breast cancer, early

**DOSE-DENSE (DD) DOXORUBICIN AND CYCLOPHOSPHAMIDE (AC) FOLLOWED BY WEEKLY FACITAXEL (P) WITH TRASTUZUMAB (T) AND LAPATINIB (L) IN HER2-POSITIVE/AMPLIFIED BREAST CANCER (BC): FIRST SAFETY RESULTS**

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Background: DD q 2 weekly (w) AC → P + T x 1 year (y) (with congestive heart failure (CHF) rate of 1/70 pts and no other unexpected toxicities (Dang, JCO 2008). Lapatinib (L) is effective in HER2+ (BC and is being tested in the adjuvant setting. We conducted a pilot study of dd AC → P + T + L to determine its feasibility and cardiac safety.

Methods: Enrolled pts had HER2 IHC + or FISH-amplified BC, LVEF > 50% and no active cardiac disease. Rx consisted of AC at 60/600 mg/m2 x 4 q 2 w (w/ pegfilgrastim 6 mg on day 2) → P at 80 mg/m2 q 12 w + T x 1 y (4 mg/kg load, 2 mg/kg q during P and 6 mg/kg q 3 w after all chemotherapy is completed); L (1000 mg daily beginning w/ P + T and continued for 1 y). MUGA is obtained at baseline and at months (mo) 2, 6, 9, and 18. Feasibility was defined as (1) > 80% pts completing the PTL phase without a dose delay or reduction at a dose level of ≥ cardiac death (≤ 4%). Patients can remain on study with one dose reduction of L from 1000 mg to 750 mg for a G 3 event or G 3 toxicity at their discretion.

Results: From March 2007 to April 2008, we enrolled 96 pts. We report the feasibility results on the first 40 patients enrolled. Median age is 49 years (range, 28-73). Among these 40 pts, 38 are evaluable (1 expired from pneumonia after AC x 2, 1 withdrew after AC x 4 w/ G 3 fatigue). Of the 38 pts, 15 (34%) withdrew from study during the PTL phase; 11 for a 2nd event of G 3 or unacceptable < G 3 toxicities (7 G 3 diarrhea, 1 G 1 diarrhea, 1 G 2 rash, 1 G 3 QTcF w/ G 3 diarrhea, 1 G 3 ALT w/ G 3 diarrhea) and 2 for other reasons (1 progression, 1 personal reason). Of the remaining 25 pts, 9 (36%) had a dose reduction of lapatinib (L). To date there are no patient drop-outs due to significant LVEF declines after dose-dense AC and there are no cardiac events during PTL phase (CHF or cardiac death).

Discussion: This is the first report demonstrating that at 1000 mg/day is not feasible in combination with standard weekly P and T because of excessive G3 diarrhea. An earlier pooled analysis reported a G 3 diarrhea rate of <10% for lapatinib-based therapy in combination with standard weekly P and T because of excessive G3 diarrhea. An ongoing and future clinical trials will need to take into account this toxicity in their design.

**SEQUENTIAL EPIRUBICIN-DOCETAXEL-CMF AS ADJUVANT THERAPY FOR NODE-POSITIVE EARLY STAGE BREAST CANCER: UPDATED RESULTS OF THE TAI2T16 RANDOMIZED TRIAL**

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Background: Doxorubicin-based adjuvant therapy improves disease-free survival (DFS) and overall survival (OS) in node-positive breast cancer (BC) patients (pts). Most BC pts are node-negative at diagnosis and the role of taxanes in such pts is not established.

Methods: Pts aged 18-71, with Ti-T3, N0, M0 operable BC and at least one St Gallen high-risk criterion (grade II/III, tumors > 2 cm, age < 35 yrs, hormone-receptor (HR) negative) were eligible. Pts were stratified by institution and menopausal status, and randomized to 6 cycles every 3 wks of TAC (docetaxel 75 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2 day 1) or FAC (fluorouracil 500 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2 day 1). Radiotherapy was mandatory after conservative surgery, and recommended for tumors >5 cm. Tamoxifen was given for 5 yrs to HR-positive pts. The primary end point was 5-yr DFS. Secondary end-points included OS, toxicity, and quality of life (QoL).

Results: Between July 1999 and December 2001, 1059 pts were randomized (TAC 539; FAC 520) and 1047 (98.9%) were evaluable. Median age was 50 years (range, 28-73). Among these 40 pts, 38 are evaluable (1 expired from pneumonia after AC x 2, 1 withdrew after AC x 4 w/ G 3 fatigue). Of the 38 pts, 15 (34%) withdrew from study during the PTL phase; 11 for a 2nd event of G 3 or unacceptable < G 3 toxicities (7 G 3 diarrhea, 1 G 1 diarrhea, 1 G 2 rash, 1 G 3 QTcF w/ G 3 diarrhea, 1 G 3 ALT w/ G 3 diarrhea) and 2 for other reasons (1 progression, 1 personal reason). Of the remaining 25 pts, 9 (36%) had a dose reduction of lapatinib (L). To date there are no patient drop-outs due to significant LVEF declines after dose-dense AC and there are no cardiac events during PTL phase (CHF or cardiac death).

Discussion: This is the first report demonstrating that at 1000 mg/day is not feasible in combination with standard weekly P and T because of excessive G3 diarrhea. An earlier pooled analysis reported a G 3 diarrhea rate of <10% for lapatinib-based therapy (monotherapy or doublets). However, it now appears that PTL significantly increases the rate of this toxicity. Ongoing and future clinical trials will need to take into account this toxicity in their design.
Radiotherapy, Turku University Hospital, Turku/FINLAND, 8Ycr Department of implications for their treatment.

We conclude that BRCA1 and BRCA2 mutations are associated with adverse outcomes in breast cancer patients. In univariate analyses, these effects were lost after adjustment for age, T and N stage. Pathology data analysis of central review of pathology reports. BRCA1 and BRCA2 mutation testing was performed on 70% and 70% of cases, respectively (NF BC cases were tested using Cox proportional hazards analysis). 3215 eligible cases were enrolled in the BCFR, with a mean age at diagnosis of 64.9 years. Median follow-up was 7.61 yrs; 565 had distant recurrences and 547 died. There were 92 cases with BRCA1 and 72 with BRCA2 mutations; 1549 (48.2%) had NF BC. BRCA1 mutations were associated with young age, ER-, PgR- and high grade; BRCA2 with node positive cases. Pathology data analysis was performed using Cox proportional hazards analysis (stratified by center). The differences in tumor size partially related to screening in SG was sufficient to explain differences in the prognosis before the administration of adjuvant chemotherapy.

The intent-to-treat population, defined as all randomized patients (pts), is 1667 PMW with stage I-IIIA HR+ BC starting Er: 2.5 mg xq 5 yrs. Pts with a minimum BMI score of 2.0 were randomized to immediate ZA arm (IM- ZA) or delayed ZA arm (D-ZA). Results: The IM-ZA had 26 (3.1%) pts with clinical fractures (including trauma related events) while the D-ZA had 28 (3.4%) pts. Sites of fracture were similar between the two arms. 1664 pts were evaluable for disease recurrence (defined as local recurrence, distant metastasis or death). 30 (3.6%) pts in the IM-ZA had disease recurrence vs 46 (5.5%) pts in the D-ZA (Fishier’s exact test: p-value = 0.0776, not statistically significant). Bone metastases were identified in 9 (1.1%) pts in the IM-ZA vs 14 (1.7%) pts in the D-ZA; 9 (1.1%) deaths were recorded in the IM-ZA vs 16 (1.9%) in the D-ZA.

In the small group who did not receive adjuvant CXT, BRCA2 carriers had significantly worse OS as compared using Cox proportional hazards (stratified by center). 3215 eligible cases were enrolled in the BCFR, with a mean age at diagnosis of 64.9 years. Median follow-up was 7.61 yrs; 565 had distant recurrences and 547 died. There were 92 cases with BRCA1 and 72 with BRCA2 mutations; 1549 (48.2%) had NF BC. BRCA1 mutations were associated with young age, ER-, PgR- and high grade; BRCA2 with node positive cases. Pathology data analysis was performed using Cox proportional hazards analysis (stratified by center). The differences in tumor size partially related to screening in SG was sufficient to explain differences in the prognosis before the administration of adjuvant chemotherapy.

At 24 mos, the number and percentage of patients with disease recurrence or fractures in the IM-ZA appears to be lower than in the D-ZA. Additional follow-up is needed to determine whether these trends will become statistically significant.

The effects were lost after adjustment for age, T and N stage, grade, ER status and year of diagnosis (DDFS HR 1.0, p=0.98; OS HR 1.13, p=0.61). In the small group who did not receive adjuvant CXT, BRCA2 carriers had a significantly worse OS after adjusting for the above factors (HR 3.63, p=0.005). We conclude that BRCA1 and BRCA2 mutations are associated with adverse prognostic factors but they do not independently impact DFS or OS. Significantly worse OS was seen in BRCA2 carriers who did not receive adjuvant CXT; this has implications for their treatment.

The effect of zoledronic acid on aromatase inhibitor (AI) associated bone loss (ABL) in postmenopausal women (PMW) with early breast cancer (EBC) receiving adjuvant letrozole: 24 months (MOS) integrated follow-up of the Z-FAST/ZO-FAST trials

The intent-to-treat population, defined as all randomized patients (pts), is 1667 PMW with stage I-IIIA HR+ BC starting Er: 2.5 mg xq 5 yrs. Pts with a minimum BMI score of 2.0 were randomized to immediate ZA arm (IM- ZA) or delayed ZA arm (D-ZA).

Results: The IM-ZA had 26 (3.1%) pts with clinical fractures (including trauma related events) while the D-ZA had 28 (3.4%) pts. Sites of fracture were similar between the two arms. 1664 pts were evaluable for disease recurrence (defined as local recurrence, distant metastasis or death). 30 (3.6%) pts in the IM-ZA had disease recurrence vs 46 (5.5%) pts in the D-ZA (Fishier’s exact test: p-value = 0.0776, not statistically significant). Bone metastases were identified in 9 (1.1%) pts in the IM-ZA vs 14 (1.7%) pts in the D-ZA; 9 (1.1%) deaths were recorded in the IM-ZA vs 16 (1.9%) in the D-ZA.

Conclusions: At 24 mos, the number and percentage of patients with disease recurrence or fractures in the IM-ZA appears to be lower than in the D-ZA. Additional follow-up is needed to determine whether these trends will become statistically significant.
Results: Patient groups and their clinical outcome based on CTCs' monitoring with CK19mRNA and HER2mRNA before and after the administration of adjuvant chemotherapy are depicted in Table. The median follow-up for patients that did not relapse was 56 months (range 10-106 months). Bad prognosis (n=53) when compared to good prognosis patients (n=181) experienced shorter disease-free (DFS) and overall survival (OS) in the triple-negative, HER2-positive and ER-negative subgroup (p<0.001 for DFS and p<0.001 for OS), of bad versus good prognosis patients were (HR: 2.087, 95%CI 1.201-3.628, p=0.009 for DFS and HR: 2.876, 95%CI 1.249-6.265, p=0.013 for OS), of bad versus good prognosis patients were (HR: 3.940, 95%CI 2.169-7.157, p=0.001 for DFS and HR: 3.862, 95% CI 1.514-9.849, p=0.005 for OS).

Conclusion: Persistent detection of CK19-positive/HER2-positive CTCs in early breast cancer patients before and after adjuvant chemotherapy predicts extremely poor clinical outcome.

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**DISCREPANCY BETWEEN TRIPLE NEGATIVE AND BASAL-LIKE IMMUNOPHENOTYPE IN POORLY DIFFERENTIATED BREAST CARCINOMAS**


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The histological grade is one of the most important prognostic and predictive factors in breast carcinomas, but poorly differentiated neoplasms are still quite heterogeneous since they comprise a group of neoplasms that can belong to basal-like, tubular formation and its relation with the triple-negative phenotype and other clinical characteristics. The Hazard Ratios (HR) of intermediate versus good prognosis patients were (HR: 2.087, 95%CI 1.201-3.628, p=0.009 for DFS and HR: 2.876, 95%CI 1.249-6.265, p=0.013 for OS), of bad versus good prognosis patients were (HR: 3.940, 95%CI 2.169-7.157, p=0.001 for DFS and HR: 3.862, 95% CI 1.514-9.849, p=0.005 for OS).

**Conclusion:** Persistent detection of CK19-positive/HER2-positive CTCs in early breast cancer patients before and after adjuvant chemotherapy predicts extremely poor clinical outcome.
ADJUVANT HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR BREAST CANCER WITH > 3 POSITIVE NODES: 15 YEARS RESULTS FROM THE GITMO REGISTRY

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Background: The role of adjuvant high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation for primary breast cancer (BC) at high risk of recurrence (> 3 LN+) has not been well defined yet. Recently reported trials have demonstrated that this approach could have a role in selected pts. Aim of this study is to retrospectively evaluate toxicity and efficacy of HDC with HSCT in a large cohort of pts receiving HDC in Italy between 1990 and 2005.

Methods: 1284 BC pts receiving HDC for poor risk BC were identified in the Italian registry (GITMO). In 1183 pts with > 3 LN, a thorough data set including biological characteristics, toxicity and follow-up was available. Median age was 46 years (24-66), 62% of pts were pre menopausal at treatment, 71% had an endocrine responsive tumours and 43% had a HER2+ tumour. The median number of LN was 15 (4-63). 76% of pts received alkylating agents-based HDC as a single procedure while 24% received Epirubicin or Mitoxantrone-containing HDC, usually in a multi-transplant program. Source of stem cells was peripheral blood in 99% of pts.

Results: Transplant-related mortality at 108 days was 0.7%, while late cardiac and secondary tumour-related mortality were around 1% overall. With a median follow up of 79 months, median disease free survival (DFS) and overall survival (OS) in the entire population was 151 months and not reached, respectively. Subgroup analysis demonstrated that OS was significantly better in endocrine responsive tumours (p=0.0009), while menopausal or HER-2 status did not affect survival. Median OS was significantly better (p=0.0001) in pts receiving multiple transplant procedures.

Conclusions: HDC with HSCT has low TRM and high efficacy. Multiple transplants seem more active than single HDC procedures. This analysis could be useful in selecting well defined patient populations in which to re-address the role of HDC as adjuvant treatment. The study was conducted on behalf of Gruppo Italiano per il trapianto di Midollo, di Cellule Stamminali emopoietici e di terapia cellulare (GITMO).

ENDOCRINE EFFECTS OF ADJUVANT LETROZOLE VERSUS TAMOXIFEN IN POSTMENOPAUSAL EARLY BREAST CANCER PATIENTS: DATA FROM THE HOBOE RANDOMIZED TRIAL

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Purpose: We compared the endocrine changes of 6 and 12-months of adjuvant treatment with letrozole versus tamoxifen in postmenopausal hormonal receptor positive early breast cancer patients, enrolled in an ongoing phase 3 trial evaluating the effects on bone mineral density of letrozole in early breast cancer (The HOBOE study, ClinicalTrials.gov id.: NCT0194222).

Patients and Methods: Oestrogenic hormonal receptor positive patients were randomised to receive tamoxifen or letrozole ≤ 6 months (kindly supplied by Novartis). Serum 17-β-estradiol (E2), FSH, LH, testosterone, androstenedione, dehydroepiandrosterone and cortisol were measured at baseline, after 6 and 12 months of treatment. We compared for each hormone, 6 and 12-months values between treatment groups, by the exact Wilcoxon-Mann-Whitney test.

Results: At December 31, 2006, 157 patients were enrolled, and hormonal data were available for 139 patients (89%), of whom 43 were assigned to tamoxifen and 96 to letrozole. Median age was 61 and 62 years in the two arms, respectively.

All baseline hormones values were similar between the two arms. Letrozole induced a stronger suppression of median E2 serum levels at 6-months (p<0.0001) and at 12-months (p<0.0001) compared with tamoxifen. Median cortisol serum levels were lower at 6-months (p=0.001) and 12-months (p=0.0001) among patients receiving letrozole, although within the normal ranges. Patients receiving letrozole also showed significantly higher levels of FSH, LH, progesterone and testosterone, both at 6 and 12 months.

Conclusions: The endocrine effects of adjuvant letrozole and tamoxifen are significantly different in postmenopausal patients, with lower levels of estradiol and cortisol, and higher levels of FSH, LH, progesterone, testosterone in patients treated with letrozole. Long term effects of such differences deserve further studies.
Conclusion: free and overall survival rates were 79% and 94%, respectively. HER2 IHC 2+ and hormone receptor-positive tumors (P = 0.092 and P = 0.087, respectively). 22% of patients were neutropenia (57%), leucopenia (14%), febrile neutropenia (2%), and headache was very well tolerated with mild-non hematologic toxicities. Grade III/IV toxicities were observed. The use of ciprofloxacin was not helpful to reduce systemic infection nor neutropenia after TAC chemotherapy. Even though larger number of patients should be enrolled to get the definitive power to define the effective role of ciprofloxacin against infection or neutropenia, we do not think that ciprofloxacin itself gives additional advantage to patients having TAC chemotherapy to go through all cycles with fewer adverse reactions.

Methods: We randomly assigned 100 patients into two groups between Jan. 2006 to Apr. 2007. Study group (A; n=50: patients, 300 cycles) was given prophylactic G-CSF (300 ug) from day 5 to day 10, and the control group (B; n=50, 300 cycles) was given G-CSF and ciprofloxacin (300 mg, orally twice daily) from day 5 to day 10. We compared the incidence of infection and neutropenia prospectively. This study was reviewed by the IRB and informed consent from the patient was compulsory for her to be included in this trial.

Results: The incidence of infection in group A was 0.5% and in group B was 0.4% (P=0.14). The incidence of febrile neutropenia was 12% (A) versus 10% (B) (P=0.09). We could not find the significant differences in grade 4 neutropenia nor leukopenia after G-CSF with/without ciprofloxacin.

Conclusions: The use of ciprofloxacin was not helpful to reduce systemic infection nor neutropenia after TAC chemotherapy. Even though larger number of patients should be enrolled to get the definitive power to define the effective role of ciprofloxacin against infection or neutropenia, we do not think that ciprofloxacin itself gives additional advantage to patients having TAC chemotherapy to go through all cycles with fewer adverse reactions.
**199P**

**REDUCTION OF DOSE INTENSITY**

**199P ANTHRACYCLINE-BASED CHEMOTHERAPY FOR BREAST CANCER - PREDICTIVE FACTORS OF DOSE INTENSITY REDUCTION**

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**Introduction:** Adjuvant chemotherapy with an anthracycline-based regimen is considered standard for treatment of breast cancer (BC). There is good evidence that reduction in relative dose intensity (RDI) result in loss of clinical benefit. This study was undertaken to define predictive risk factors for reduced RDI.

**Methods:** A retrospective study was conducted between 1998 and 2007. Information on 631 BC patients (pts) was available. Pts under anthracycline based-chemotherapy regimens were not candidates for primary G-CSF prophylaxis. DEEPI® software (Dose Intensity Evaluation Programme) was developed to allow calculation of RDI, and includes demographic data, clinical and treatment characteristics, chemotherapy dose modifications and delays, haematological toxicities and patterns of use of G-CSF. Univariate and multivariate analysis was employed to identify factors related to RDI < 90% of standard. A value of p < 0.05 was considered of statistical significance.

**Results:** Pts distribution according to chemotherapy: doxorubicin/cyclophosphamide (A60 C600) - 17%, 5-fluourouracil/cyclophosphamide (F500 E100 C500) – 22.5%, 5-fluorouracil/doxorubicin/cyclophosphamide (F500 A50 C500) – 60.5%, Median RDI was 97% in AC, 94.6% in FEC and 97.1% in FAC. RDI < 90% was delivered in 139 (22%) pts. According to univariate analysis, factors related to reduction of RDI were: age ≥ 65 years (p = 0.035), number of patients with at least one G-CSF administration on secondary prophylaxis (p = 0.013), number of patients with at least one G-CSF administration due to neutropenia or febrile neutropenia (p = 0.001) and FEC regimen (p = 0.001). In multivariate analysis, independent predictors of RDI < 90% were: FEC regimen (p = 0.0011), age ≥ 65 years old (p = 0.027) and secondary G-CSF prophylaxis (p = 0.002).

**Conclusion:** A significant proportion of BC pts treated with anthracycline based-chemotherapy, in particular older pts and those treated with FEC regimen, have an important reduction of RDI. G-CSF secondary prophylaxis does not avoid dose reduction. These subgroups of BC pts might be candidates for primary G-CSF prophylaxis.

**Acknowledgments:** The authors wish to thank AMGEN (Portugal) for supporting the DEEPI database.

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**201P**

**COMPARISON OF ADJUVANT! ONLINE SURVIVAL PREDICTION WITH THE 10-YEAR FOLLOW-UP RESULTS ACCORDING TO THE PR-STATUS IN SLOVENIAN EARLY BREAST CANCER PATIENTS**

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**Background:** In the era of targeted therapy it is difficult to make an appropriate decision for individualized treatment of early breast cancer (EBC) patients. Adjuvant! online computer program can make this decision easier. It is well known that HR influence EBC prognosis and treatment results; however, Adjuvant! takes into account only ER but not PR. AIM: To evaluate the difference between predicted overall survival by Adjuvant! and observed OS on the overall data set of Slovenian EBC patients, and also according to the PR status.

**Methods:** 245 EBC patients diagnosed and primary treated in the year 1997 at the Institute of Oncology Ljubljana were included. All patients had radical local therapy, and adjuvant systemic therapy was given according to the then current guidelines. The basic clinicopathological characteristics were assessed routinely. HR was determined biochemically (cutoff 10 femol/mg protein). For the overall data set and for both PR-defined subsets the 10-year OS were calculated. For the same data, the average Adjuvant! (Version 8.0) predicted OS were calculated, and the observed and predicted OS were compared.

**Results:** The predicted 10-year OS for the overall data set of 245 EBC patients (median age 56 years) was 64.5%, while the observed OS was 62.4%. The predicted 10-year OS for PR-positive (n=133) was 68.4% and the observed OS was 69.2%. The predicted 10-year OS for PR-negative (n=112) was 60.0% and the observed OS was 54.5%. The differences between predicted and observed OS were within tolerable limits for the overall data set and for the PR positive subset (2.1% and 8.8%, respectively), but no so for the PR-negative subset (5.5%).

**Conclusions:** Adjuvant! is a reliable tool for prognosis assessment of Slovenian EBC patients. However, our data also indicates that Adjuvant! seems to overestimate OS for PR-negative patients. While it is not realistic for PR status to be included into the Adjuvant! model due to lack of data, the clinicians should be aware that Adjuvant! predictions can be misguided when they are evaluating prognosis and deciding on treatment for PR negative EBC patients.

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**202P**

**FEASIBILITY OF USING CORE NEEDLE BIOPSIES FOR THE 70-GENE PROGNOSIS SIGNATURE**

J.I. Mayordomo1, A.M. Roig2, C.D. Rallo3, S. Morales4, A. Gläs5, A. Flore6, F. de Snoo7, L. Soria-Slots8

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**Introduction:** A 70-gene microarray prognosis signature was previously discovered to improve the selection of patients with lymph-node negative disease for adjuvant therapy. This diagnostic test known as “MammaPrint”™ was recently validated in an independent cohort and implementation was shown to be feasible in community hospitals. However, most breast cancer patients will undergo core needle biopsies. We investigated whether the 70-gene prognosis signature could be assessed from core needle biopsies.

**Patients and methods:** We determined the negative and positive predictive value of the MammaPrint assay in patients with breast cancer stage II-III presenting to 4 ONCAMI hospitals from November 2006 up to present who had core needle biopsies (14-gauge) and subsequent neo-adjuvant treatment with 6 courses of doxorubicin (50 mg/m2) plus docetaxel (75 mg/m2) given every 21 days with G-CSF support. Core needle biopsies from 52 patients before treatment were subjected to microarray expression analysis using the 70-gene prognosis signature and were classified as being at either low or high risk for distant metastasis. Results: Thirty four signatures were obtained in this study. In this neo-adjuvant data set three (9%) of the 34 cases were assigned low risk category for recurrence and thirty-one (93%) were predicted to be high risk. In the group of patients with tumors smaller than 2 cm, only 1 out 7 was rejected on the grounds of insufficient tumor percentage. Updated and further results including correlation with response to chemotherapy will be presented at the meeting.

**Conclusion:** The MammaPrint assay was originally designed for tumor tissue from surgical specimens. We show here that MammaPrint prognosis signatures can be obtained in the majority of core needle biopsies. The results of this study have broadened the clinical applicability of the MammaPrint prognosis signature.
MAMMAPRINT® PREDICTIVE TOOL OF RESPONSE AND RESISTANCE TO PRIMARY CHEMO-ENDOCRINE TREATMENT IN ELDERLY BREAST CANCER (BC) PATIENTS

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Background: gene expression analyses, such as Mammaprint®, are a promising approach for predicting future behaviour of tumours and for defining responsiveness to chemotherapy by interrogating the molecular signature of BC. The neoadjuvant model provides a valuable test to predict the therapeutic role of clinical and biological variable such as gene profile. Recently we published data regarding ER postmenopausal model provides a valuable approach to test the predictive role of clinical and biological level. This study was undertaken to evaluate Mammaprint® ability to predict response and resistance to chemo-endocrine therapy in elderly BC patients.

Methods: 13 women with T2-4 N0-1, estrogen receptor positive BC were treated with Letrozole (L) (2.5 mg/daily) and oral “metronomic” cyclophosphamide (50 mg/daily) (LC). Mammaprint® test was performed by Agenda on tumour tissues, previously stored in RNA later, obtained at the diagnosis through incisional biopsy. Clinical response was measured by caliper by the same clinician, before and after treatment. All tested tumours were ductal and G3.

Results: 7 out of 13 valuable patients attained a complete clinical response (CR) whereas 5 did not respond (NR). Mammaprint® classified 4 patients as ”low risk” and 9 women as ”high risk”. The ”low risk” was confined to T2.5 cm. All patients underwent to a CR (1 pCR) and a great reduction of Ki67 after treatment (median BT: 16.7; AT: 2.3). The ”high risk” profile was linked to T2 cm. 5 patients out of 9 showed NR with low reduction of Ki67 expression after treatment. 4 patients obtained a CR but with less pronounced reduction of Ki67 expression as compared to ”low profile” (median BT: 9.5; AT: 4). 2 patients classified as ”high risk” showed a disease progression at bone level after 22 months.

Conclusion: Small sample size limits the generalization of the results but our observations suggest that Mammaprint® assay can be not only a promising prognostic but also a predictive factor for cytotoxic drug activity. Moreover, the microarray gene expression profiling can be used to develop models with the ability to optimize the decision-making process for the appropriate application of adjuvant therapy. However, more studies are warranted.

A COMPARISON OF 18F FDG –PET AND MRI IN THE PREDICTION OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER (BC): FINDINGS FROM THE ARIANI 01 PROJECT

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Background: Pathological complete remission to primary chemotherapy (PCT) correlates with a better prognosis. The primary aim of this study is to compare FDG PET and MRI in the prediction of pathological response to primary chemotherapy and taxane-based PST for BC.

Methods: Thirty T2-4 N0-3 BC pts were enrolled. MRI and PET scan were done at baseline, every 2 courses and at the end of PST. Metabolic response was measured by SUVmax within the primary lesion and by % SUVmax decrease. According to ROC curves analysis we considered as PET response a decrease 2.65% and 27,6% of SUV max after the 2nd cycle and the end of PST. MRI response was defined as complete or partial remission according to WHO criteria. Pathological response was evaluated according to Miller and Payne, from grade 1 (no response) to grade 4-5 (only small clusters or no malignant cells).

Results: At PET we observed 40 % grade 4-5 pathological responses. A PET response was observed in 63% and in 66% of pts after 2 courses and at the end of PST. The corresponding figures for MRI were 57% and 80%. PET responses after 2 cycles of PST (83% vs 33%, p<0.01) and at the end of PST (100% vs 55%) were more frequent in pts who obtained a grade 4-5 pathological response, while MRI responses were not.

Conclusion: A decrease of SUVmax ≥ 65% after the 2nd cycle of PST is significantly more frequent in grade 4-5 pathological responders (p<0.01) with a PPV of 86%, higher than that of MRI (68%). Therefore we can exclude with high probability an optimal pathological response in pts who do not obtain a 265% reduction in SUVmax after 2 courses of PST. PET is more accurate than MRI also at the end of PST: the absence of a PET response excludes a grade 4-5 pathological response (PPV 100%), but a PET response cannot rule out a cancer residual (NPV 53%).

K67 EXPRESSION AFTER PREOPERATIVE CHEMOTHERAPY IN STAGE II-III BREAST CANCER IS AN INDEPENDENT PREDICTOR OF PATIENT OUTCOME

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Introduction: Preoperative chemotherapy (PCT) allows for in vivo testing of treatment effects on tumor and its microenvironment, and might lead to the identification of predictive biomarkers. Moreover, the variations induced by treatment on biomarker expression (molecular response) might have prognostic implications. Aim of this analysis is to evaluate the effect of PCT on tumor biomarkers expression, and their potential predictive and prognostic role.

Patients and methods: 221 stage II-III breast cancer patients (pts) treated with PCT were included. The following parameters were evaluated at baseline, and on surgical specimens after PCT: ER, PgR, HER2, K67, p53, IEGR, VEGFR2 (all of them by IHC); apoptosis was evaluated by tunel test.

Results: Pts characteristics were as follows: median age 51 yrs (range 27-73), clinical stage IIA-B 77%; III A-B 33%; ER positivity: 63% of the pts; HER2 positivity: 24% of pts; nuclear Grade 3: 63% of the pts. A pathologic complete response (pCR) was observed in 8.6% of the pts; the probability of achieving a pCR was significantly higher in case of ER negativity, HER2 positivity, nuclear Grade 3, and p53 >10%. Baseline K67 <15%, p53 <10%, and IEGR <1% were significant predictors of a better disease free survival (DFS). Baseline p53<15% was also associated with a prolonged overall survival (OS). P53 (OR 9.98 vs 54%, p<0.0001). PCT induced a reduction in the expression of tumor biomarkers: ER by 38% (p<0.0001), PgR by 20% (p<0.0001), K67 by 15% (p<0.0001), IEGR by 2% (p<0.0001), Tunel by 3% (p<0.0001), VEGFR2 by 6% (p=0.08). As multivariable model, K67 ≥30% and nodal positivity after PCT were significant predictors of worse DFS (HR 3.91, p<0.0001 and HR 2.41, p=0.033 respectively). Ki67 ≥15% after PCT was also a significant predictor of OS (HR 3.8, p<0.01).

Conclusions: PCT induces profound variations in the expression of several tumor biomarkers. Ki67 expression after PCT is an independent prognostic parameter and might be used to discriminate patients at higher risk of relapse.

STUDY OF DETECTIONS FOR PERIPHERAL BLOOD MICROMETASTASIS IN BREAST CANCER

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Objective: The aim of this study was to detect micrometastasis (CK19) in peripheral blood by immunocytochemical staining, reverse transcription polymerase chain reaction (RT-PCR), flow cytometry in 46 breast cancer patients. The results of the work are the groundwork to developing a novel platform for micrometastasis detection with Microfluidic chip in a single cell scale.

Methods: Peripheral blood samples were obtained from 46 breast cancer patients postoperatively. We detected the micrometastasis with immunocytochemical staining, RT-PCR and flow cytometry. The results of these techniques were compared. We also researched the method to detect the micrometastasis on a designed and developed microfluidic chip.

Results: The micrometastasis in peripheral blood samples were detected with immunocytochemical staining, RT-PCR and flow cytometry in 46 breast cancer patients. The positive rates were 23.9% (11/46), 39.1% (18/46) and 34.7% (16/46), £0.001 and 0.01, respectively). Patients with stage III/IV lesions had higher positive findings than those with stage I/II lesions (P<0.001 and 0.01, respectively). We detected the micrometastasis with immunocytochemical staining, RT-PCR and flow cytometry. The latter was the best of these methods. Microfluidic chip is a promising novel platform for micrometastasis detection. The realization of this technique will be valuable for improving the accuracy and speed of clinical examination, and for the possibility of processing the detection at home. This research was supported by the National Nature Science Foundation of China (Key Project no. 30570479).
The VEGF C96T and G634C polymorphisms affect the expression of the vascular endothelial growth factor (VEGF) gene in breast cancer (BC) cells. The cells also produce the angiogenic protein endostatin (ES), produced by the COL18A1 gene. COL18A1 D104N polymorphism was associated to increased sporadic BC (SBC) risk. Furthermore, by promoting the glutathione-dependent antioxidant, the glutathione S-transferase (GST) enzymes facilitate the hypoxic factor activity, stimulating the angiogenesis (AG). The GSTM1 wild genotype was associated to a high angiogenic phenotype. Intratumoral microvessel density (IMVD) in tissues is used to quantify the AG. Since it is not well established whether VEGF C96T and G634C, COL18A1 D104N polymorphisms are related to angiogenesis, and IMVD in SBC and controls with the genotypes of the respective genes. The IMVD was similar in patients with the VEGF and GST genotypes. However, the IMVD in patients with DD was higher than in those with NN genotype of the COL18A1 (19.0 and 28.7; P= 0.02). These results suggest that the VEGF 634CC and COL18A1 104NN genotypes increase risk for SBC and the COL18A1 104NN genotype was associated to a high angiogenic phenotype. Since several VEGF proteins levels raise similar in individuals with the distinct genotypes of the three polymorphisms, we hypothesized that the variant alleles, C and N, code proteins with abnormal functions on AG. Financial support: FAPESP and CNPq.

Conclusions: The normality of MSCTCI substantiates the hypothesis that RT cardiotoxicity is due to microvascular damage. It is important to follow these patients to see if these abnormalities are transient or permanent, to screen for new MDP after a longer FU and to detect early clinical manifestation of CAD the presence of which would make these MDP pre-clinical signs of CAD. It is mandatory to screen for other risk factors for CAD to treat them aggressively and to reduce RTA-CHT cardiotoxicity.

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three month after radiotherapy in comparison with pre radiotherapy values (P=0.001, P=0.006 respectively). SpO2 had no significant difference between two groups and was also in each group after one and three month.

Conclusion: Locoregional radiotherapy of chest wall and suprapubically lymph node cause reduction in FEV1 and FVC three month after radiotherapy but no differences was present between three fields and four fields techniques. We recommend this study be completed by using pulmonary function tests.

MUSCULOSKELETAL COMPLAINTS AND ADJUVANT AROMATASE INHIBITOR (AI) THERAPY

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Background: Musculoskeletal complaints are common in postmenopausal women (PMW) and are related to estrogen deprivation. Not surprisingly, these problems are also reported in PMW receiving adjuvant endocrine therapy. These problems are often described differently by patients and reflected in various adverse events reported, making it difficult to evaluate across trials.

Methods: The incidence of musculoskeletal problems in phase 3 clinical trials of AIs (anastrozole [ANA], letrozole [LET], and exemestane [EXE] vs tamoxifen [TAM]) (ATAC, BIG 1-98, IES) or placebo (PLA) (MA.17) and in several small AI studies were evaluated.

Results: Among women taking AIs, ady, stiff joints and joint pain were the most frequent complaints and have been reported to cause discontinuation of AI therapy. The incidence of arthralgia was significantly greater with ANA in ATAC at 68 months (35.6% vs 29.4%; P=0.0001), with LET in BIG 1-98 at 25.8 months (20.3% vs 12.3%; P=0.001), and with EXE in IES at 55.7 months (18.6% vs 11.8%; P=0.001). Myalgia was not reported in ATAC, but the incidence was similar with LET vs TAM in BIG 1-98 at 25.8 months (6.4% vs 6.1%; P=0.61). In IES, EXE was associated with more musculoskeletal pain (25.7% vs 20.3%; P=0.0001) and joint stiffness (1.9% vs 1.0%; P=0.009). Carpal tunnel syndrome was more common with ANA in ATAC (3% vs 1%; P=0.0001) and EXE in IES (2.8% vs 0.3%; P=0.0001). Compared with PLA in MA.17, there was significantly more arthralgia (29% vs 21%; P=0.001) and myalgia (15% vs 12%; P=0.004) with LET, but not bone pain (5% vs 6%; P=0.67). Higher rates of AI-related joint pain (47%) and joint stiffness (44%) have been reported in clinical practice than in clinical trials. Measures can be taken to manage these problems. Results from ALIQUOT showed that >50% of patient with joint symptoms on one nonsteroidal AI do not experience symptoms on the other nonsteroidal AI. Analgesics and glucocorticoids also reduce bone pain.

Conclusions: Musculoskeletal complaints are common but can be managed by analgesics, anti-inflammatory agents, and lifestyle changes. Also, changing from one nonsteroidal AI to another may reduce joint symptoms. Thus, the benefits of adjuvant AI therapy may be maintained.

RETURN TO WORK AFTER BREAST CANCER: WHY NOT? PREDICTORS RISK FACTORS AND IMPACT ON QUALITY OF LIFE IN A PROSPECTIVE MONO-CENTRE RESEARCH

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The work experience of women who have had a breast cancer (BC) is still an unexplored area of survivorship research. The purpose of the present longitudinal mono-centre study was to investigate whether socio-economic, disease- and/or treatment-related factors were associated with the ability of returning to work in a sample of 146 consecutive patients treated at our Institution for early BC who were working at the time of diagnosis. The research three main goals were 1) to evaluate the percentage of women returned to work after 24 months from diagnosis in the cohort of survivors, 2) to identify risk factors associated with the ability of patients to continue their employment, 3) to quantify work disability that survivors associated with cancer and its treatments. At 24-month analysis, 97 out of 131 eligible women (74%) had returned to work. Most were state-employed (85%), full-time working in 69% of cases, and >60% had an intellectual job; 69% benefited from flexible hours working. Discrimination because of cancer diagnosis was reported by 35% of patients and occupational intervention by 25% of re-employed women. Among the 34 women who had not returned to work after 24 months from diagnosis, 38% were sick-listed, 30% received a disability work pension, 23 were early retired, and 12 were out of work. Statistical analysis showed that the duration of disease (odds ratio= 2.96, 95%CI 1.25 to 7.03) and the nature of work (odds ratio= 3.9, 95%CI 1.57 to 9.82) were the strongest predictors of work disability. Analysis of factors related to quality of life and quality of work (EORTCQLQ-C30, EORTC-Br23, FACT-an and VIBBA validated questionnaires) suggest that fatigue adversely affected the return to work in our sample, while perceived good quality of job was associated with a greater likelihood of work resumption. Our results confirm that work disability after BC remains a critical issue; strictly disease- and work-related variables can significantly affect the probability of return to work, also involving remarkable socio-economical aspects. There is a need of improving social support and occupational rehabilitation to BC patients, for which returning to work is an important measure of recovery from the disease and a positive step toward the future.

TRASTUZUMAB THERAPY FOR EARLY BREAST CANCER IN THE REAL-WORLD

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Background: Various trials have shown substantial benefits of addition of Trastuzumab (Herceptin)® to adjuvant chemotherapy in Early Breast Cancer (EBC). Our breast oncology unit is a tertiary centre catering to screen detected and symptomatic cancers. The target breast screening population is 245,000 women. We analysed our breast cancer population to determine the number of patients eligible for and receiving trastuzumab therapy in EBC.

Methods: Data for all patients diagnosed with EBC in 2006 was recorded prospectively in a database. Case notes were consulted where the HER2 positive patients, determined by a combination of IHC and FISH, had not received trastuzumab, to ascertain the reasons.
ADJUVANT ZOLREDONIC ACID (ZOL) THERAPY DECREASES THE PREVALENCE OF DISSEMINATED TUMOR CELLS (DTCs) IN BONE MARROW (BM) OF PATIENTS WITH EARLY-STAGE BREAST CANCER (EBC): 2 YEAR RESULTS

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Background: DTCs in BM, particularly after adjuvant therapy, are associated with distant recurrence (DR) and death in EBC patients. Bisphosphonates exhibit antitumor activity via various mechanisms including inhibition of angiogenesis, reduction in tumor cell proliferation, and induction of tumor cell apoptosis. Clodronate reduced the incidence of metastases and improved survival in patients with DTCs in BM at BC diagnosis. This pilot study is designed to evaluate ZOL in patients with EBC with BM DTC. Decrease in DTCs may serve as a clinical surrogate marker for antitumor effect.

Methods: Eligible patients have stage I-II BC and > 4 DTC/mL BM (2.5 standard deviations > 50 normal BM samples; Park, Proc ASCO, 2002) after neoadjuvant or adjuvant therapy. DTCs are detected by immunomagnetic BM enrichment using anti-EPICAM-PE, then by flow cytometry for EPICAM, CD45, and nucleic acid content. Patients receive 4 mg IV ZOL monthly for 2 yr. Concomitant hormone therapy is allowed. Serum creatinine and toxicity are evaluated for identification of independent predictors of survival.

Results: 45 patients were enrolled. Interim analysis of baseline, 1-yr and 2-yr BM data is presented here. Mean baseline DTCs are 25.6/mL (range 4.9-332) and mean follow-up is 19.8 mo (range 2-38). Baseline DTCs > 30/mL predict DR (P = .007). Of 35 patients with > 1 yr ZOL, 32 had BM assessments at 1 yr, 23/32 (66%) had a DTC decrease (P = .018). At 2 yr, 12/17 (71%) patients had a BM DTC decrease (P = .01). Of 35 cases, 32 had BM assessments at 1 yr, 23/32 (66%) had a DTC decrease (P = .018). Most cases decreased during the treatment period. These 2-year data suggest that ZOL treatment decreases the prevalence of DTCs in EBC. Updated data from this study will be presented.

Conclusions: The HER2 positivity rate is lower than that previously reported suggestive of changing demographics secondary to a high screen-detected cancer population. Only 50% of HER2 positive EBC patients received trastuzumab therapy. Of those who did not receive trastuzumab, the commonest reason was low risk status or age and co-morbidities precluded chemotherapy. HER 2 positivity alone confers high risk irrespective of pathological stage. Further trials are required to evaluate whether the substantial number of patients who are at present not eligible for trastuzumab therapy might also benefit.

BREAST CANCER IN THE ELDERLY: TREATMENT AND SURVIVAL PATTERNS

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Background: Breast cancer (BC) is the most common malignancy in women. Half of new cases of BC is diagnosed after 65 years old. We purpose to identify patterns of treatment and follow-up, evaluating differences between younger (<65-74 years old) and older pts (≥75 years old).

Methods: retrospective study based on clinical records of pts older than 65 years admitted with BC from January 2003 to January 2005. Demographic and clinical data was collected, including follow-up information. Differences between age groups were evaluated by univariate analysis. Survival analysis was performed by Kaplan-Meier and log-rank test and Cox Regression for identification of independent predictors of survival.

Results: Data from 414 pts was analysed. 71% of pts were younger than 74 years old. Median age was 71 years old. There was no difference between groups according to TNM stage and hormonal receptors status. Only 6% of the younger group pts was submitted to conservative surgery, compared to 33% of pts in the younger group (p<0.001). Chemotherapy was administrated to 13% pts in the older group, compared to 40% of pts in the younger group (p<0.001). Overall survival at the end of follow-up was 85%, with a statistical significant difference (p<0.002) between ages groups 65-74 (90%) and ≥ 75 (67%). Pts with higher ECOG, with tumours at advanced stage and negative hormonal receptors had worse overall survival (p<0.001). A statistical significant difference persisted in the overall survival for age group adjusted for hormonal receptor (p<0.002) and for stage (p<0.03). A multivariate Cox Regression identified as independent prognostic factors for overall survival: TNM stage (p<0.001) and hormonal status (p<0.03), and, for disease free survival: ECOG (p<0.006) and TNM stage (p<0.0001).

Conclusions: For older pts with BC TNM stage is the single more important factor related to survival. Older pts and those with ECOG ≥1 have a dismal prognosis even after adjusted for other prognostic related variables. That may be related to a less aggressive treatment.
FATIGUE, QUALITY OF LIFE (QOL) AND COGNITIVE FUNCTIONS IN PATIENTS TREATED WITH ADJUVANT CHEMOTHERAPY (ACT) AND/OR RADIOTHERAPY (RT) FOR LOCALIZED BREAST CANCER (LBC): A FRENCH LONGITUDINAL STUDY

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Most LBC patients given ACT complain of fatigue during or after RT. They also report cognitive function disorders and decrease in QoL.

Methods: A longitudinal study was performed to compare QoL, fatigue and cognitive function changes with time after ACT and RT (Group 1) or RT alone (Group 2). Assessments were made before, during, at the end of, and 4 and 12 months after RT. Instruments were the FACT-G (QoL) with breast and fatigue modules, and the HADS; the MMSE, Digit Span, Trail Making Test and Rey Auditory Verbal Learning Test were used to assess cognitive functioning. Biological tests were performed included blood count, inflammatory markers (ILs, TNFα, CRP), TSH, FT4 and anti-TPO and anti-TG antibodies.

Patients: From May 2004 to December 2006, 302 patients were enrolled, 161 in Group 1 and 141 in Group 2. At entry, major differences between groups were: mean age 52 ± 58 years, mastectomy vs. lumpectomy 23% vs. 1%, use of hormonal support 23% vs 8.5% in Groups 1 and 2, respectively.

Results: Before RT, 60% of Group 1 patients expressed fatigue vs 33% (p<0.001). After RT, these proportions were 61% vs 33% (p=0.1). Although fatigue improved with time, it remained present in more than 40% of patients at 12 months. No biological disorders were observed in patients with or without chronic fatigue. Anxiety was present before and after RT in 70% of patients in both groups. In contrast, depression was more frequent in Group 1 patients: 28% vs 16% (p=0.03) before RT; at the end of RT, 25% of patients expressed depression in both groups. Fatigue and depression levels correlated (p=0.001). While significant differences (p<0.02) in QoL parameters were present between Groups 1 and 2, these proportions were 61% vs 53% (p=0.1). Although fatigue improved with time, systemic toxicity decreased. Breast module scores were always significantly (p<0.001) lower in Group 2 patients.

Conclusion: Results on cognitive functions will be presented at the meeting.
were positive. We suggest to carry out FISH to evaluate the status of HER-2 in BC.

In the 10 cases of IHC score 2 negative. We found that 5 of the 16 IHC score 3 pts. were IHC score 0 and FISH positive, and 5 were IHC score 3 negative. We found a significant discordance in 9 cases (15%) of our group of 60 cases of BC. The size was 21 mm (range 3-80). Median number of resected sentinel lymph nodes was 2 (range 1-5). The HER2 status review, IHC was used with a polyclonal antibody (CB11-1/500), antigenic recovery, dianobenzidine (DAKO) and ENVISION system of detection (DAKO). Manual method per protocol of work was used (National Plan Her2). The results were interpreted by using scores 0 to 3+. FISH was used to assess HER-2 gene amplification. The tumors were tested in two reference centres. All procedures were applied to de-paraffinised tissue sections of BC samples.

Results: From July 2007 to April 2008, 60 cases of infiltrative BC were studied and correlation with HER-2 overexpression between IHC and FISH was determined. Mean age of women was 51.35 (24-78) years. 73.3% of tumours were infiltrative ductal carcinoma, 8.3% were lobular carcinoma and 5% canicular carcinoma. 40% of pts presented with stage IIA disease, 21.6% with stage IIB and 15% with stage I. 3 was used to assess HER-2 status in patients (pts) with BC being considered for trastuzumab therapy.

Methods: For HER2 status review, IHC was used with a polyclonal antibody (CB11-1/500), antigenic recovery, dianobenzidine (DAKO) and ENVISION system of detection (DAKO). Manual method per protocol of work was used (National Plan Her2). The results were interpreted by using scores 0 to 3+. FISH was used to assess HER-2 gene amplification. The tumors were tested in two reference centres. All procedures were applied to de-paraffinised tissue sections of BC samples.

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