47 S2). Cosmesis study results are presented.

Methods: 2296 women were randomised and cosmesis was assessed in 382. Cosmesis and telangiectasia were assessed as excellent, good, moderate and poor for patients having wide local excision (WLE) while telangiectasia alone was assessed for those having mastectomy. Photographs were taken for 301 patients for blinded independent review using a consensus method (Havlind 2008 Clin Oncol 20:497). Patient perception was assessed using EORTC BR23 quality of life questionnaire (Q 39-42). Assessments were made at baseline, 1, 2 and 3 years post surgery.

Results: The results of clinician assessed cosmetics and telangiectasia are shown below. There was no statistically significant difference between the arms. Data on independent assessment of change in breast appearance after WLE was available for 145 (98%) patients. Minimal, mild and marked changes were observed in 70, 29 and 1% of patients respectively for the Syn arm and 72, 28 and 0% for the Seq arm. There was no difference between treatment arms (OR, mild/marked vs minimal, 1.10, 95% CI 0.54-2.26, p = 0.8). There was no change in patient’s perception of their breast appearance (baseline vs. final assessment questionnaire).

Conclusions: There was no significant difference in cosmetics or telangiectasia between the two arms as assessed by the clinician or by independent photographic review. There was no difference in patient perception of breast appearance. Contrary to the result of the main study, which showed a borderline significant worsening of telangiectasia in the Syn arm, no such difference was seen in the cosmetics syn. Chemoradiotherapy reduces local recurrence in EBC without affecting cosmetics.

Disclosure: All authors have declared no conflicts of interest.

Table: 253PD

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<td>99 (62)</td>
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PATHOLOGICAL COMPLETE RESPONSE TO TRASTUZUMAB SUBCUTANEOUS FIXED-DOSE FORMULATION IN THE HANNAH STUDY: SUBGROUP ANALYSIS OF PATIENT DEMOGRAPHICS AND TUMOR CHARACTERISTICS INFLUENCE OF BODY WEIGHT (BW) AND SERUM TROUGH CONCENTRATION (CTROUGH) OF TRASTUZUMAB

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Background: Intravenous (IV) trastuzumab (H) is the standard of care for HER2-positive breast cancer. The Phase III, neoadjuvant/adjuvant HannaH study (Jackisch et al. EBCC 2012) demonstrated the non-inferiority of H subcutaneous (SC) vs. H-IV with respect to serum Ctrough, of H and pathological complete response (pCR), with comparable safety profiles for the two formulations. The aim of the presented analyses was to determine whether pCR rates (H-SC vs. H-IV) were influenced between subgroups, and to investigate the relationship of pCR with BW and serum Ctrough of H.

Methods: Subgroup analyses of pCR were performed in the per-protocol population (PPP) based on patient demographics (race, age [≤ 65 and ≥ 65 years]) and disease characteristics (breast cancer type/subtype/histological grade, hormone receptor status). Further analyses, including multiple logistic regression (MLR), investigated the relationship of pCR rate with BW and serum Ctrough of H. Covariates in the MLR model included treatment arm, serum Ctrough, BW, and all interactions between covariates, in order to account for the different dosing schemes (BW-based vs. fixed dosing).

Results: pCR subgroup analyses showed that the numerically higher pCR rate point estimate in H-SC vs. H-IV was reflected in the majority of subgroups, with all confidence intervals for the rate difference (SC-IV) containing '0'. The findings of the PPP analysis were supported by results obtained in the ITT population. Further analyses, including MLR, showed that neither BW nor serum Ctrough of H correlated with pCR rates in either treatment arm.

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Conclusions: BW and serum C\textsubscript{\text{ough}} of H did not impact on efficacy (pCR). The 600 mg fixed dose of H-SC is efficacious irrespective of BW. This finding supports H-SC as a treatment alternative to the registered IV formulation.

Disclosure: B. Melchior, Prof. Melchior has participated in advisory board meetings and received honoraria from F. Hoffmann-La Roche Ltd. L. Li; Jing Li is an employee of F. Hoffmann-La Roche Ltd, and owns stock in Roche Holdings. T. van der Horst: Tina van der Horst is an employee of F. Hoffmann-La Roche Ltd. S. Muehlbauer. Susanne Muehlbauer is an employee of F. Hoffmann-La Roche Ltd and owns stock in Roche Holdings. C. Jackisch: Christian Jackisch has participated in advisory board meetings for F. Hoffmann-La Roche Ltd. All other authors have declared no conflicts of interest.

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**CORRELATION BETWEEN CIRCULATING TUMOR CELLS (CTCS), PET/CT RESPONSE AND PATHOLOGICAL COMPLETE RESPONSE (pCR) IN PRIMARY HER2-POSITIVE (HER2+) BREAST CANCER PATIENTS: A SUB-STUDY FROM THE NEOALTOO TRIAL**

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Background: Although CTC detection has been studied in patients receiving preoperative chemotherapy, fewer data exist for preoperative chemotherapy combined with anti-HER2 agents. Here, we report a sub-study of CTC detection within the NeoALTOO trial.

Methods: NeoALTOO is a randomized phase III trial in which patients with primary HER2+ breast cancer were randomized to trastuzumab, lapatinib or placebo combined with taxanes. Here, we report a sub-study of CTC detection within the NeoALTOO trial.

Results: Out of 455 patients randomized, samples for CTC analysis were collected in 3/31 (10%) patients. No significant association was observed between CTC detection and primary tumor characteristics, pCR and PET/CT response (at week 2 & 6) were assessed using the chi-square test.

Conclusion: The rationale behind PCI is to control or eradicate undetectable micro-metastases before they become clinically significant without inducing severe adverse effects. PCI associated with decreased incidence of CNS metastases tolerated toxicities and did not negatively affect patient survival. This may be translated into therapeutic gain at least for this short follow up period which warrants further evaluation after a longer follow up period.

Disclosure: All authors have declared no conflicts of interest.

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**EGFR AND P53 EXPRESSION IN ANDROGEN RECEPTOR (AR)-POSITIVE, TRIPLE NEGATIVE BREAST CANCER (TNBC)**

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Background: TNBCs are a heterogeneous group characterized by lack of ER/PR/HER2 expression. In contrast, no association was observed with p53 and AR. These results are consistent with published reports, where AR expression in TNBCs is low and p53 expression is more frequent in AR- than AR+ tumors. EGFR was expressed more frequently in AR- than AR+ tumors (111/143 (78%) vs 9/164 (6%)).

Methods: Methods: We identified 1,032 patients (pts) with resectable, TNBC (ER/PR < 1%; HER2 < 2 + /FISH < 2) who had surgery at MSKCC (1998-2006). Exclusions: neoadjuvant chemotherapy, prior XRT, inflammatory/metastatic BC. TMA's were constructed from 210 readily available primary tumors (> 1 cm) with each tumor represented by 3 cores. AR was determined with DAKO Clone AR441, dilution (dil) 1:500; ratio of DAB nuclear staining to hematoxylin signal >1 SD above mean was defined as AR+. EGFR and p53 were tested with Thermo-Scientific Clone EP80, dil 1:50 and DAKO Clone D07, dil 1:50, respectively. Scoring: 0-1+ negative, 2-3+ positive. Fisher's exact test used to evaluate correlation between AR with EGFR and p53. RFS and OS evaluated using Kaplan-Meier methods. Clinical-pathologic variables by AR status were compared using Chi-square test.

Results: 166 pts had adequate cores for AR testing. 10% were AR+ (17/166). 160 pts were evaluable for EGFR and 164 pts for p53. Median (med) followup: AR+ = 6 years (yr), AR- = 5.6y. Adjuvant chemotherapy received: AR+ 82%, AR- 87%. P=0.40. EGFR was expressed more frequently in AR- than AR+ tumors (111/143 (78%) vs 9/17 (53%); P=0.04). p53 expression was similar in AR- and AR+ TNBCs (82/147 (56%) vs 7/17 (41%); P=0.30). Clinical-pathologic variables based on AR and EGFR status appeared similar. 3y RFS and OS data are available.

Conclusion: Consistent with published reports, loss of EGFR expression correlates with p53 expression and clinicopathologic features of AR+ TNBC from a retrospective cohort at MSKCC.

Methods: We identified 1,032 patients (pts) with resectable, TNBC (ER/PR < 1%; HER2 < 2 + /FISH < 2) who had surgery at MSKCC (1998-2006). Exclusions: neoadjuvant chemotherapy, prior XRT, inflammatory/metastatic BC. TMA's were constructed from 210 readily available primary tumors (> 1 cm) with each tumor represented by 3 cores. AR was determined with DAKO Clone AR441, dilution (dil) 1:500; ratio of DAB nuclear staining to hematoxylin signal >1 SD above mean was defined as AR+. EGFR and p53 were tested with Thermo-Scientific Clone EP80, dil 1:50 and DAKO Clone D07, dil 1:50, respectively. Scoring: 0-1+ negative, 2-3+ positive. Fisher’s exact test used to evaluate correlation between AR with EGFR and p53. RFS and OS evaluated using Kaplan-Meier methods. Clinical-pathologic variables by AR status were compared using Chi-square test.

Results: 166 pts had adequate cores for AR testing. 10% were AR+ (17/166). 160 pts were evaluable for EGFR and 164 pts for p53. Median (med) followup: AR+ = 6 years (yr), AR- = 5.6y. Adjuvant chemotherapy received: AR+ 82%, AR- 87%. P=0.40. EGFR was expressed more frequently in AR- than AR+ tumors (111/143 (78%) vs 9/17 (53%); P=0.04). p53 expression was similar in AR- and AR+ TNBCs (82/147 (56%) vs 7/17 (41%); P=0.30). Clinical-pathologic variables based on AR and EGFR status appeared similar. 3y RFS and OS data are available.

Conclusion: Consistent with published reports, loss of EGFR expression correlates with p53 expression and clinicopathologic features of AR+ TNBC. In contrast, no association was observed with p53 and AR. These

Disclosure: All authors have declared no conflicts of interest.
data are hypothesis generating regarding the mechanism of interaction of AR and EGFR in TNBC.

Disclosure: All authors have declared no conflicts of interest.

**PROGNOSTIC FACTORS IN EARLY-STAGE TRIPLE NEGATIVE BREAST CANCER (TNBC), THE LIMITS OF CLINICAL AND PATHOLOGICAL FEATURES**

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Background: Triple negative breast cancer (TNBC) patients (pts) is an heterogeneous population regarding prognostic. Therefore, clinical and histological features were evaluated in a large monocenter cohort of patients treated for localized TNBC to identify good-prognostic TNBC.

Methods: All consecutive early-stage TNBC (ER 0%, PR 0%, HER2 neg) patients treated at European Georges Pompidou Hospital, Paris, France, between 2000 and 2011 were included. Records were reviewed for demographic, clinical and pathological data. Prognostic factors were determined using univariate and multivariate stepwise log-rank analysis on disease-free survival (DFS) and overall survival (OS).

Results: This analysis included 128 women with early-stage TNBC. Clinical and histological characteristics are summarized below. After a median follow-up of 37 months 36 relapses and 19 deaths were observed. The 3-years recurrence rate was 30% (95%CI 22-40) in the whole population. For DFS, bad prognostic factors in univariate analysis were: large tumor size (T3-4), node involvement (N1-3), node capsular effraction, lymphovascular invasion (LVI) and high grade (SBR 2-3). Multivariate analysis identified tumor size (T3-4) (HR 3.70, 95%CI 1.61-8.52) and LVI (HR 2.87, 95%CI 1.39-5.93) as independent factors. The 3-years recurrence rate remained high in patients with good prognostic features. Therefore, new biomarkers are mandatory for a better stratification of this heterogeneous population.

Table: Clinical and histological characteristics

<table>
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*Due to neoadjuvant chemotherapy **Due to small biopsies.

Disclosure: S. Haouas: Grant from Association pour la Recherche en Therapeutiques Innovantes en Cancerologie (ARTIC). All other authors have declared no conflicts of interest.

**CLINICAL BEHAVIOR AND PROGNOSIS OF DIFFERENT IMMUNOHISTOCHEMISTRY-DETECTED SUBTYPES OF INVASIVE BREAST CANCER: A MONOINSTITUTIONAL SERIES**

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Background: Invasive breast cancer (IBC) is a heterogeneous disease. Gene expression profiling has identified several biologically distinct subtypes of IBCs. As proposed by Cheang et al, immunohistochecmical (IHC) markers can be used as a surrogate for the molecular classification of IBC.

Purpose: To evaluate different clinical behavior, relationship with other clinical-pathological features and survival outcomes of patients (pts) with different subtypes of IBC as classified using IHC markers.

Methods: We evaluated 3461 IBC pts treated from 1995 to 2008 classified as: luminal A (ER and PR +, HER2- and Ki67 <14%), luminal B (ER and/or PR +, HER2- and Ki67 ≥14%), luminal C (ER and/or PR +, HER2 +, any Ki67), HER2+ (ER and PR +, HER2 +, any Ki67), triple-negative TN (ER- and PR-, HER2-), any Ki67). Log-rank test and Cox regression model were performed to evaluate the impact of IHC subtypes on overall survival (OS), Event Free Survival (EFS) and their correlation with other known prognostic factors.

Results: We identified 909 (26.4%) luminal A, 1722 (49.9%) luminal B, 325 luminal C (9.4%), 209 (5.7%) HER2+ and 296 (8.6%) TN. Median age was 61 years. A was more frequently associated with older age, smaller size, negative axilla involvement, low grade (p <0.001). There were 644 (18.6%) events (local and distant relapses, contralateral and second tumors): 100 in luminal A (11%), 334 in luminal B (19.4%), 62 in luminal C (19%), 66 in HER2+ (31%) and 84 in TN (28%). Different subtypes showed preferential sites of first local or distant relapses: luminal A had more bone and loco-regional and less visceral relapses than other subtypes. Median disease free interval (DFI) was longer in luminal A (60.3 months) than in luminal B (39.1 m), C (27.8 m), HER2 (30.8 m) and TN (23.3 m). At median follow up of 77 months, EFS and OS were 94.0 and 92.1% in luminal A, 86.2 and 82.7% in luminal B, 86.2 and 86.8% in luminal C, 72.7 and 72.7% in HER2 +, 78.0% and 73.9% in TN (p <0.001). Luminal A presented the best prognosis among other luminal subtypes. IHC-based subtypes prognosis (EFS and OS) was independent of nodal status, grading, tumor size and age.

Conclusions: In our experience IHC-based classification appeared to be useful to divide IBCs in different biological entities. Its application could help the tailoring of adjuvant therapies improving patient outcomes.

Disclosure: All authors have declared no conflicts of interest.

**PERITUMORAL VASCULAR INVASION AS PRINCIPAL ISTOLOGICAL PROGNOSTIC FACTOR IN TNBC**

Oncology Division, Fondazione Salvatore Maugeri, Pavia, ITALY

Purpose: Triple-negative breast cancers (TNBC) is a specific histological subclass of breast cancer that has gained attention in recent years for its clinical and molecular heterogeneity with still no evidence of an optimal therapeutic strategy. Aim of this study is to identify clinical and pathological features of TNBC reviewed in our center and try to figure out prognostic factors that can drive therapeutic approach.

Methods: In this retrospective study we reviewed 127 cases of TNBC (median Age 59) that underwent surgical treatment from 2003 to 2008 analyzing the outcome (in terms of Disease Free Survival) in relation to clinical and pathological features.

Results: Univariate analysis performed on the entire cohort revealed that the cha Staging (P <0.0001, HR = 7.8245 [1.59-38.27]), the lympho-plasmacytic peritumoral reaction (P = 0.011, HR = 3.1600 [0.6133 to 6.1164]), node involvement (P = 0.012, HR = 1.9083 [1.0210 to 3.5667]) and peritumoral vascular invasion (PVI) (P <0.0001, HR: 4.0261 [1.6808 to 9.7602]) are all prognostic factor of DFS. Multivariate analysis confirmed, in particular, PVI, observed in 24% of cases, as the main prognostic factor (P <0.0001, HR 3.5655 [1.2-10.3]).

Conclusions: In the TNBC several genes involved in angiogenesis are frequently pointed out. In our hands peritumoral vascular invasion is a major prognostic factor that would identify a subgroup of TNBC with worse prognosis and therefore this would require a more aggressive therapeutic regimen with the inhibition of angiogenesis as a possible tool for the optimal treatment.

Disclosure: All authors have declared no conflicts of interest.
Background: Tumor characteristics and patterns of recurrence in luminal A, luminal B, Her2 pos and triple negative breast cancer (bc) patients (pts) 70 years and older are still an area of uncertainty. In this investigation clinical pathological characteristics, disease recurrence and death were analysed according to the four bc subcategories and age in pts 70-79 years.

Methods: Data of 274 elderly bc pts (≥70 years of age) diagnosed between 1998 and 2004 were retrospectively analysed by computer based chart information. Baseline tumor characteristics, patient demographics and patterns of recurrence were compared between luminal A, luminal B, Her2 pos and triple negative bc pts and 3 age categories (70-75, 76-80, ≥81 years).

Results: Mean age was 76.95 years and mean time of follow-up was 52.23 months (range 0-144 months). Overall, recurrences were detected in 18.4% of pts. At the end of follow-up 69.0% of pts were alive, 15.0% and 16.1% died from bc and from other causes, respectively (p < 0.001). Median overall survival (OS) was 114.1 months (95% confidence interval 100.3-181.7 months). 41.1%, 20.4%, 16.1% and 12.5% of patients had luminal A, luminal B, Her2 pos and triple negative bc, respectively. No significant differences were found regarding recurrences according to bc subtypes (p = 0.24). Triple negative bc had a significantly shorter OS compared to luminal A, luminal B and Her2 pos bc (72.7 months vs 124.1, 119.4 and 105.0 months, respectively (p < 0.001)). Overall, 21.5% of pts received no therapy. Pts aged ≥81 years (15.8%) received significantly less (p < 0.01) chemotherapy/anti-hormonal therapy compared to pts ≤80 years. Pts aged 70-75 years (42.7%) had significantly (p = 0.032) more recurrences compared to pts 76 years or older. Pts aged 70 - 75, 76 - 80 and ≥81 years had median OS of 116.9, 115.4 and 73.1 months.

Conclusions: Pts aged 70-75 years had significantly more recurrences; perhaps due to their lower risk of death from other causes. These data emphasize the necessity to foresee all bc subgroups of the elderly for adjuvant treatment irrespective of age but carefully considering co-morbidities, performance status and life expectancy.

Disclosure: All authors have declared no conflicts of interest.

Discussion: The Asian ethnic minority population had a younger age at diagnosis, shorter follow-up and better outcome than non-Asian. The Asian ethnic minority population had a younger age at diagnosis, and more likely to undergo mastectomy (46% vs 34%) and chemotherapy (28% vs 68%) than non-Asians. Tumour grade, stage and receptor status were not different statistically between the two groups. Median age, tumour size, number of nodes involved, disease-free survival and overall survival, respectively, was 52.5 years, 22mm, 2/19, 148 months and 177 months. Multivariate analysis identified risk factors of tumour size > 2cm (hazard ratio HR = 1.51, confidence interval CI 1.06-2.41, p value 0.02), >10 lymph nodes involved (HR = 2.64, CI 1.75-3.98, p-value <0.0001) and receptor positivity (HR = 0.40, CI 0.26-0.60, p-value <0.0001).

Conclusion: Characteristics and outcome in our cohort are consistent with the literature. The Asian ethnic minority population had a younger age at diagnosis, higher mastectomy and adjuvant chemotherapy rates.

Disclosure: All authors have declared no conflicts of interest.
Results: Of the 400 patients, 139 (34.8%) were under 35 years old and 261 (65.2%) were 35-39 years old with a median follow-up of 72.5 months (range, 1-211 months). Postoperative radiation therapy was associated with longer DFS (HR, 0.13; p = 0.007) and OS (HR, 0.017; p = 0.001) in multivariate analysis of the 400 patients. However, there were no significant differences in clinicopathological factors, DFS and OS between under 35 years and those 35-39 years of age.

Conclusion: Our results suggested that postoperative radiation therapy improved the prognosis in young breast cancer patients. However, age at diagnosis was not associated with DFS or OS in patients under 40 years. Therefore, we recommend patients under 40 years to receive unified therapy.

Disclosure: All authors have declared no conflicts of interest.

BREAST CANCER IN YOUNG WOMEN IN INDIA

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Background: The incidence of breast cancer is rising in India. It presents at a younger age in Indian population as compared to the western countries. Aims and objectives: This is a retrospective study of all breast cancer patients less than 40 years of age treated in single tertiary care center from June 2006 to June 2011. The aim was to assess the factors that may influence clinical outcome and prognosis including demographics, clinical characteristics and pathological findings and treatment.

Materials and methods: Clinical data was collected from medical records. Variables like age, stage at presentation, surgery type, chemotherapy, radiation, tumour size, grade, nodal status, perinodal extension, lymphovascular emboli, ER, PR and Her2 neu status were analyzed in relation to outcome.

Results: Out of 613 breast cancer patients, 91 were under 40 years of age corresponding to an incidence of 14.8%. Median tumour size was 3 cm and lymph node positivity was 56.9%. Lymphovascular emboli was positive in 42 patients (48.8%) and perinodal extension was positive in 36 patients (41.8%). Thirty patients (34.8%) were ER positive, while 39 patients (45.3%) were PR positive. Her 2 neu receptors were positive in 20 patients (23.2%). Thirty nine patients were triple negative (45.3%). The median follow up period was 27 months with the DFS being 73.2% and OS being 87.2%. In univariate analysis, factors significantly associated with survival were stage at presentation, presence of lymphovascular emboli, presence of perinodal extension and grade of the tumour.

Conclusions: Breast cancer in India is seen in younger patients and most of these are triple negative breast cancers. Patients with breast cancer below 30 years of age are surviving more than the age group of 30 to 40 years. Survival of young breast cancer patients in India is comparable to western studies.

Disclosure: All authors have declared no conflicts of interest.

TUMOR CHARACTERISTICS, TREATMENT AND OVERALL SURVIVAL (OS) IN BREAST CANCER PATIENTS (PTS) OVER 80 YEARS: A COHORT FROM A SINGLE INSTITUTION

C. Batkin1, A. Donnadieu1, A. Kramar2, V. Servent1, J. Bonnettem3

1Breast Cancer, Centre Oscar Lambret, Lille, FRANCE, 2Biostatistics, Centre Oscar Lambret, Lille, FRANCE, 3Breast Cancer, Centre Oscar Lambret, Université Lille Nord de France, Lille, FRANCE

The incidence rate of breast cancer in elderly women over 75 years old is 220 per 100000 in France and is likely to increase in the future. We studied the impact of tumor and treatment characteristics on overall survival.

Patients and methods: Data were collected for 208 non metastatic breast cancer pts over 80 years (pts1) treated, from January 2006 to December 2009. Pathological data were obtained on a biopsy or on mastectomy specimens if patients had not received presurgical treatment.

Statistical methods: Survival rates were estimated by Kaplan-Meier method. Tests were performed with the logrank test. Five year relative survival rates were estimated by Ederer2 method.

Results: Median age at diagnosis was 83 years (80-95). 29% tumors were T1, 58% T2 and 15% T3, 4% T4 (66%) were ductular, 34% (16) lobular and 38 (18%) had another histological type. SBR grade (I/II/III) was 22/49/29 and unspecified in 42 (20%). 167 pts (80%) were ER+, 129 (62%) PR+; 40 (19%) ER- and 171 (81%) ER+/PR-. HER2 status was known in 126 pts, positive in 18 (14%), and negative in 108 (86%). Tumours were strongly triple negative (5%)(ER0, PR0, HER20); Ki67<14%.

Of the 400 patients, 91 were under 40 years of age corresponding to an incidence of 14.8%. Median tumour size was 3 cm and lymph node positivity was 56.9%. Lymphovascular emboli was positive in 42 patients (48.8%) and perinodal extension was positive in 36 patients (41.8%). Thirty patients (34.8%) were ER positive, while 39 patients (45.3%) were PR positive. Her 2 neu receptors were positive in 20 patients (23.2%). Thirty nine patients were triple negative (45.3%). The median follow up period was 27 months with the DFS being 73.2% and OS being 87.2%. In univariate analysis, factors significantly associated with survival were stage at presentation, presence of lymphovascular emboli, presence of perinodal extension and grade of the tumour.

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Disclosure: All authors have declared no conflicts of interest.

PROLIFERATION DETERMINED BY Ki67 MARKER DEFINES PATHOLOGICAL COMPLETE RESPONSE IN A DOSE-DENSE NEOADJUVANT CHEMOTHERAPY SCHEDULE IN LOCALLY ADVANCED BREAST CANCER PATIENTS

M.Y. Plata Fernandez1, A. Sanchez-Muñoz2, A. Jaén-Morago3, M. Lomas-Garvido3, M. Fernández1, C. Llacer2, M. Fernández1, N. Ribelles3, E. Alba-Conejo1, P. Sánchez-Rovira1

1Oncología Médica, Complejo Hospitalario de Jaén, Jaén, SPAIN, 2Oncología, Hospital Universitario Virgen de la Victoria, Malaga, SPAIN

Background: The value of Ki67 proliferation biomarker during neoadjuvant chemotherapy (NC) is less clear than with neoadjuvant endocrine therapy. We study the role of proliferation according to Ki67 marker measured by immunohistochemistry (IHC) as a predictive factor of pathological complete response to NC.

Methods: From May 2002 to June 2005, 127 pts diagnosed as stage II-III, including inflammatory tumors, breast cancer patients (pts) received one of the 2 NC regimens every 2 weeks with prophylactic growth factor support. Study A: adriamicin 40mg/m2 d1 plus P 150mg/m2 GT 2000 mg/m2 d2 for 6 cycles (n = 54); study B: epirubicin...
Background: The ECTO-1 study demonstrated the efficacy of concurrent chemoradiotherapy in operable breast cancer (Gianni L. et al. Clin Cancer Res 2005). With the purpose of ameliorating the tolerability of the regimen, we designed the ASTER study to reduce both the duration and the total dose of neo-/adjuvant treatment with AT followed by CMF. Herein we report on the efficacy of the neoadjuvant portion of the trial.

Methods: A total of 70 patients with operable breast cancer were enrolled between September 2008 and November 2011. Median age was 51 years (range 32-73); 74% of patients presented with hormone receptor positive (HR +) and 26% of patients with hormone receptor negative (HR -); 48% of patients had T1 tumours (30% T1a), 40% of patients had T2 tumours (20% T2a); 41% of patients had N0 tumours, 43% N1 and 26% N2; 31% had Her2 tumours, 69% not Her2. Patients were treated with neoadjuvant Adriamycin (60 mg/m²) + Paclitaxel (200 mg/m²) q21 for 3 cycles followed by CMF i.v. 1, 8q28 for 3 cycles in the neoadjuvant treatment of operable breast cancer (Gianni L. et al. Clin Cancer Res 2005). The rate of pCR matched perfectly with the data obtained with the original schema AT x 4 followed by CMF x 3. Pathological complete response (pCR) defined as absence of invasive cells in breast and lymph node was achieved in 35 pts (28%). Univariate and multivariate logistic regression models were used to study the association of each clinical-pathological variable with pCR.

Results: High Ki67 was the main predictive factor of pCR to NC. In the univariate analysis histological grade (p = 0.001), HR (p < 0.001), Ki67 (p = 0.001) and p53 (p < 0.001) were statistically associated with pCR. A multivariate logistic regression showed only high Ki67 (p = 0.02; OR = 5.3, C.I.95% 1.2-18) and HR (p = 0.045; OR = 2.5, C.I.95% 0.05-1.07) were predictive for pCR.

Conclusion: High proliferation determined by Ki67 marker is an independent predictive factor for pCR in locally advanced breast cancer patients treated in two dose-dense NC schedules.

Disclosure: All authors have declared no conflicts of interest.

Background: In breast cancer, positive Hormone Receptors (HR) constitute a favourable prognostic factor whereas HER-2 overexpression is an adverse prognostic factor associated with a more aggressive tumor. In a retrospective database of 282 breast cancer patients diagnosed from 1991 to 2006, we analysed the overall survival (OS) and the disease-free survival (DFS) of 4 phenotypes: HR+/HER-2- (triple negative, TN), HR+/Ki67 ≤ 20% (luminal A), HR+/Ki67 > 20% or HER2+ (luminal B), HER2+ HER-2 overexpression (HER2+ HER-2+).

Patients and methods: Median diameter of the invasive tumour was 40 mm [10-130]. 231 (82%) patients had a canalicular carcinoma. 33% of the tumours were grade III SBR. Patients received either an anthracycline-based chemotherapy (47%), a taxane chemotherapy (21%) or a combination of both (32%). The median number of NCT courses was 6 [1-8] followed by a surgery for 97.6%, a radiotherapy for 93%, an adjuvant chemotherapy for 20% and/or an hormone therapy for 56%. Only 5 patients received adjuvant herceptin for 1 year. In the different subgroups, we had 123 luminal A tumors (44%), 15 luminal B tumours (24%), 21 HER2+ tumours (7%) and 71 TN tumours (25%) of patients.

Results: According to tumour’s phenotype, the pCR (Chevaller’s classes 1 + 2) was: 3.3% for luminal A, 16.6%; for luminal B, 33.3% for HER2+ HR- and 26% for triple negative tumours. On 2 April 2012, the median follow-up was 148 months (range, 63-252). We evaluated the OS and the DFS in the four subgroups, at 10 years. For TN: OS and DFS were 58.6% and 56.2%. For luminal A: OS and DFS were 76.1% and 64.7%. For luminal B: OS and DFS were 81.7% and 72.4%. For HER2+HR- subgroup: OS and DFS were 64.5% and 56.4%. pCR is an objective improvement method after NCT, but it is variable among subgroups, and may constitute an acquired prognostic factor. However, it was much smaller in hormonal-positive tumours subsets and may there be not an endpoint per se. We observed a significant improvement of DFS and OS for patients who reached a pCR only in TN breast cancer. However HER2 subset may be too small to reach significance here.

Conclusion: OS and DFS were better in luminal A and B subgroups. Conversely OS and DFS decreased for TN and HER2+ subtypes. When TN breast cancer patients reached a pCR, OS and DFS were significantly improved.

Disclosure: All authors have declared no conflicts of interest.

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Methods: A total of 70 patients with operable breast cancer were enrolled between September 2008 and November 2011. Median age was 51 years (range 32-73); 74% of patients presented with hormone receptor positive (HR +) and 26% of patients with hormone receptor negative (HR -); 8% of patients presented HER2 overexpression (HER2 +); amplification of most of the patients had c2 (36%); half presented with node involvement cN1 (54%). Patients were treated with neoadjuvant Adriamycin (60 mg/m²) + Paclitaxel (200 mg/m²) q3 for 3 cycles followed by CMF i.v. 1, 8q28 for 3 cycles.

Results: The pathological complete response (pCR), defined as the absence of neoplastic cells in the primary tumor was obtained in 11.5% of cases; pTnCR, defined as the absence of neoplastic cells in the primary tumor and in nodules, was obtained in 10% of cases. Overall, 29% of patients with triple negative breast cancer achieved a pCR, while only 6% of HR positive breast cancer achieved a pCR.

Conclusions: Neoadjuvant treatment with three cycles of AT followed by three cycles of CMF is effective in patients with operable breast cancer. The rate of pCR matched perfectly with the data obtained with the original schema AT x 4 followed by CMF x 4 in 69 patients treated with primary chemotherapy at our institute, within the ECTO-1 study. The ASTER study sets the base for developing a less toxic chemotherapy regimen sequential and non-cross resistant containing anthracycline and taxane for the treatment of operable breast cancer.

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Results: The pathological complete response (pCR), defined as the absence of neoplastic cells in the primary tumor was obtained in 11.5% of cases; pTnCR, defined as the absence of neoplastic cells in the primary tumor and in nodules, was obtained in 10% of cases. Overall, 29% of patients with triple negative breast cancer achieved a pCR, while only 6% of HR positive breast cancer achieved a pCR.

Conclusions: Neoadjuvant treatment with three cycles of AT followed by three cycles of CMF is effective in patients with operable breast cancer. The rate of pCR matched perfectly with the data obtained with the original schema AT x 4 followed by CMF x 4 in 69 patients treated with primary chemotherapy at our institute, within the ECTO-1 study. The ASTER study sets the base for developing a less toxic chemotherapy regimen sequential and non-cross resistant containing anthracycline and taxane for the treatment of operable breast cancer.

Disclosure: All authors have declared no conflicts of interest.
Disclosure: C. Jackisch: I have participated in an advisory board for Roche. M. Johnston: I am currently an employee of Genentech Inc. D. Heinzmann: I am currently an employee of F. Hoffmann-La Roche. H. Weber: I am currently an employee of F. Hoffmann-La Roche. G. Ismael: I declare that my institute has received funding research from Roche and honoraria for attendance at conferences. All other authors have declared no conflicts of interest.

SUBCUTANEOUS INJECTION OF TRASTUZUMAB – ANALYSIS OF ADMINISTRATION TIME AND INJECTION SITE REACTIONS

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Background: Intravenous (IV) trastuzumab (H) is the standard of care for HER2-positive breast cancer (BC). A subcutaneous (SC) formulation of H has been developed. H SC formulation contains recombinant human hyaluronidase, which transiently hydrolyses hyaluronan to facilitate delivery of H to the circulation. The HannA study (Jackisch, et al. EBCC 2012) demonstrated the non-inferiority of H SC (vs. H IV) in terms of pharmacokinetics and efficacy in patients with HER2-positive early BC. Safety observations for the two routes of administration were also similar.

Methods: H SC injection was via handheld syringe, and an injection time of about 5 minutes was recommended by the study protocol. The actual time taken was measured in the safety population at each administration. Injection site reactions (ISRs) associated with H SC were identified using a predefined basket of preferred terms from the medical dictionary for drug regulatory activities.

Results: Duration of SC injections was generally between 1–5 minutes, with an average duration of 3.3 minutes (Table 1) compared with 60–90 minutes taken for IV administration. A low incidence of ISRs were seen with SC injections (Table 1), with all but two cases (grade 2) being grade 1, every case was reversible.

Injection duration (minutes) Number of injections n (%) Incidence of ISRs n (%)
< 2 51 (1.1) 0 (0)
≥ 2 to < 3 2331 (49.2) 27 (1.2)
≥ 3 to < 4 961 (21.2) 15 (1.6)
≥ 4 to < 5 200 (4.4) 6 (3.0)
≥ 5 to < 6 1024 (22.6) 27 (2.6)
≥ 6 45 (1.0) 9 (20.0)
Missing 25 (0.5) 0 (0)
Total 4537 (100) 84 (1.9)

Summary of injection duration and ISRs (injection site pain) in the H SC arm of the HannA study (safety population) (N = 297) Incidence of ISRs was highest for injection durations of ≥6 minutes with 6 pts reporting 9 ISRs over the course of their treatment. In 3 pts (6 ISRs) injection time was prolonged due to injection pain. The remaining three ISRs constituted transient tissue tenderness at injection site.

Conclusion: In the HannA study, injection of H SC was generally well tolerated with a low incidence of ISRs (grades 1 and 2). These findings support the potential of H SC to provide improved convenience for patients compared to the existing IV formulation.

Disclosure: X. Pivot: X. Pivot has served as a consultant or advisor for Hoffmann-La Roche, Novartis, GlaxoSmithKline and has received honoraria from sanofi-aventis. S.D. Moody: SD Moody has served as a member of an advisory board for Roche Hoffman-La Roche, sanofi-aventis, Britol Meyers Squibb, Nayer Schering, and has received consulting fees from sanofi-aventis, Sanofi-Warner, and sanofi-aventis. A. Bouhlel: A Bouhlel is an employee of Hoffmann-La Roche Inc. C. Jackisch: C. Jackisch has served on advisory boards for Hoffmann-La Roche Inc. All other authors have declared no conflicts of interest.

A PHASE I DOSE ESCALATION AND BIOEQUIVALENCE STUDY OF A TRASTUZUMAB BIOSIMILAR (FTMB) IN HEALTHY MALE VOLUNTEERS

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FTMB is a biosimilar of trastuzumab (Herceptin®), a humanized monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2). Herceptin® is registered for treatment of HER2-positive breast cancer and metastatic gastric cancer. Pharmacokinetic profiles of FTMB were compared to Herceptin® in this combined dose escalation and bioequivalence study. In the dose escalation part healthy male volunteers received single doses of 0.5, 1.5, 4.5, and 6.0 mg/m² FTMB in consecutive cohorts to assess the safety profile. At each dose level, subjects were randomized to FTMB (n = 6) or placebo (n = 2), with the exception of the 6 mg/kg cohort, where subjects were randomized to FTMB (n = 9), Herceptin® (n = 9) or placebo (n = 2). Safety data were evaluated by an independent data safety monitoring board. To establish bioequivalence a total of 92 healthy male subjects, including those of the 6 mg/kg dose escalation cohort, were randomized equally to FTMB or Herceptin®. Blood samples were taken prior and at regular, predefined time points up to 12.3 months. At post-BL were similar to those observed pre-BL. One pt was pos for ADAs to both H and HrPH20. No neutralizing ADAs to H or HrPH20 were seen. The pCR rate did not differ significantly between Anti-H (AHA)-neg (30% [IV n = 10], 55% [SC n = 20]) and AHA-neg (36.5% [IV n = 10], 41.6% [SC n = 20]) pts. Anti-HrPH20 status did not correlate with pCR (41.2% [IV] vs 41.7% [SC]). The pCR rate in the SC arm was pos for ADAs to H and/or HrPH20.

Conclusion: Using a highly sensitive assay, ADAs against both H (IV/SC) and HrPH20 (SC only) were observed transiently and were of no relevance in terms of efficacy or safety. Immunogenicity monitoring in the study is ongoing.

Disclosure: T. Piekonski: Dr Piekonski has carried out research supported by F Hoffmann-La Roche. N. Al-Sakaff: I have an interest in relation of one or more organisations that could be perceived as a conflict of interest in the context of the subject of this abstract. Interest - other substantive relationship: Employee of F. Hoffman-La Roche Ltd. D. Heinzmann: I have an interest in relation of one or more organisations that could be perceived as a conflict of interest in the context of the subject of this abstract. Other substantive relationship: Employee of F. Hoffman-La Roche and stockholder. G. Kolaitis: Dr Kolaitis is an employee and stockholder of F Hoffman-La Roche. The other authors have declared no conflicts of interest.


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to 9 weeks after dosing. Trastuzumab levels were determined in serum with a validated bridging ELISA method. The mean area under the concentration-time curve from time zero to infinity (AUC0-inf) was calculated for each subject, normalized to 1 mg/kg and corrected for T1/2. The T1/2 was 88 µg/dL. For Test and 245.4 µg/dL for Reference. The In-transformed Test/Reference (T/R) ratio for AUC0-inf was 89.6% (90% confidence interval (CI): 85.1%-94.4%), demonstrating bioequivalence based on the acceptance interval of 80.0-125.0%. For the secondary efficacy parameter, the maximum concentration (Cmax) was 221.4 µg/mL for Test and 245.4 µg/mL for Reference. The bioequivalence study with a trastuzumab biosimilar in healthy male volunteers, single dose study of trastuzumab (fever, influenza-like illness, and fatigue) did not occur, and signs of cardiotoxicity were not observed. In conclusion, in this first bioequivalence study with a trastuzumab biosimilar in healthy male volunteers, single administration of FTMB was considered well tolerated in doses up to 6 mg/kg, and FTMB was demonstrated to be bioequivalent to Herceptin®.

Disclosure: All authors have declared no conflicts of interest.

Efficacy and safety of trastuzumab in HER2 positive small tumors: A single institution experience

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Background: Patients affected by breast cancer with negative lymph-node are considered at high risk if at least one of the following factors is present: tumor size > 2 cm, HR negative, histological grade 2 or 3, age < 35 years. However, some patients with HER2 positive cancers develop a recurrence despite small tumor size (< 2 cm) and none of these factors. In this study, we reviewed the treatment of HER2 positive patients cases that were successfully treated with trastuzumab in our institution during the period January 2005 and February 2012. Patients and methods: Between January 2005 and February 2012, 88 patients with small (pT1) Her2 positive node negative breast cancers were retrospectively reviewed at our institution. These patients (10.2%) were staged pT1a (7.1%), pT1b (13.6%) and 3/4 pT1b stage pN0 and 65.7%/38% pT1c/pN0. Among them 83/94 patients were treated with adjuvant anthracyclines regimens for 4 or 6 cycles followed by one year of trastuzumab (52 weeks). Median age at diagnosis was 51.5 years (range 28-73) Fifty-two patients were followed up for at least 1 year, the median follow up was 35 months (range 13–63). The Left Ejection Ventricular Fraction (LEVF) was assessed at baseline and every three months.

Results: Two patients relapsed; (one lung metastasis during treatment, one local recurrence 13 months after the last dose). An asymptomatic absolute decrease in LEVF by 10% was recorded in three patients. No patients discontinued the treatment.

Conclusions: The use of trastuzumab in HER2 positive small tumors seems safe and effective. More data should be available for tumors smaller than 1 cm.

Disclosure: All authors have declared no conflicts of interest.
invasion and HER-2/neu status. Estrogen receptor (ER), PR, and HER-2 status were determined using immunohistochemistry. Patients were classified into four groups; ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR-. Pearson Chi-Square test and Kaplan-Meier with log-rank test were performed for statistical analysis.

Results: 575 (66.6%) patients had ER+ + PR+, 64 (7.4%) had ER+ + PR-, 43 (5.0%) had ER+/PR- and 182 (21.1%) had ER-/PR-. The median age of patients was 48 years (20-83) and were similar in all groups (p = 0.18). Majority of patients with PR+ tumors were postmenopausal at the time of diagnosis (p = 0.021). The follow-up period was 39.5 (1-273) months.

Conclusions: Patients in PR- groups are more likely to have large-size and HER-2 positive breast cancer. ER- groups are associated with high grade disease. Patients with PR+ breast cancer have significantly longer overall survival, compared to patients with ER+ tumors. Our data suggest that HER-2 status is an important prognostic factor for node-negative breast cancer survival.

Disclosure: All authors have declared no conflicts of interest.

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PROGESTERON RECEPTOR STATUS IN DETERMINING THE PROGNOSIS OF ESTROGEN RECEPTOR POSITIVE / HER2-NEGATIVE BREAST CARCINOMA

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Background: The aim of this retrospective study was to determine whether progesteron receptor (PgR) status have an influence on the prognosis of estrogen receptor positive (ER+)/HER2-negative breast carcinoma (BC).

Methods: We retrospectively reviewed the medical files of 1680 operable BC patients (pts) diagnosed between 1996 and 2011 and 456 of which ER/pG and HER2 status known were included in this study. Patients were categorized into 2 groups; as group A (ER+/PgR-/HER2-negative) and group B (ER+/PgR+/HER2-negative).

Results: Median follow up was 33.5 (0-177) months. Median age was 54 (21-90) years. Sixty-one percent (22%) of the pts had node-positive BC. Sixty percent (27%) of the pts were postmenopausal. Eighty percent (365) of the pts received adjuvant chemotherapy (ACT). Adjuvant hormoneotherapy (AIHT) was recommended to nearly all patients (mostly tamoxifen). Pts in group A had significantly higher lymph node positive disease as compared to group B (670 vs 59%, p = 0.046). Although there was no statistically significant difference between two groups for the first site of recurrence (mostly bone and soft tissue, p = 0.51), the number of recurrence and mortality events in group B were proportionally less than group A (27.8% and 21.2% for group B and 42.7% and 32.2% for group A; p < 0.005 and p = 0.004, respectively). In the node-negative subgroup, an important difference for relative risk RR of BC recurrence between groups A and B was found (34/68 vs 75/207, RR 1.3, CI 0.2-1.86, p = 0.034). But, the mortality risk was similar for lymph node-positive pts in groups A and B (16/63 vs 50/201, RR 1.0, CI 0.62-1.86, p = 0.93). Although DFS for group B was shorter, it was not statistically significant (5-year DFS rate 45% vs 35% p = 0.24). However, 5-year overall survival (OS) was significantly longer for pts in group A (78% vs 67%, p = 0.043). Although DFS for group B was shorter, it was not statistically significant (5-year DFS rate 45% vs 35% p = 0.24). However, 5-year overall survival (OS) was significantly longer for pts in group A (78% vs 67%, p = 0.043).

Conclusions: PgR status has a great influence on the prognosis of BC pts especially negative PgR may have a significant negative influence on the prognosis of node-positive ER+ /HER2+ BC pts.

Disclosure: All authors have declared no conflicts of interest.

280P
ADJUVANT AROMATASE INHIBITORS (AIS) HORMONE THERAPY (HT); WHICH REASONS LEAD PATIENTS (PTS) TO DISCONTINUE TREATMENT? A MONO INSTITUTIONAL ANALYSIS

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Background: AIs represents the standard HT for the adjuvant treatment of post menopausal endocrine sensitive early breast cancer. A percentage of pts interrupt treatment because of toxicity. In this setting the switch to other AIs or tamoxifen (TAM) may represent an option to allow the prolongation of HT. We reported the main reasons for interruption of the AIs in our institution from 2006 to the present.

Methods: 236 pts with a minimum treatment time up of 6 months were considered eligible for analysis. Pts characteristics: median age 64 yrs (35-89), median follow up 24 months (6-28). Prior adjuvant CT: taxanes based: 47 pts, anthracyclines based: 43 pts. 118 pts (49%) had received letrozole (L), 101 (43%) anastrozole (A), 18 (8%) exemestane (E). An alternative HT (AIs or tamoxifen [T]) was offered to pts who wanted or needed to interrupt permanently the ongoing drug.

Results: According to the CTC NCI, arthralgia was the main toxicity observed (G1 19.4%, G2/3 5.5%/1.7%). Overall 24 out of 236 pts (10%) needed discontinuation of AIs as a result of toxicity. Grade 2 and 3 arthralgia was the main reason for discontinuation in 13/24 pts (54%). No differences in the incidence of arthralgia were noted in pts who had received taxanes or anthracyclines. Headache (n = 2), alopecia (n = 2), G3 itching (n = 2), diffuse skin reaction (n = 1) allergic reaction with hypertensive crisis (n = 1), xerostomia and xerophthalmia (n = 1), insomnia (n = 1) and somnolence (n = 1) were the other reasons for discontinuance. In the multivariate logistic regression analysis, age (65 yrs) and HT represent independent factors associated with the onset of arthralgia (respectively p = 0.006 and 0.008, OR 2.65, CI95: 1.32-5.31). 17/24 pts were switched to E, 5 to T and 1 each to L and A. In pts who switched to another AI we observed a reduction in the severity of the arthralgia but not its complete resolution. A complete resolution of symptoms was observed for the other toxicities except for allergic reactions that recurred after switching from L to A. Moreover, the patient with the diffuse skin reaction, chose discontinuation of HT.

Conclusions: In our analysis, 10% of pts discontinued AIs due to toxicity. Switching to alternative HT, and monitoring the toxicity, represent an option to offer to pts in order to avoid a premature and permanent interruption of an effective treatment.

Disclosure: All authors have declared no conflicts of interest.

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FOR WHICH PT1A, BNM0 HORMONE RESPONSIVE INVASIVE BREAST CARCINOMAS COULD ENDOCRINE THERAPY BE AVOIDED?

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Background: Overtreatment is a daily concern in adjuvant setting for invasive breast carcinoma. Although chemotherapy is the most controversial issue, endocrine therapies must also be discussed.

Methods: In this monocentric retrospective study, we analysed results of patients treated for hormone responsive invasive pT1a,bN0M0 breast cancer, focusing on the population without adjuvant endocrine treatment. Women with previous history of invasive carcinoma were excluded.

Results: In our institution, 382 patients with hormone responsive invasive breast carcinoma pT1a,bN0M0 carcinoma were treated between 1997 and 2007. Local treatment involved either mastectomy or partial breast surgery followed by breast radiotherapy. After multidisciplinary discussion, among the 382 patients, 162 patients (42 %) did not receive any adjuvant endocrine treatment. Comparatively to the group treated with endocrine therapy, these patients had significantly more grade 1 tumors (81.4 % versus 47.2 %, p< 0.0001) and Ki67 < 14% (89.6% versus 72.4%, p < 0.0001). In patients not treated with endocrine therapy, after a 10 years in the grade I group.

Conclusion: This series of patients treated without adjuvant endocrine therapies raise the issue of avoiding anti tumor endocrine therapy in patients with hormone responsive pT1a,bN0M0, age> 50 years and grade 1 tumors.

Disclosure: All authors have declared no conflicts of interest.

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EVALUATION OF BONE MINERAL DENSITY (BMD) IN EARLY BREAST CANCER (EBC) PATIENTS TREATED WITH UP-FRONT OR SWITCH SCHEDULES OF AROMATASE INHIBITORS (AIS): RESULTS OF A SINGLE CENTRE RETROSPECTIVE STUDY

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Background: Aromatase inhibitors (AIs) are the standard adjuvant treatment of hormone responsive early breast cancer (EBC) in postmenopausal women. AIs are well tolerated but are associated with specific toxicities, including effect on bone (accelerated bone loss, bone fracture, osteoporosis) and musculoskeletal symptoms (ostearthralgia, myalgia) Aim: The present observational study investigated the effect of BMD in postmenopausal women with EBC scheduled to receive AIs up-front or switch treatment after standard 2-3 years of adjuvant Tamoxifen (TAM-AIs).
Patients and methods: We reviewed data for 89 patients with hormone receptor-positive EBC: 64 postmenopausal women received up-front ALs for 5 years; 25 patients received TAM-ALs. BMD was assessed at baseline and during hormonal treatment once a year. Osteoporotic patients received Calcium and vitamin D; osteoporotic patients received also oral biphosphonates.

Results: No patient with a normal baseline BMD (T-score >1) became osteoporotic during 5 years of follow-up. However, it was noted that more women receiving ALs up-front became osteoporotic, as compared with TAM-AL treated women (Al = 58% vs. TAM-ALs = 26%, p< 0.001). In addition, women with osteoporosis at baseline, treated with biphosphonates, became osteoporotic. Using the linear regression model approach we found that only patient with a baseline T-score less than -1.5 became osteoporotic on treatment (Table 1). Supplementary comediations have improved reduction of musculoskeletal symptoms.

Conclusion: The data suggest that only those women with a T-score of less than -1.5 are at risk of developing osteoporosis during the ALs adjuvant therapy. This cut-off value might reduce the costs both for BMD monitoring and supplementary comediations. Finally, the correct management of treatment-related symptoms might improve patient’s compliance and the adherence to treatment.

Disclosure: All authors have declared no conflicts of interest.

MODEST VALUE OF STAGING INVESTIGATIONS IN HEAVILY NODE POSITIVE EARLY BREAST CANCER PATIENTS

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Background: Staging investigations for metastatic disease are not recommended for asymptomatic patients with early breast cancer. However, it is relatively common practice to perform staging in patients who are heavily node positive (4 or more nodes involved). This study explored the benefit of routine investigations in this patient group.

Methodology: All patients operated in Castle Hill Hospital, Hull, UK between January 2005 and December 2011 for early breast cancer and found to have 4 or more nodes involved on pathological assessment were identified. Staging investigations, consisting of CT chest, abdomen and pelvis and isotope bone scan, were reviewed. The need for additional investigations was recorded.

Results: A total of 231 patients were identified. 59 patients were excluded as no additional investigations were performed. In the remaining 172 patients staging investigations were positive in 12% (21/172). An additional 17% (29/172) required further investigations for equivocal scans and were not found to have metastatic disease. On univariate analysis with chi-square T stage (T1 3%, T2 9%, T3 14%, T4 18% vs. T1+2 9%, T3 24%, T4 22%) and number of involved nodes (≤2 7%, 3-4 14%, 5-9 19%, 10+ nodes 27%) were significant for predicting positive staging investigations (see Table). On multivariate analysis using logistic regression only T4 breast cancers were significantly associated with positive staging investigations (p = 0.008).

Conclusions: Routine staging investigations have a modest pick up rate of metastatic disease in heavily node positive patients. Importantly, 1 in 6 patients will require further investigations to exclude metastatic disease. Staging is recommended for all patients with locally advanced/inflammatory breast cancers but is probably not necessary in every pN2 patient.

Univariate analysis of factors predictive of positive staging investigations

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OSNA Cohort</th>
<th>Historical cohort</th>
</tr>
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<tbody>
<tr>
<td>Age, median (range)</td>
<td>58 (33-86)</td>
<td>57 (30-93)</td>
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<tr>
<td>Tumor size, mean (range) mm</td>
<td>16.63 (2-60)</td>
<td>14.16 (2-55)</td>
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<td>Tumor histology</td>
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<tr>
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<tr>
<td>&gt; 10%</td>
<td>86</td>
<td>124</td>
</tr>
</tbody>
</table>

Results: SLN metastasis was found in 45 patients in the OSNA group and in 49 in the historical group. There were no differences in rates of macrometastases (27 by OSNA, 41 by HE) and we found differences in micrometastasis rate (18 by OSNA and 8 by HE p<0.007). Axillary node dissection (ALND) was performed in 45 patients in the OSNA group and in 49 in the historical group. There were no differences in rates of macrometastases (41 by OSNA, 41 by HE p =0.007). Axillary node dissection (ALND) was performed in 45 patients in the OSNA group and in 49 in the historical group. There were no differences in rates of macrometastases (27 by OSNA, 41 by HE) and we found differences in micrometastasis rate (18 by OSNA and 8 by HE p<0.007). Axillary node dissection (ALND) was performed in 45 patients in the OSNA group and in 49 in the historical group. There were no differences in rates of macrometastases (27 by OSNA, 41 by HE) and we found differences in micrometastasis rate (18 by OSNA and 8 by HE p<0.007).

WHAT DO CLINICIANS DO WITH THE RESULTS OF THE SYSTEMATIC STAGING IMAGING AT THE TIME OF BREAST CANCER DIAGNOSIS?

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Introduction: Asymptomatic distant metastases are often looked for at the time of initial diagnosis of early breast cancer. However, there is no consensus on when to perform it and on the consequences on the treatment.

Patients and methods: 125 asymptomatic women receiving systemic neoadjuvant (33 patients (pts)) or adjuvant treatment (92 pts) for breast cancer at the Oscar Lambret Center in 09/2011 were considered. The staging imaging was a PET scan: 59 pts, a CT scan + a bone scan: 61 pts and both: 5 pts. Results for each procedure were considered normal, abnormal but typically benign or potentially malignant. In this

Disclosure: All authors have declared no conflicts of interest.

ADVANTAGES OF ONE STEP NUCLEIC ACID AMPLIFICATION (OSNA) WHOLE NODE ASSAY IN SENTINEL LYMPH NODE (SLN) ANALYSIS IN BREAST CANCER

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The aim of this study is to present our first results with OSNA assays performed in a routine clinical setting in 168 patients with invasive and in situ breast cancer and compare them with conventional histopathology results for SLN biopsies in a historical cohort in our institution.

Methods: 412 patients (total study population) with clinically node negative early stage breast cancer underwent an axillary SLN in our institution. The SLN was assessed with OSNA in 168 patients. The OSNA results were compared with conventional histopathology results from 244 patients who has undergone a SLN biopsy few years earlier. Patients characteristics were evaluated in both groups and the rate of metastases detected by both methods and the surgical procedures were compared.

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Univariate analysis of factors predictive of positive staging investigations

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OSNA Cohort</th>
<th>Historical cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.7% (1/37)</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>2</td>
<td>8.9% (7/79)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>14.3% (5/35)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>38.1% (8/21)</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0% (0/4)</td>
<td>p&lt; 0.751</td>
</tr>
<tr>
<td>2</td>
<td>12.7% (9/71)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12.3% (12/97)</td>
<td></td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>11.8% (14/118)</td>
<td>p&lt; 0.838</td>
</tr>
<tr>
<td>Neg</td>
<td>13.0% (7/54)</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>16.7% (7/42)</td>
<td>p&lt; 0.284</td>
</tr>
<tr>
<td>Neg</td>
<td>10.5% (13/124)</td>
<td></td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>13.7% (14/102)</td>
<td>p&lt; 0.636</td>
</tr>
<tr>
<td>Neg</td>
<td>10% (7/70)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>10.7% (6/56)</td>
<td>p&lt; 0.806</td>
</tr>
<tr>
<td>≥50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodes+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 nodes</td>
<td>12.9% (15/116)</td>
<td>p&lt; 0.009</td>
</tr>
<tr>
<td>7-9 nodes</td>
<td>9.1% (3/33)</td>
<td></td>
</tr>
<tr>
<td>10+ nodes</td>
<td>21.1% (15/71)</td>
<td></td>
</tr>
<tr>
<td>NAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>10.3% (7/68)</td>
<td>p&lt; 0.637</td>
</tr>
<tr>
<td>N</td>
<td>13.5% (14/104)</td>
<td></td>
</tr>
<tr>
<td>Node Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>2.1% (1/48)</td>
<td>p&lt; 0.037</td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>16.3% (20/123)</td>
<td></td>
</tr>
</tbody>
</table>
case, another imaging technique was carried out to confirm the suspected diagnosis. The patient was considered metastatic if the results of two different procedures were concordant and eventually in case of response to chemotherapy, the patient had a biopsy (liver). 22 pts were Stage 1, 58 Stage 2, 4 Stage 3, 1 other patient had an excision of a recurrence on mastectomy scar.

<table>
<thead>
<tr>
<th>Bone scan + CT scan</th>
<th>PET scan</th>
<th>Both</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts 61</td>
<td>59</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>Potentially malignant lesions</td>
<td>13</td>
<td>8</td>
<td>23 (including confirmed malignant)</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>5</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Benign lesions</td>
<td>33</td>
<td>15</td>
<td>48</td>
</tr>
<tr>
<td>Confirmatory Procedures</td>
<td>19</td>
<td>19</td>
<td>2</td>
</tr>
</tbody>
</table>

Results: 9 pts were considered metastatic (7%): 5 bone, 2 liver, 1 lung and 1 spleen. There was 1 Stage 1, 4 Stage 2, and 4 Stage 3. 3 of the 5 pts in the neoadjuvant setting were operated on (2 after the planned chemotherapy; 1 complete response of lung metastasis and 1 sternal lesion treated by boost and 1 after modified protocol for unique liver lesion which will be treated by CyberKnife®). The 2 others had bone lesions, received modified protocol and did not have surgery. For the pts in the adjuvant setting, 2 received the full treatment (1 continued Trastuzumab beyond the year protocol). 1 received modified protocol of chemotherapy then radiotherapy and hormone therapy and the last one received chemotherapy alone.

Conclusion: In this population of 125 pts selected for (neo) adjuvant chemotherapy, 40 imaging procedures were performed to check the lesions. 9 pts were considered as metastatic and only 5 had a significant modification of their treatment. A systematic imaging staging in pts selected for adjuvant chemotherapy should not be recommended.

Disclosure: All authors have declared no conflicts of interest.

PROGNOSTIC AND PREDICTIVE VALUES OF BI-RADS CLASSIFICATION IN BREAST CANCER PATIENTS

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Objective: The goal of this study is to determine the prognostic and predictive values of the Breast Imaging Reporting and Data System (BI-RADS) classification in breast cancer patients.

Patients and methods: 1045 patients with breast cancer were diagnosed between January 1, 1999, and December 31, 2007, and 512 (48.9%) of them were classified as BI-RADS 5. Overall survival and disease-free survival were estimated with the Kaplan-Meier method and compared across the two groups (BI-RADS 5 versus BI-RADS 4) using the log rank test. Univariate and multivariate analyses were used to identify the prognostic factors.

Results: The median follow-up time was 87.8 months. Kaplan-Meier analysis showed a significant difference between the two subgroups in five-year overall survival (p < 0.0001) and five-year disease-free survival (p < 0.0001). On multivariate analysis, the BI-RADS mammographic findings, lymph node status, HER-2 status, and tumor grade were significant factors related to five-year overall survival and disease-free survival.

Conclusion: The BI-RADS classification is a reliable prognostic and predictive factor. Taiwanese breast cancer patients with BI-RADS 5 mammographic finding showed a higher relapse rate than patients with BI-RADS 4 mammographic finding.

Disclosure: All authors have declared no conflicts of interest.

STUDY OF STROMAL CD10 OVEREXPRESSION IN INVASIVE BREAST CANCER AND ITS RELATIONSHIP WITH CLINICOPATHOLOGIC FACTORS

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Background: Carcinoma of the breast is the most common non-skin malignancy in women. Invasion and metastasis are considered as the major causes of cancer-related morbidity and mortality. It has long been proposed that secreted proteinases, including the matrix metalloproteinases, play an important role in tumor progression and mediating extracellular matrix remodeling. More recently, it has been suggested that extracellular proteinases also regulate growth factors and cytokines that may contribute to tumor progression. CD10 is a 90-110kd cell surface zinc-dependent metalloproteinase. Since CD10 is structurally similar to matrix metalloproteinase and stromelysin it may facilitates cancer cell invasion and/or metastasis. The aim of this study was to investigate the rate of CD10 expression in the stromal cells of invasive ductal carcinomas of breast immunohistochemically and clarify its correlation with other clinicopathological factors of the disease.

Methods: 100 patients with histopathologic diagnosis of IDC and 50 patients with fibroadenoma of breast (as the control group) were selected and 150 paraffin blocks were obtained. The stained slides by IHC method for CD10 marker were examined separately by two pathologists and discrepancies were reviewed in a common session to get the final result.

Results: Stromal CD10 was detected in 28% of the IDC. No immunoreactivity was identified in the stromal cells of normal breast. Stromal CD10 expression in IDC was significantly correlated with tumor size (P < 0.001), histologic grade (P < 0.001), the presence of nodal metastases (P < 0.001) and estrogen receptor negative status (P = 0.003).

Conclusion: Stromal CD10 expression in IDC is closely correlated with invasion and metastasis and it may play an important role in the pathogenesis of IDC.

Disclosure: All authors have declared no conflicts of interest.

PROGNOSTIC TOOLS IN EARLY BREAST CANCER: PREDICTING BENEFIT OF ADJUVANT CHEMOTHERAPY

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Introduction: Adjuvant chemotherapy (CT) in early breast cancer reduces the risk of mortality. However, absolute reductions in mortality can be small. For patient with low risk disease prognostic tools such as ‘Adjuvant! Online’ (AO) and ‘Predict’ (PD) can be used to estimate the benefit of adjuvant chemotherapy. We compare the survival gains estimated using AO and PD in routine clinical practice, assessing the characteristics of patients in which AO and PD disagree.

Methods: In a retrospective study using the hospital electronic database, the clinical and pathological details of all patients with early breast cancer referred for adjuvant therapy at the Northern Ireland Cancer Centre in a 3 month period in 2011 were collected and were entered in to AO and PD to assess percentage benefit (absolute reduction in mortality at 10 years) from CT. We categorised patients into three prognostic groups: those where risk from CT outweighs benefit (<2% predicted benefit), marginal benefit (2 to 5%) and significant benefit from CT (>5%). We excluded patients with metastatic disease at presentation, DCIS, a second primary breast cancer or receiving neo-adjuvant treatment.

Results: Of the 200 patients identified, 43 (21.5%) fell in to different prognostic groups depending on whether AO or PD was used to calculate benefit from CT. In total, AO suggested marginal or significant benefit in 69.8% of patients, compared to 60.4% using PD. Eight patients had “major” comorbidities, which is weighted only in AO, and were excluded in subsequent analysis. Of those without major comorbidities, AO offered at least 2% benefit in 80% of cases, and PD in only 57.1%. The majority (91.4%) of cases were ER positive, and node negative (82.9%). This difference was notable in women aged 65 or less, with 83.3% with >2% benefit using AO, and 61.1% using PD. AO estimates of benefit were on average 3.7% higher for this age group. HER2 status had little impact, with similar recommendations using either AO or PD.

Conclusions: This study highlights lack of concordance between two available online prognostic tools, notably in ER positive, node negative patients. For patients with a marginal benefit from CT, care must be used when making adjuvant treatment decisions.

Disclosure: All authors have declared no conflicts of interest.

A STUDY OF THE IMPACT OF THE 21-GENE BREASTCANCER ASSAY ON THE USE OF ADJUVANT CHEMOTHERAPY IN WOMEN WITH BREAST CANCER IN A MEXICAN PUBLIC HOSPITAL

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Background: The majority of early stage breast cancer patients in Mexico are treated through the public health system, and >80% are treated with chemotherapy (CT). The 21-gene assay (OncoType DX™) is available in Mexico but has been utilized primarily within the private health system. There are no data that describe the potential impact of the assay on adjuvant treatment decision-making for public
sector patients. The aim of this study is to characterize how assay results impact the decision-making process and confidence of public sector physicians in Mexico to determine adjuvant therapy. This is the first decision impact study of the Oncotype DX assay in Latin America.

Methods: At total of 98 consecutive patients with ER +, HER2-, stage I-IIIa, N0- N1-3 breast cancer from the Instituto Nacional de Cancerología in Mexico City, Mexico, were enrolled in the study. Via consensus discussion in multidisciplinary team meetings, physicians completed pre- and post-assay questionnaires regarding adjuvant treatment recommendations for each enrolled patient. The primary endpoint was the overall change in physician treatment recommendations resulting from the addition of the Recurrence Score® result in the decision-making process.

Results: Pre- and post-assay results were available for 96 patients. Treatment decisions changed for 31/96 (32%; 95% CI 23%-43%; patients; 16/72 (22%; 95% CI 14%-30%) N0 and 14/34 (41%; 95% CI 25%-59%) N1-3 patients. Pre-assay, 8/50 (16%) of patients initially recommended hormonal therapy (HT) were recommended chemohormonal therapy (CHT) or CT, and 21/46 (46%) of patients initially recommended CHT/CT were recommended HT alone. The proportion of patients recommended CT decreased from 48% pre- to 34% post-assay (p = 0.024), a decrease of 14% overall, 6% in N0, and 26% in N1-3 patients.

Conclusions: These results suggest that use of the 21-gene assay in the Mexican public health system has an impact on adjuvant treatment recommendations and may reduce the use of chemotherapy.

Disclosure: C. Yoshizawa: Genomic Health- Employment and Stockholder, E. Burke: Genomic Health. Employment and Stockholder, C. Chao: Genomic Health- Employment and Stockholder. All other authors have declared no conflicts of interest.

BROWN FAT SEEN ON FDG PET/CT IS INCREASED IN BREAST CANCER PATIENTS COMPARED TO THEIR AGE- AND WEIGHT-MATCHED CONTROLS WITH OTHER CANCERS

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Purpose: We previously found increased brown fat deposits in mammary tissue of Rcc1a mutant breast cancer mouse models suggesting a potential role of brown fat environment in the early breast tumorigenesis. The goal of the current human study is to test the hypothesis that the prevalence of brown fat activity seen on FDG PET/CT is increased in breast cancer (BC) patients.

Methods: We conducted a retrospective study to assess the distribution and intensity of brown fat activity on FDG PET/CT in female BC patients compared to age- and weight-matched control subjects with other cancers mostly colon cancer. We analyzed 124 FDG PET/CT scans of BC patients done at the University of Maryland and 124 age- and weight-matched control subjects who had FDG PET/CT scan on the same day for staging of other cancers (the majority were colon cancer).

Results: The prevalence of brown fat was higher in BC (12.9% or 16/124) than in their age- and weight-matched control subjects (5.6% or 7/124) (p < 0.05). The data was stratified by age, among those who were ≤50 years old, the prevalence of brown fat was 35.5% (11/31) in BC patients versus 91% (3/33) in the controls (p = 0.005). In contrast, among those who were > 50 years of age, there was no difference in brown fat prevalence between BC patients and controls (5.4% or 5/93 vs 4.4% or 4/91; p = NS), respectively. Brown fat was more commonly identified in the bilateral supravacuicular regions in BC patients than controls (22 vs 6, p = 0.0049). There was no difference in the intensity of brown fat between the 2 groups (mean SUV max = 3.5 ± 1.5 in BC vs 3.4 ± 0.7 in controls, p = NS).

Conclusion: The prevalence of brown fat seen on FDG PET/CT is increased in BC patients compared to their age- and weight-matched controls with other cancers, particularly in patients aged ≥ 50, and in the supravacuicular region. These clinical data provide further support to the experimental studies that brown fat may play a role in breast cancer tumorigenesis.

Disclosure: All authors have declared no conflicts of interest.
QUANTIFICATION OF TUMOR-SPECIFIC DNA IN BLOOD OF HEALTHY WOMEN AND BREAST CANCER PATIENTS

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Despite of tumor location DNA from cancer cells was shown to got in circulating blood, thus DNA circulating in blood represent the valuable source of diagnostic material for non-invasive blood based tests for cancer.

Material and methods: Blood from healthy female (n = 50) and breast cancer patients (n = 23, T1-2, N0-1, M0) were fractionated into plasma and cellular fractions, cell-surface-bound ctdNA and ctDNA were eluted from cell surface with PBS/EDTA and trypsin solutions [1]. Total DNA was quantified with TaqMan PCR for LINE-1 repeats [2], methylated DNA of RARβ1 gene promoter was quantified with methylation-specific SYBR Green Real Time PCR [3].

Results: Breast cancer patients had significantly higher mean concentration of methylated RARβ1 gene promoter in circulating DNA (ctDNA) and ctdDNA fractions as compared to healthy controls: 192 vs. 132 pg/ml and 619 ng/ml vs. 413 pg/ml respectively; P < 0.005. No correlation was found between ctdDNA levels and stage of tumor. ROC-curve analysis demonstrated specificity and sensitivity of ctdDNA as a breast cancer marker detection as 52% and 65% respectively for cut-off value of 0.61 for plasma tumor ctdDNA and 70% and 61% respectively for cut-off value of 0.75 when ctdDNA and ctDNA were analysed simultaneously. The data obtained demonstrate that along with ctDNA ctdDNA provides a valuable source of material for breast cancer diagnostics. J. Clin. Chem., 2005. V. 51. P. 1317-1319. 2, B. Biochem., 2011. V. 408. P. 354-356. 3. Eur. J. Cancer Prev., 2011. V. 20. P. 453-455.

Disclosure: All authors have declared no conflicts of interest.

HIGH FREQUENCY OF BRCA1/2 MUTATIONS AMONG ISRAELI NON ASHKENAZI BREAST CANCER PATIENTS

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Background: Inherited mutations in the breast cancer susceptibility genes (BRCA1 and BRCA2) are associated with a high risk of developing breast (BC) and ovarian cancers (OC) in females of different age and ethnic groups. The spectrum of mutations in these genes varies between populations, with some showing a high frequency of unique mutations. Ashkenazi Jews have a high rate of founder mutations in BRCA1/2, in some other Jewish communities in Israel (Jews who immigrated to Israel from Iraq, Iran and Yemen), other founder mutations had been identified. Still high proportions of Israeli BC cases with strong family history have none of the known mutations at the BRCA1/2 genes.

Methods and patients: Over 3000 breast cancer patients were evaluated in the oncogentic clinic during 1997-2011. One hundred thirty seven of them underwent full sequencing of the BRCA1/2 genes due to strong family history of breast and/or ovarian cancer or young age at presentation. Clinical and pathological characteristics of these patients were evaluated.

Result: Sixty seven percent were non Ashkenazi Jews, mean age at BC onset was 44 (22-77). In 20 patient (15%) BRCA1 (N = 8) or 2 (N = 12) mutations were identified. Thirty percent of the carriers had bilateral BC and 5 had OC as second primary. 17 were of non Ashkenazi origin. Ninety five percent of the carriers had first degree family history of breast or ovarian cancer. The pathological information was available in half of the carriers. All had high grade (2-3) tumor, 90% of them were HER2 negative and 60% ER positive. Ager at presentation had no affect on BRCA1/2 status. BRCAPro is a predictive model to assess BRCA status and has been assessed in 9 carriers, in 6 of them, the probability was >80% and in one - 5%.

Conclusions: A full sequence of the BRCA1/2 genes was performed in a selected group of BC patients, who were negative for the common founder mutation in Israel. Fifteen percent were found to carry other BRCA1/2 mutations. We recommend that, patients with the following clinical features: Spheredic origin, first degree family history of BC or OC, high grade tumor, HER-2 negative, should be offered full BRCA1/2 testing. The role of BRCAPro and other predictive model should be further evaluated.

Disclosure: All authors have declared no conflicts of interest.

ITEM RESPONSE THEORY AND FACTOR ANALYSIS AS MEAN TO CHARACTERIZE OCCURRENCE OF RESPONSE SHIFT FOR LONGITUDINAL QUALITY OF LIFE STUDY IN BREAST CANCER PATIENTS

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Aims: Health-related quality of life (HRQoL) is a dynamic process which depends on the adaptation of the patient and reflected by a Response Shift (RS) effect. RS results in a recalibration, a reprioritization and a reconceptualization of key HRQoL domains. Longitudinal analyses of HRQoL have to take into account the possible occurrence of RS. However, there is no standard of statistical analysis to characterize RS. Two complementary methods are investigated to characterize RS.

Methods: This work builds on data of a prospective multicenter study including all primary breast cancer patients or suspicion. HRQoL was evaluated using the EORTC QLQ-C30 and QLQ-BR23 at baseline, after surgery, at 3 months and 6 months, according to the then-test/post-test design: the retrospective assessments done after surgery and at 3 months refer to baseline HRQoL; the retrospective measurement done at 6 months refers to HRQoL at 3 months. The order then-test and post-test of HRQoL questionnaires was randomized. Recalibration was explored by Multiple Correspondence Analyses (MCA) and the

The CYP2D6 enzyme is primarily involved in the metabolism of tamoxifen into its most important metabolite endoxifen. The efficacy of tamoxifen therapy may be influenced by genetic polymorphisms of this enzyme and CYP2D6-inhibiting co-medication (e.g. antidepressant drugs). It is therefore generally recommended to avoid potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine) in tamoxifen patients. In this study, we examined whether women using tamoxifen still received strong CYP2D6-inhibiting antidepressants concomitantly during the period 2005-2010. Drug dispensing data for tamoxifen and seven antidepressants associated with CYP2D6 inhibition (paroxetine, fluoxetine, sertraline, fluvoxamine, (es)citalopram and venlafaxine), were retrieved from the community pharmacy database of the PHARMO Institute. This database contains dispensing data of >3 million people in the Netherlands. Concomitant use of CYP2D6-inhibiting antidepressants in women using tamoxifen, as well as the use of antidepressants in the total population, were determined per year using PASW Statistics 17.8 (SPSS Inc., Chicago, IL). Prevalence of the use of the four most common antidepressants among tamoxifen users, expressed as the number of women receiving an antidepressant concurrently with tamoxifen per 1000 tamoxifen users, is shown in the Table. Although there is a slightly rising trend for paroxetine, this drug is still one of the most frequently used antidepressants in tamoxifen patients. In addition, a similar trend was observed in the total population of the database. Venlafaxine and citalopram, associated with weak CYP2D6-inhibiting properties, are increasingly co-prescribed.

Despite the strong biological rationale to avoid potent CYP2D6-inhibiting co-medication in tamoxifen treated patients, paroxetine is still often used along with tamoxifen. In clinical practice, one should be extremely alert to co-medication in tamoxifen patients. It is advised that strong CYP2D6 inhibitors are switched to weaker CYP2D6-inhibiting alternatives, if possible.

Disclosure: All authors have declared no conflicts of interest.
Conclusion: Answers were associated with both region of residency and medical subspecialty. Up to 76% declared individual routine trt decisions for oncologists, 21% surgeons, 17% pathologists and 12% radiation oncologists. 77% of professionals accounted in international/national treatment guidelines. We evaluated their need for consensus guidelines. We evaluated their need for consensus guidelines.

Disclosure: All authors have declared no conflicts of interest.

PROFILE OF MALE BREAST CANCER: SINGLE INSTITUTION STUDY OF 76 PATIENTS FROM NORTHERN INDIA

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5Background: Male breast cancer (MBC) is a rare disease and accounts for 1% of all breast cancer. The aim of our study was to assess clinical, pathological parameters and outcome in MBC.

Methods: This analysis was carried out in 76 male breast cancer patients with confirmed case of MBC who were registered in our breast cancer clinic between 1996-2011 at Institute Rotary Cancer Hospital, All India Institute of Medical Sciences (AIIMS). Analysis was performed with descriptive statistics, the log rank test was used to compare outcome.

Results: The median age was 56 years (range 28-80). The median duration of symptoms was 10 months (range 0.5-120). Breast lump was the commonest (93%) presenting symptom (right > left side). TNM Stage distribution was stage I - 3 %, stage II - 20%, stage III - 55%, and stage IV - 22%. Positive family history was elicited in 8 (10.5%) patients. Tumour size (median) was 3.9 cm. Modified Radical mastectomy was the commonest surgical procedure. 76% of tumours were high grade and 55% had pathological node positive disease. ER/PR, her2neu status was available in 75% and 65% respectively. ER/PR and her2neu positivity was 90% and 30% respectively. Triple negative breast cancer (TNBC) constituted 20%. Median follow up was 36 months. Ten patients had relapsed of which 70% were distant, bone being the most common site followed by lung and liver. Five years disease free (DFS) and overall survival (OS) was 40% and 60%.

Conclusion: Our population had more advanced disease at presentation, higher her2neu positivity and higher triple negative status as compared to western population results in poorer outcome.

Disclosure: All authors have declared no conflicts of interest.

ASSOCIATION OF ALPHA2A AND BETAZ2 ADRENOCEPTORS EXPRESSION WITH CLINICAL OUTCOME IN BREAST CANCER

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Previous studies have shown that alpha2a-adrenoceptor antagonists can inhibit the growth of breast cancer cells. The expression of betaz2 adrenoceptors on cell proliferation is still controversial. In this study, we investigated the association of alpha2a and betaz2 adrenoceptors expression with tumor-relevant biological markers and clinical outcome. Immunohistochemistry assay was performed on paraffin-embedded tumors to detect alpha2a and betaz2 adrenoceptor expression in 220 operable breast tumors.

We initially demonstrated that alpha2a expression was associated with Her-2 status (P = 0.048) and simultaneously Her-2 positivity was associated with alpha2a expression and ER (P = 0.061). We also find that betaz2 expression was not associated with any tumor-glandular biologic markers. Multivariate analysis demonstrated that associations between different beta2 expression and DFS (P = 0.092). Further analysis was made and we found in hormone receptor positive breast cancer patients, strong betaz2 expression correlated with better DFS than weak beta2 expression (P = 0.031). Multivariate analysis demonstrated that betaz2 adrenoceptor expression (HR = 0.31, P = 0.039) and lymph node (HR = 2.85, P = 0.031) were independent predictors of DFS in hormone receptor positive breast cancer patients. In conclusion, this study showed that strong alpha2a expression occurred in ER positive and Her-2 negative breast cancers.

Introduction: Breast cancer (BC) is associated with different molecular profiles and histological types. Different histological types contain cells with different phenotype and genotype. Many hypotheses have been taken for understanding the causes of breast cancer’s heterogeneity. One of these is breast cancer stem cell hypothesis. The hypothesis was proposed that cancer cell population contain a subpopulation of cells with characteristics of both epithelial and mesenchymal stem cells. There are many methods used for identification of BC stem cells. One of these methods is using cell surface markers. BC stem cells are defined by the phenotype CD44+/CD24-/low/Lin-. The aim of this study is to investigate the percentages of CD44+/CD24-/low/Lin- cells and the correlation between stem cells and prognostic factors in primary BC.

Material and method: Twenty three women who underwent surgery for BC between May 2010 and January 2011 were enrolled in this study. Fresh tumor tissues were...
broken up enzymatically and CD44+/CD24-/low/Lin- cell phenotype was identified by using surface marker antibodies. The percentage of this phenotype was determined by surface marker expression of the cells by using flowcytometry. Results: The mean age of the patients (pts) was 47 and 52% were early stage BC. CD44+/CD24-/low/Lin- cells were present in all tumor tissues and the mean percentage of these cells was 1.43 ± 1.16%. The percentage of CD44+/CD24-/low/Lin- cells was higher in postmenopausal women, early stage, Her-2 negative and low grade tumors, but it was not statistically significant. There was a significant correlation between involved lymph node numbers and the percentage of CD44+/CD24-/low/Lin- cells but it was not statistically significant. There was no statistically significant correlation between the percentage of CD44+/CD24-/low/Lin- cells and menopausal status, stage, grade, number of lymph nodes, hormone receptors and HER-2 status. Conclusion: In our study CD44+/CD24-/low/Lin- cells were present in all tumor tissues and the mean percentage of these cells was 1.43 ± 1.16% as shown in previous studies. But there was no statistically significant correlation between prognostic factors and the percentage of the CD44+/CD24-/low/Lin- cells.

Disclosure: All authors have declared no conflicts of interest.

301 EARLY BREAST CANCER AGRRESSIVENESS DOES NOT DIFFER BETWEEN INSULIN-SENSITIVE AND INSULIN-RESISTANT POSTMENOPAUSAL NON-DIABETIC WOMEN

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Background: The metabolic syndrome is known to negatively influence breast cancer outcome. One of the syndrome’s components is hyperinsulinism, which can exert tumor-promoting effects directly or through increased hepatic IGFI-production. A fasting insulin concentration > 10 µIU/ml and/or a HOMA score > 2.6 are considered diagnostic for the metabolic syndrome. We performed a pilot study to evaluate the relation between insulin resistance and tumor characteristics.

Study design: Prior to surgery we collected blood samples of 33 consecutive non-diabetic postmenopausal women with early breast cancer to measure fasting insulin and glucose concentration. Correlation analyses were performed for both fasting insulin and HOMA-score (insulin resistance index) and parameters tested for their influence on tumor characteristics.

Results: Median age was 66 (49-86) years and median BMI was 25.8 (18.6-45.4)/kg/m2. Median MAI was 7 (1-52), median tumor diameter was 12 (3-70) mm and 9 patients had node-positive disease (2 N0itc, 5 N1, 2 N2). Insulin resistance was found in 5 (15%) patients. BMI showed a strong positive correlation with insulin resistance (r = 0.42, p = 0.01) and an inverse correlation between involved lymph node numbers and the percentage of CD44+/CD24-/low/Lin- cells but it was not statistically significant. There was no statistically significant correlation between the percentage of CD44+/CD24-/low/Lin- cells and menopausal status, stage, grade, number of lymph nodes, hormone receptors and HER-2 status. Conclusion: In postmenopausal non-diabetic women with early breast cancer insulin resistance is encountered quite often. It does however not appear to alter cancer biology.

Disclosure: All authors have declared no conflicts of interest.

302 STUDY ON SERUM HER2 EXTRACELLULAR DOMAIN EXPRESSION IN EARLY STAGE BREAST CANCER PATIENTS

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Background: The measurement of the human epidermal growth factor receptor 2 (HER2) protein in the serum of metastatic breast cancer patients has now been reported, but there are no consistent data to support the clinical utility of serum HER2 extracellular domain (ECD) for patients with early breast cancer. We aimed to evaluate the correlation between serum HER2 ECD levels and tumor HER2 status, and analyze their relationship with clinicopathological parameters in patients with early stage disease.

Methods: A prospective study was conducted on 232 breast cancer patients with stage I-II diseases before treatment. Preoperative serum samples were measured by enzyme-linked immunosorbant assay (ELISA). Tissue HER2 status was analyzed by immunohistochemistry and fluorescence in situ hybridization assays.

Results: The median serum HER2 ECD concentration was 6.8 ng/ml (range 1.3-42.1 ng/ml). The best diagnostic cut-off value was 7.4 ng/ml (with 72.9% sensitivity and 85.3% specificity), which was lower than HER2 ECD cut-off value with metastasis breast cancer (15 ng/ml). High serum HER2 ECD levels were reported in 89 patients (38.3%) and HER2 tissue positive expression was observed in 77 patients (33.2%) with a moderate concordance of 76.7%. Elevated serum HER2 ECD correlated with postmenopausal (p < 0.01), high tumor grade (p < 0.01), negativity of both estrogen (p = 0.007) and progesterone receptors (p < 0.001), high level of carbohydrate antigen 153 (CA153) (p = 0.039) and tissue polypeptide specific antigen (TPS) (p = 0.018). Conclusion: HER2 ECD, which is associated with poor prognosis, may provide more additional information compared with HER2 tissue alone. We support that it is necessary to decrease the cut-off value in evaluating serum HER2 ECD level for early stage breast cancer.

Disclosure: All authors have declared no conflicts of interest.

303 CLINICAL RELEVANCE OF HORMONE RECEPTORS, KI67 AND HER-2 STATUS AS BIOMARKERS SURROGATE FOR BREAST CANCER MOLECULAR SUBTYPES: A RETROSPECTIVE ANALYSIS OF DISEASE FREE SURVIVAL IN PATIENTS WITH T1 NO/N+ BREAST CANCER

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Background: Early breast cancer (EBC) is a heterogeneous disease with distinct clinical, pathologic, and molecular features and different treatment responsiveness and outcomes. Aim of study was to evaluate outcomes according to molecular subtypes breast cancer classified by four biomarkers using immunohistochemistry (IHC).

Patients and methods: We retrospectively reviewed 264 women with T1 N0/N+ breast cancer, referred to a single centre (1986 - 2009) and treated according to European guidelines. The relationships between classical prognostic factors, molecular subtypes classified by IHC and Disease free survivals (DFS) were analyzed.

Results: Univariate survival analysis showed a significantly different DFS at 5- and 7-years for N0 and N+ patient populations, with a better outcome for patients with node-negative tumors (5y: N0 = 95.9% vs. N+ = 88.8, p = 0.03; 7y: N0 = 94.8% vs. N+ = 86.0%, p = 0.02). Nevertheless, long-term outcome (15-yrs) displayed an inversion of the survival curves with a lower DFS rate of 65% in N0 vs. 86% in N+ patients (p = 0.0001). Regarding to Ki-67 tumor expression, patients with low Ki67 values (Ki-67 < 14%) had a better 5-y DFS compared to patients with high Ki-67 (Ki-67 ≥ 14%). A significant difference in DFS has been observed also considering the tumor grading (G1: 100%, G2: 88%, G3: 94.4%, p < 0.03). Based on molecular subtypes breast cancer classification by IHC, the 5-y DFS rate was 98.4% for Luminal A (HR +, HER2-, Ki-67 < 14%), 96.3% for Luminal B HER2 negative (HR +, HER2-, Ki-67 ≥ 14%), 83.3% for Luminal B HER2 positive (HR +, HER2+, any Ki-67), 86.3% for HER2-like (HR-, HER2+) and 74.5% for Basal-like tumors (HR-, HER2+).

Conclusions: At long-term follow-up, patients with T1N0 and patients with G2 EBC showed worst outcomes, probably because they are considered to have a low recurrence risk and not received adjuvant chemotherapy. Ki-67 expression is an important prognostic factor in hormone-receptors positive disease, allowing better definition of Luminal A and B molecular subtypes. Classic prognostic factors evaluated by IHC could be used as biomarkers surrogate for breast cancer molecular subtypes and might improve therapeutic decision in EBC patients.

Disclosure: All authors have declared no conflicts of interest.

304 PROGNOSTIC VALUE OF CIRCULATING TUMOR CELLS IN EARLY BREAST CANCER PATIENTS DETECTED BY RT-PCR OF MAMMAGLOBIN

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Background: The identification of circulating tumor cells (CTC) could potentially become an important prognostic factor in breast cancer patient. The aim of this prospective study is to detect CTC in the blood of breast cancer patients and to correlate between detection of CTC and other prognostic factors, disease free survival and overall survival.

Material and methods: The study was conducted at medical oncology department NC, Cairo University during the period from August 2008 to August 2011. Forty two consecutive consenting female patients with non metastatic breast cancer who ended their adjuvant chemotherapy and radiotherapy at least 2 years were recruited. Detection of CTC in the blood of our patients was done by measuring the gene expression for mammaglobin by RT-PCR, and then the relative fold change was calculated relatively to normal samples.
**Results**: The median CTC fold changes were 9.3, ranging from 0 to 20.8 in the whole studied group while zero for the control group. There was a highly statistically significant difference (p = 0.001) between CTC fold changes for stage II tumor, and a statistical significant (p = 0.070) for higher CTC fold changes in those with Her2-neu receptor positivity. There was no significant correlation between higher CTCs and other factors related to the patients or disease characteristics. There was also no relation between CTC fold changes and overall survival or disease free survival.

**Conclusion**: In this small study, mammaglobin is considered a sensitive marker for detection of CTC in breast cancer. CTC fold changes are correlated with tumor stage and Her2 status. Further studies including larger number of patients and followed for longer period are recommended to evaluate this protocol more thoroughly.

**Disclosure**: All authors have declared no conflicts of interest.

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**IMMUNOHISTOCHEMICAL Ki67 LABELING INDEX HAS A SIMILAR PROLIFERATION PREDICTIVE POWER AS VARIOUS FIRST-GENERATION GENE SIGNATURES IN BREAST CANCER**

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**Background**: Immunohistochemical assessment of Ki67 labeling index (IHC Ki67) has been described as a prognostic and predictive marker for breast cancer. On the other hand, several genetic prognostic markers have been described for breast cancer. However, few clinical data sets provide information on correlations between genomic markers, mRNA Ki67, and IHC Ki67 in the same cohort of patients with survival data. The objective of this study is to examine the association between immunohistochemical Ki67 labeling index, Ki67 mRNA expression level, and first-generation gene signatures in a cohort of breast cancer patients.

**Patients and methods**: We assessed associations between IHC Ki67 and first-generation gene signatures in a panel of 40 tumor samples, using an oligonucleotide microarray. Gene expression analyses included Ki67 alone (MK67), 21-gene signature, Mitosis Kinome score signature (MKS), and Genomic grade index (GGI). Correlation coefficients were calculated by Spearman’s rank correlation test. To assess the relationship between IHC Ki67 and survival outcomes, survival curves were calculated by the Kaplan–Meier method and compared with the log-rank test according to IHC Ki67.

**Results**: Median age at diagnosis was 51 years. Treatments included adjuvant chemotherapy (32 patients) and endocrine therapy (21 patients). IHC Ki67, MK67, and 3 genetic markers were highly correlated in all cases (Rho: 0.71–0.83). ER-negative cases displayed slightly lower correlations (Rho: 0.61–0.74). In ER-positive cases, the low IHC Ki67 group –0.74). In ER-positive cases, the low IHC Ki67 group displayed significantly longer relapse-free survival (RFS) than the high IHC Ki67 group (p = 0.007). This difference was confirmed by multivariate analysis.

**Conclusions**: Our data indicate that IHC Ki67 exhibits similar predictive power for proliferation in ER-positive cancers as genomic markers. Further study of IHC Ki67 correlation between genomic markers, mRNA Ki67, and IHC Ki67 in the same cohort of patients with survival data is needed to define prognostic factors and predictive factors for chemotherapy using central laboratory assessment.

**Disclosure**: All authors have declared no conflicts of interest.

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**ONCOTYPE DX® - THE SIRIO-LIBANES HOSPITAL CANCER CENTER EXPERIENCE**

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**Background**: The Oncotype Dx® recurrence score (RS) assay quantifies the risk of distant recurrence (rDR) and its use has increased despite the lack of prospective studies.

**Methods**: This is a cross-sectional study of consecutive patients (PTS) from our Institution with histologically confirmed invasive breast cancer (IBC) who underwent surgery with curative intent and in whom Oncotype Dx (ODx) was performed. The main objectives were to compare (1) the predicted rDR by RS and Adjuvant! (2) Risk allocation by RS and St Gallen Criteria and (3) the agreement between histological grading (HG) and RS.

**Results**: From October/2006 to April/2012, 105 PTS with ER positive IBC were evaluated. Median age: 55y. Sixty-eight (68.4%) were EGIA; axillary lymph node involvement was seen in 25 PTS (14 micro and 11 macrometastases). The rDR by RS was low in 64 PTS (60%), intermediate in 34 (32.4%) and high in 7 (6.7%). According to Saint Gallen, 12 (12%), 68 (68%) and 20 PTS (20%) were classified as low, intermediate and high risk, respectively, among 100 classifiable PTS. There was no statistically significant agreement between risk allocation by RS and Saint Gallen criteria (Kappa coefficient = 0.43; p = 0.401). Ki-67 data was available for 89 PTS: <15% in 46; 15-19% in 9 and ≥20% in 34 PTS. There was correlation between RS and Ki-67 (Pearson chi-square = 6.472; p = 0.167). Among the 80 node-negative PTS, there was no significant correlation between the predicted average rDR, using ODx, and the adjuvantOnline (Pearson correlation coefficient = 0.082, p = 0.792) with median risk of 10% vs 15.6%, respectively. HG was available in 103 PTS: 28 (27.2%) were grade 1, 69 (67%) grade 2 and 6 (5.8%) grade 3. A linear trend association between HG and RS was observed, i.e., for increasing levels of the RS, we observed lower frequencies of grade 1 and higher frequencies of PTS with grade 2 (Linear trend chi-square = 4.62; p = 0.032).

**Conclusions**: We found no statistically significant agreement between Oncotype Dx®, the Saint Gallen criteria, Adjuvant/Online, or Ki-67. However, a potential association between HG and RS was noted. The rDR may be overestimated by clinicopathological-based classifications.

**Disclosure**: All authors have declared no conflicts of interest.

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**STUDY ON MICROMETASTASIS IN SENTINEL LYMPH NODE OF PATIENTS WITH BREAST CANCER**

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**Introduction**: The nodal ratio is one of the most important factors when delivering a prognosis in breast cancer, and survival is closely related with the number of affected nodes. During the last few years the technique of the sentinel lymph node (SLN) has demonstrated to be a useful tool to predict the nodal status, being necessary until today to evaluate if a lymphadenectomy is needed when this node is affected. Due to this, a clear prognosis in these particular cases relating micrometastasis (NMI) with a needed axillary lymph node dissection (ALND), in our hospital we analyze the SLNs evaluated.

**Methods**: We perform a descriptive retrospective study in 216 patients of the Hospital Universitario Puerta de Hierro who have gone through a SLN biopsy (SLNB) of breast carcinoma between January 2010 and March 2012, being introduced the OSNA technique in May 2011. We analyze the following factors: histology, processing method of the SLN, number of SLNs, intraoperative and definitive diagnosis, performance of ALND, number of nodes dissected along the procedure and total number of affected nodes.

**Results**: Among 216 patients treated with SLNB, 26.8% (58) showed a positive SLN, subdivided in Nmic 8.8% (19 patients) and metastasis 18%, (39 patients). Out of the total number of nodes, 57% of them were processed with the OSNA method and the other 43% with histopathological (HP) examination. The specificity of the HP technique in these series was of a 100%, with a sensitivity of 73.33%. Out of the 58 SLN that presented SLN positive, 96.6% (56) received an ALND. Out of the 19 SLN with Nmic, 17 cases had an ALND, and 3 cases were affected again later. The other two SLNs, processed by histopathology, presented a negative intraoperative diagnosis for infiltration, and therefore it was decided not to proceed with a delayed lymphadenectomy.

**Conclusions**: Although we still don’t know the impact of the persistence of tumoral disease in nodes with disease free survival and overall survival, with the data gathered in our study and given that more than 15% of the nodes removed were positive, we conclude that lymphadenectomy should not be dismissed after detecting Nmic in the SLN. It is necessary to carry out studies with a larger number of patients, under a long-term monitoring, to determine the real impact on survival.

**Disclosure**: All authors have declared no conflicts of interest.

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**POPULATION BASED OUTCOME OF HER2 POSITIVE EARLY BREAST CANCER IN TRASTUZUMAB ERA**

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**Introduction**: About 15% of breast cancer (BC) patients are HER2 positive (HER2+) with high risk of cancer recurrence and death. With adjuvant trastuzumab (T) treatment the risk of recurrence almost halved and the risk of death for one third. Adjuvant treatment with T has been available in Slovenia since August 2005, immediately after the first positive trial results.
Aim: Retrospective analysis of relapse free (RFS) and overall survival (OS) in HER2+ BC patients treated with adjuvant trastuzumab in years 2005-09. Results: Adjuvant T received 317 patients, median age 53 (min 23; max 78) years. Nine percent of patients had invasive ductal carcinoma and 97% grade 2/3, 55% were ER positive. Tumor stage was T1 (29%), T2 (48%), T3 (11%), T4 (10%), unknown (2%). N stage was N0 (26%), N1 (50%), N2 (16%), N3 (7%), unknown (1%). All patients received adjuvant chemotherapy, 41% anthracycline-based, 48% anthracycline and taxane-based. The median follow-up time was 4.5 (min 0.7; max 6.9) years. There were 66 relapses and 28 deaths. RFS was 98.1, 92.3, 84.2 and 80.8% at 1, 2, 3, 4 years, resp. OS was 99.7, 96.6, 93.4 and 92.5%, at 1, 2, 3, 4 years, resp. The independent prognostic factor for RFS were T stage (HR 1.2 95% CI1.0-1.4) and N stage (HR 1.1-1.5). Chemotherapy regimen was not found as a prognostic factor for RFS. Conclusions: This is one of the first reports of the population based results of the adjuvant T treatment. Our results, based on adjuvant T treatment of real-life HER2+ BC patients, are fully comparable to the results obtained in HERA and Joint American study with 4-years RFS around 80%. Disclosure: All authors have declared no conflicts of interest.

Methods: Postmenopausal patients with the diagnosis of early-stage hormone-sensitive breast cancer receiving AI therapy at our institution were included prospectively between 2010-2012. We performed a specific survey to evaluate articular toxicity collecting presence of arthralgia, EVA scale, use of analgesic, start time and localization of the pain. Clinical data was collected from our department database. Univariate analysis was used to compare those with AI-related arthralgia and different demographic and clinical features. Results: A total of 83 women were included, with a mean age 63.2, BMI 28.4, menopause mean age 48.2. Regarding to the features of the primary tumor, 81.9% had ductal carcinoma histology, 28.9% stage I, 54.2% stage II, 16.8% stage III. At the moment of the evaluation, 68.7% (57/83) were receiving treatment with anastrozole, 15.7% (13/83) letrozole, 15.7% (13/83) exemestane. 86.7% (72/83) had joint pain, of them 68.1% (49/72) related their pain to the hormone therapy, 31.9% (23/72) to previous diseases or other treatments. The articulations more frequently affected were located in the back, knees and hands. Regarding to the pain intensity, mean maximum EVA was 6.03, minimum 1.06. Only 2 of the patients affected stopped therapy, and it was changed for another aromatase inhibitor. No differences were seen between the different aromatase inhibitors. Conclusions: The incidence of arthralgia associated with aromatase inhibitors was superior in our series compared with results previously published in clinical trials. Further research in this field should be developed to clarify the prevalence and severity of joint symptoms related to AI and to define factors that may be associated with an increased risk of this treatment-related adverse effect. Disclosure: All authors have declared no conflicts of interest.


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Table: Chemotherapy uptake within MWRH

<table>
<thead>
<tr>
<th>Decision-making tools (DMT)</th>
<th>Chemotherapy Uptake</th>
<th>Offered</th>
<th>Undertaken</th>
<th>Not offered</th>
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<tbody>
<tr>
<td>Nottingham Prognostic Index (NPI) - Excellent (≤ 2.40) - Good (2.41 – 3.40) - Moderate (3.41 – 5.40) - Poor (≥ 5.41)</td>
<td>2/7 16/41 21/29 0/0</td>
<td>1/7 13/41 21/29 0/0</td>
<td>5/7 25/41 8/29 0/0</td>
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<tr>
<td>Adjuvant: Online (AO) – additional 10-year survival benefit of chemotherapy and hormonal therapy</td>
<td>0.0 – 2.5%</td>
<td>2.6% – 5.0%</td>
<td>5.1% – 7.5%</td>
<td>≥ 7.5%</td>
</tr>
<tr>
<td>Oncotype Dx Recurrence Score (RS) assay – Low (1–17) - Intermediate (18–30) - High (&gt;31)</td>
<td>8/21 12/33 9/13 10/0</td>
<td>6/21 10/33 9/13 10/0</td>
<td>13/2/1 21/33 4/13 0/10</td>
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<td>TA, TC, TX, and AC-T regimens were given in 34.8%, 19.7%, 17.4%, 5.3%, and 2.2% respectively. TAC was used more frequently in triple-negative breast cancer (TNBC) than other patients (43.0% vs. 32.7%, P = 0.004). Of 1682 patients in adjuvant setting, 729 (43.3%) were treated with triplet (TAC or AC-T). In 290 patients receiving neoadjuvant chemotherapy, only 94 (32.4%) used TAC and none used AC-T (P = 0.013).</td>
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Conclusions: Docetaxel was widely used in the treatment of breast cancer in China, especially in the (neo)adjuvant setting. TAC regimen was the most frequent option, especially in patients with TNBC or LN-positive BC. Although AC-T was also recommended in adjuvant setting by most guidelines, it was less commonly used compared to TAC regimen in China.

Disclosure: All authors have declared no conflicts of interest.

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DOCETAXEL IN THE TREATMENT OF BREAST CANCER: A MULTI-CENTER RETROSPECTIVE STUDY FROM CHINA

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Background: Docetaxel is considered as a fundamental drug in the treatment of breast cancer. It has been extensively incorporated into the neoadjuvant, adjuvant and metastatic treatment. The aim of this study was to investigate how breast cancer patients are treated with docetaxel in China.

Methods: A retrospective review of chemotherapy with docetaxel performed from 2009 to 2011 was carried out in China. Study included all patients diagnosed with invasive breast cancer and treated with docetaxel-containing regimens in forty-two cancer centers from 12 provinces in China. Regimens were compared in different subgroups based on stage, subtype, and lymph node (LN) status. Patterns of chemotherapy were also compared to published guidelines.

Results: Among 2188 breast cancer patients treated with docetaxel, 1881 (86.0%) were in adjuvant or/and neoadjuvant setting (including 91 in both settings). The mean age was 55.9 years (range: 30.6 – 72.3 years). Median follow-up: 20.9 months. Findings are shown below in tabular form.

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Disclosure: All authors have declared no conflicts of interest.

315TIP

SAFEBER: A STUDY OF ASSISTED- AND SELF-ADMINISTERED SUBCUTANEOUS TRASTUZUMAB (H-SC) AS ADJUVANT THERAPY IN PATIENTS WITH EARLY HER2-POSITIVE BREAST CANCER (EBC)

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Purpose: One year of H-based therapy, consisting of 18 q3w cycles, is standard of care for the adjuvant treatment of HER2-positive EBC. H is administered
intravenously (IV) over 30–90 mins. An SC formulation of H has been developed, which is rapidly administered (up to 5 mins), potentially improving convenience for patients and clinical staff, and reducing administration costs. The Phase III HannaH study (NCT01566721) demonstrated that the pharmacokinetics and efficacy of H-SC were non-inferior to that of H-IV, meeting the co-primary endpoints. The safety profile of H-SC was comparable and consistent with the known safety profile of H-IV. SafeHer is designed to further evaluate the safety and tolerability of H-SC in a broader patient population; to allow greater understanding of a range of safety data. H-SC will be administered via one of two different routes (handheld syringe [vial formulation] or single-use injection device [SID]; which allows self-administration). Supportive data on sid safety and patient satisfaction with self-administration will be collected.

Methods: SafeHer is a multicentre, international, Phase III open-label trial (NCT01566721). The primary objective is the safety and tolerability of H-SC. Secondary objectives include disease-free survival, overall survival and patient satisfaction with SID administration. Immunogenicity of H and recombinant human hyaluronidase in a subset of patients using the SID at select sites is an exploratory objective. Planned enrolment is 2500 patients, assigned to one of two cohorts at the investigators’ discretion ± concurrent/sequential chemotherapy. All patients will receive H-SC at a fixed dose of 60mg regardless of body weight, for a total of 18 cycles (q3w) via injection into the thigh over a period of up to 5 minutes. Patients in cohort A (n = 1800) will receive H-SC using handheld syringes. Patients in cohort B (n = 700) will receive H-SC using an SID, first via assisted administration and then self-administered (in select patients). Enrolment began in May 2012 and parallel substudies may be performed at selected centres to evaluate medical resource utilisation (“time and motion study”).

Disclosure: J. Gilgore: I disclose potential conflict of interest : advisory boards and speaker honoraria for Roche laboratories. H.A. Azim: I serve on the advisory board of Roche in the middle east. B. Ataseven: I am a Roche International Steering Committee member for the SafeHer trial. I have received speaker honoraria from Roche for giving lectures. I participated in and received a travel grant from Roche for SABCS 2011. M. Delaurentiis: I am a member of a Roche Advisory Board. F. Herbst: I am an employee of, and am a stockholder in, F. Hoffmann-La Roche. A. Llombart: I am a member of a Roche Advisory Board. S. Osborne: I am an employee of Roche. X. Pivot: I am a member of Roche and GSK Advisory Boards. All other authors have declared no conflicts of interest.

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DENOSUMAB VERSUS PLACEBO AS ADJUVANT TREATMENT FOR WOMEN WITH EARLY-_STAGE BREAST CANCER AT HIGH RISK OF DISEASE RECURRENCE (D-CARE): AN IN PROGRESS, PHASE 3 CLINICAL TRIAL

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Background: Bone represents approximately 40% of all first recurrences in women with early-stage breast cancer and is a common site of distant recurrence. In preclinical studies, RANKL inhibition significantly delays skeletal tumour formation, reduces skeletal tumour burden, and prolongs survival of tumour-bearing mice. Denosumab is approved for the prevention of skeletal-related events (SREs) in patients with established bone metastases from solid tumours.

Purpose: 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 are safety, breast density, incidence of SREs (following the development of bone metastasis), patient reported outcomes, and biomarkers.

Methods: In this international, randomized, double-blind, and placebo controlled phase 3 trial, approximately 4,500 women with stage II or III breast cancer, at high risk for recurrence and with known hormone and HER-2 receptor status, are eligible. High risk is defined as biopsy evidence of breast cancer in regional lymph nodes, tumour size ≥ 5 cm, (T3), or locally advanced disease (T4). Standard-of-care adjuvant or neoadjuvant chemotherapy, 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 metastatic oral bisphosphonate (BP) use within 1 year of randomization, or any intravenous BP use, are not eligible. Patients are 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 (≥ 400 IU) and calcium (≥ 500 mg) will be administered. The trial, sponsored by Amgen Inc. and registered with the ClinicalTrials.gov identifier NCT01077154, began enrolling patients in June 2010 and is expected to complete enrolment in late 2012.