breast cancer, locally advanced and metastatic

**FIRST EFFICACY RESULTS FROM THE TURANDOT PHASE III TRIAL COMPARING TWO BEVACIZUMAB (BEV)-CONTAINING REGIMENS AS FIRST-LINE THERAPY FOR HER2-NEGATIVE METASTATIC BREAST CANCER (MBG)**

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**Background:** TURANDOT is the first prospective trial to compare BEV combined with either paclitaxel (PAC) or capcitabine (CAP). We report the planned interim analysis (IA) of efficacy.

**Methods:** Patients with HER2-negative mBC who had received no prior chemotherapy for mBC were randomised to receive either BEV-PAC (BEV 10 mg/kg d1 + 15 ± PAC 90 mg/m² d1, 8 & 15 q2w) or BEV-CAP (BEV 15 mg/kg d1 + CAP 1000 mg/m² bid d1-14 q2w) until disease progression or unacceptable toxicity. The primary objective is to demonstrate non-inferior overall survival (OS) with BEV-CAP vs BEV-PAC. Interim and final OS analyses were planned after 175 and 389 deaths, respectively, in the per protocol (PP) population to reject the null hypothesis of inferiority (hazard ratio [HR] ≥1.33) with 80% power and overall α = 0.025. Secondary endpoints include response rate (RR), progression-free survival (PFS), safety and quality of life.

**Results:** Median follow-up was 19 months at data cut-off for this IA (1 Sep 2011). Baseline characteristics were generally similar in the 2 treatment arms.

<table>
<thead>
<tr>
<th>BEV-PAC</th>
<th>BEV-CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>59</td>
</tr>
<tr>
<td>Visceral metastases, %</td>
<td>65</td>
</tr>
<tr>
<td>Prior (neo)adjuvant taxane, %</td>
<td>20</td>
</tr>
</tbody>
</table>

Events, %

- 33
- 1-year OS rate, %
- 81
- HR (97.5% RCI)
- 1.04 (<α to 1.69)
- p = 0.593
- for non-inferiority

PFS

- 44
- Overall, %
- 27
- CMH test (superiority)
- p < 0.001

Median, months

- 11.0
- 8.1

HR (95% CI)

- 1.36 (1.09 to 1.68)
- Log-rank (superiority)
- p = 0.0052

RCI = repeated confidence interval

αPP population (n = 533)

αKaplan-Meier estimate

αUsing O’Brien-Fleming boundaries

αNon-inferiority not shown as p > 0.00105 (α at IA) AEs were consistent with the known safety profiles of BEV, PAC and CAP. The most common grade ≥3 AEs were neutropenia (18%), peripheral neuropathy (14%) and leucopenia (7%) with BEV-PAC and hand-foot syndrome (16%), hypertension (6%) and diarrhoea (5%) with BEV-CAP.

**Conclusion:** In this planned IA, the non-inferiority criterion has not been met but OS results do not indicate relevant differences. Final results are expected in 2014. PFS and RR were better with BEV-PAC and very similar to previous data for BEV–PAC (E2100) and BEV–CAP (RIBBON-1).

**Disclosure:** R. Greil: RG has received research support and honoraria from Roche. S. Beslija: SB has received research support and honoraria from Roche. D. Messinger: Employee of IST GmbH, CRO which is providing various services and consultancies for Hoffmann-La Roche and CECOG. T. Brodowicz: TB has received honoraria from Roche. All other authors have declared no conflicts of interest.

**PH 1B/II STUDY OF BMK120 PLUS TRASTUZUMAB (T) IN PATIENTS WITH T-RESISTANT HER2+ ADVANCED BREAST CANCER (BG)**

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**Background:** PI3K/AKT/mTOR pathway upregulation has been implicated in T resistance, and thus the impact of pathway inhibition on restoration of therapeutic sensitivity is being investigated. The RP2D of BMK120, an oral pan-class I PI3K inhibitor, plus T is 100 mg/d. Here, we present PH II results of BMK120 + T in pts with T-resistant advanced HER2+ BC.

**Methods:** Pts with HER2+ locally adv/metastatic BC resistant to T (progression while on T, or within 4 wkks [metastatic] or 12 mths [adjuvant] of last T dose) received daily BMK120 (100 mg) and the standard wkly dose of T. Ph II eligibility criteria: ≥1 measurable lesion, ≥1 but ≤4 prior anti-H/ER2 regimens (incl. trastuzumab [required], lapatinib, and/or T-DM1), and ≥3 lines of prior chemotherapy for metastatic disease. Ph II pts treated at the RP2D who met Ph II eligibility criteria were included in the analysis.

**Results:** As of 1 March 2012, 53 pts were included in the PH II analysis (safety set; incl. 8 pts from Ph Ib). 49 pts were evaluable for response (full analysis set); median age 52 yrs (28–75); median prior antineoplastic regimens 4 (1–10); 5 pts had a baseline CNS lesion (3 measurable target; 2 non target). At data cut-off, 9 pts were still on study. Most pts discontinued treatment due to disease progression (55%); 8 pts (16%) withdrew due to AEs. Mean duration of BMK120 exposure was 11 wks (0.1–41). Most common suspected study-drug related G3/4 AEs: ALT increased (5 pts), rash (5 pts), photosensitivity, hyperglycemia (2 pts each). Partial responses (RECIST) were seen in 4 pts (8%), and stable disease (SD) was noted in 20 pts (41%); the disease control rate (CR, PR, or SD) was 49%. Preliminary results indicate that, of the 5 pts with baseline CNS mets (BM), 2 pts had SD in the CNS without evidence of progression at study withdrawal; 2 pts had overall SD (1 for 90 days and 1 for 106 days) before progression in the CNS; 1 pt was not evaluated in the CNS after study entry.

**Conclusion:** BMK120 in combination with T has an acceptable safety profile, and has shown encouraging preliminary activity in heavily pretreated HER2+ metastatic BC pts with T resistance, including pts with BM.

**Disclosure:** Q. Ru: Employee of Novartis. S. Ruquet: Employee of Novartis. D.W. Sternberg: Employee of Novartis. All other authors have declared no conflicts of interest.

**SIGNIFICANT ANTITUMOR ACTIVITY OF E-3810, A NOVEL FGFR AND VEGFR INHIBITOR, IN PATIENTS WITH FGFR1 AMPLIFIED BREAST CANCER**


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**Background:** Amplification of the FGFR1 gene occurs in subsets of tumors, notably breast cancer (BC), where the altered FGFR pathway may be clinically relevant.

**Conclusion:**
**Methods:** E-3810 is a kinase inhibitor targeting FGFR1 and VEGFR1, 2, 3. Its safety and activity, at the daily oral dose of 20 or 15 mg on a continuous schedule, are being assessed in patients with solid tumors and FGFR1 amplification or potentially sensitive to antiangiogenic agents. The study is an open label non-comparative extension of the first in man dose-escalation trial; the efficacy threshold, set for the FGFR1+ cohort only, requires 3/14 confirmed objective RECIST responses or non-progressive disease ≥ 6 cycles (one-stage Fleming design: HO 5%, HI 30%, power 80%).

**Results:** 46 patients with various tumor types (including 13 FGFR1+ cancers) were recruited. 8 patients (4/13 and 4/33 treated respectively at 20 and 15 mg. none in the FGFR1+ cohort) were withdrawn for toxicity: including G3 proteinuria (5), headache and vomiting (2), pancreatic enzymes increase (1), recovered in all cases. Hypertension G2-3, proteinuria G2, G1 intolerance, asthma and weight loss led to dose reduction in 20 patients; frequent TSH increase required supplementation. Tolerability was better in the FGFR1+ cohort, in line with a limited prior exposure to antiangiogenic treatments. Antitumor activity is shown in the table:

<table>
<thead>
<tr>
<th>Antiangiogenic Sensitive</th>
<th>FGFR-amplified (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Evaluable PR SD PD</td>
</tr>
<tr>
<td></td>
<td>1 1 9 4 3 2</td>
</tr>
<tr>
<td>Other</td>
<td>Evaluable PR SD PD</td>
</tr>
<tr>
<td></td>
<td>23 3... 13 7 2 1</td>
</tr>
<tr>
<td>Total</td>
<td>Evaluable PR SD PD</td>
</tr>
<tr>
<td></td>
<td>24 3 14 7 11 4 4 3</td>
</tr>
</tbody>
</table>

(1) incl. the two BC patients with 11q amplification; * SD ≥ 24 weeks; ** 1 PET response (bone lesions); ***2 thyroid; 1 thymic carcinoma. 12 women with BC were recruited (9 HR +, 1 HER2 +/HR +, 2 TN); 8 were FGFR1 +, 2 more had 11q amplification, with 3 responders still on treatment.

**Conclusions:** E-3810 has shown significant activity in heavily pretreated BC, with 3 responders still on treatment.

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

**References:**


**ClinicalTrials.gov Identifier:** NCT00912444.

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**Methods:**

- **Patient scheduling:** A TREATMENT-INTERACTION ANALYSIS BALANCING PATHOLOGICAL COMPLETE RESPONSES (PCR) AND CARDIOXOTOICITY OF SINGLE- (S)- OR DUAL- (D) HER2 INHIBITION AND NEOADJUVANT CHEMOTHERAPY (CT) BACKBONE IN OPERABLE/LOCALY ADVANCED BREAST CANCER (O/LABC) PATIENTS

- **Objective:**
  - To evaluate the activity and safety of docetaxel plus cyclophosphamide (TC) compared with docetaxel, anthracycline and cyclophosphamide (TAC) in neoadjuvant treatment of triple negative or HER2 positive breast cancer, which may help us to determine the role of anthracycline in breast cancer treatment.

- **Methods:**
  - **Clinical stage III or IIIB breast cancer patients were treated with six cycles of TC (docetaxel 75 mg/m2 and cyclophosphamide 600 mg/m2) or TAC (docetaxel 75 mg/m2, anthracycline, and cyclophosphamide 500 mg/m2).** Either epirubicin 60mg/m2 or adirubicin 50mg/m2 was allowed as an anthracycline regimen. The primary end point was pathological complete remission (pCR), defined as no residual invasive cancer in breast and axillary lymph node. Second end points included safety, clinical response rate, event free survival (EFS), disease free survival (DFS), and overall survival (OS).
  - **Results:** 102 patients were randomized and 96 patients were available for analysis (TC: n = 45; TAC: n = 51). After surgery, pCR rate was 6.8% (3/45) and 17.6% (9/51) respectively, in TC and TAC group, respectively. p = 0.113. There was also no difference in clinical response rate. However, with mean follow up of 20 (3-36) months, TAC treatment, compared with TC, resulted in a significantly superior EFS (80.4% vs 60.0%, respectively; adjusted HR = 2.42 (95% CI 1.11 to 5.30); P = 0.027), better DFS (84.3% vs 64.4%, respectively; adjusted HR = 2.85 (95% CI 1.21 to 6.74); P = 0.017) and a trend towards less death (96.1% vs 86.7%, respectively; adjusted HR = 2.52 (95% CI 0.41-15.38); P = 0.13). Among patients treated with TAC had relapse high rates of grade 3-4 neutropenia and leukopenia, and rates of other adverse severe events were similar and no patients died on treatment.

- **Conclusions:** pCR rate was not significantly different between TAC and TC in neoadjuvant treatment of triple negative or HER2 positive breast cancer. Adding anthracycline to TC can significantly improve patients' outcome, which deserves further investigation.

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

**References:**


**ClinicalTrials.gov Identifier:** NCT00912444.

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**Methods:**

- **Objective:** To evaluate patients outcome with multifocal or multicentric breast cancer after neoadjuvant chemotherapy by type of surgery.

- **Methods:** Patients and methods: Participants of the GeparTriao and GeparQuatro trials with operable or locally advanced tumors received anthracycline-taxane (+/- anti-HER2-based neoadjuvant chemotherapy and were classified as having unifocal (one lesion detected by physical examination, sonography, mammography 2 MRI), multifocal (2-2 lesions in one breast quadrant), or multicentric (≥ 2 lesion in ≥2 quadrants) disease. Breast conservation was allowed when tumor-free margins were achieved.

- **Results:**
  - Tumors of 3,562 patients were classified as unifocal (N = 2793; 78.4%), multifocal (N = 429; 12.0%), and multicentric (N = 340; 9.5%). Breast conservation was performed in 71.7%, 56.2%, and 35.1%, respectively (P = 0.0001). At surgery pathological complete response (PCR) rates were 18.7%, 14.1%, and 14.9%, respectively (P = 0.047). After median follow up of 46.3 months locoregional and distant-relapse-free survival were worse in patients with multicentric disease versus uni- or multifocal disease treated with mastectomy (P = 0.007 and 0.061, respectively), but not when treated by breast conservation (P = 0.634 and 0.650, respectively).
  - Patients with PCR showed a low locoregional relapse rate irrespective of pecularity (P = 0.713) but a higher distant relapse rate in case of multicentric disease (P = 0.003). Prognostic factors for locoregional recurrence in multivariable analysis were tumor and nodal status at surgery, grading, hormone-receptor status, and type of surgery, but not focality of the tumor. Overall survival was not statistically different through all focality groups.

- **Conclusions:** Breast conservation for multifocal or multicentric breast cancer after neoadjuvant chemotherapy is feasible and seems not to impair outcome if tumor-free margins were achieved.

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

**References:**

Results: 8 trials (2092 pts) with 1955 pts treated with anti-HER2 therapy (Trastuzumab, Lapatinib and Pertuzumab), were gathered; pCR rates according to HER2 inhibition follow:

<table>
<thead>
<tr>
<th>CT</th>
<th>HER2-Inhibition Rates (95% CI)</th>
<th>Interaction (p)</th>
<th>NNT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthra-TAX</td>
<td>S: 37.0 [34.0, 40.0]</td>
<td>0.22</td>
<td>2.7</td>
</tr>
<tr>
<td>TAX</td>
<td>D: 44.3 [33.3, 55.2]</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>21.7 [18.1, 25.3]</td>
<td>&lt;0.0001</td>
<td>4.6</td>
</tr>
<tr>
<td>D</td>
<td>42.4 [36.4, 48.5]</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

pCR rates were significantly higher in the HRs negative population, regardless of the HER2 inhibition and CT backbone [Neg vs. Pos. Anthra-TAX [S] AD 9.4%, p = 0.002; TAX [S] AD 15.3% p < 0.0001; TAX [D] AD 28% p < 0.0001]. With regard to CT, a significant interaction (p < 0.0001) in favor of adding Anthra to TAX was found in the context of s-HER2 inhibition subgroup with regard to pCR (AD 15.4%) and BCs (AD 10.8%) with no interaction in the D-subgroup. No significant differences in FN and cardiotoxicity were found according to HER2 inhibition and CT. In the Anthra-TAX [S] population weighted for cardiotoxicity, LHH was 77.

Conclusions: On the basis of the available data, anthracyclines should be considered for O/LABC patients receiving TAX-based CT plus HER2 inhibition, given the likely 70-times greater to achieve pCR than to be harmed by clinically meaningful cardiotoxicity.

Disclosure: All authors have declared no conflicts of interest.

Introduction: Postmenopausal women with hormone receptor-positive (HR+) breast cancer (BC) who relapse or progress on a nonsteroidal aromatase inhibitor (NSAI) have limited treatment options. At a median follow-up of 18 months, BOLERO-2 demonstrated that the exploratory (EVE) plus exemestane (EXE, a steroidal aromatase inhibitor, plus exemestane (EXE), a steroidal aromatase inhibitor, prolonged progression-free survival (PFS) compared with EXE alone in this setting (7.8 vs 3.2 mo, respectively; hazard ratio [HR] = 0.45 [95% confidence interval (CI) = 0.38, 0.54]; log-rank P < 0.001).

Methods: BOLERO-2 is a phase 3, double-blind, randomized study that compared EVE (10 mg/d) + EXE (25 mg/d) vs placebo (PBO) + EXE (n = 239) in postmenopausal women with advanced HR+ HER2- BC who had progression or recurrence after NSAI therapy. The primary endpoint was PFS by local investigator assessment. In view of the lack of efficacy of endocrine therapies in patients with visceral involvement, EVE + EXE was evaluated in patient subgroups defined by the presence of visceral metastases (including lung, liver, spleen, pleural effusions, pericardial effusion, peritoneum, ascites, ovary and central nervous system).

Results: At a median follow-up of 18 months, adding EVE to EXE prolonged median PFS versus PBO + EXE in patients with visceral metastases (n = 406: 6.8 vs 2.8 mo, respectively; HR = 0.47 [95% CI = 0.37, 0.60]). Similarly, EVE + EXE extended PFS in patients without visceral metastases (n = 318: 9.9 vs 4.2 mo for PBO + EXE; HR = 0.41 [95% CI = 0.31, 0.51]). Patients with visceral involvement had shorter PFS compared with patients with bone-only disease regardless of treatment. Nonetheless, PFS improvements with EVE + EXE were similar in patients with visceral and bone-only disease (n = 151; 12.9 vs 5.3 mo for PBO + EXE; HR = 0.33 [95% CI = 0.21, 0.53]).

Conclusions: Adding EVE to EXE markedly extended PFS by 2-4 mo among patients with advanced HR+ HER2- BC regardless of the presence of visceral metastases.

Disclosure: M. Campone: M. Campone is a consultant to and has received honoraria from Novartis. S. Noguchi: S. Noguchi has received grant support and honoraria from AstraZeneca, Chugai, Pfizer, sanofi-aventis, GSK, Taiho, Novartis, and Takeda. K. Pritchard Consult sanoven AZE Roche PFE NVR AMG GSK res funding NCICCT Grp contracted AZE BMS AVE BMS NVR & AMG paid expert test SanAven AVE & GSK AdCom SanAven AZE Roche PFE NVR AMG & AMG. H. Rugo: H. Rugo has received grant support from Novartis, Pfizer, and Merck, and has received travel support from Novartis. G.N. Hortobagyi: Member of the Scientific Advisory Board of Allergan, consultant to Allergan, Novartis, Genentech, and sanofi-aventis, received grant support from Novartis, and travel expense reimbursement from Novartis, Genentech, and sanofi-aventis. J. Baselga: J Baselga is a consultant to Novartis, Roche, Merck, sanofi-aventis, Verastem, Bayer, Chugai, Exelixis, Onyx, Constellation, A. Panneerselvam. Employee of Novartis with stock/stock options. T. Tarani: Employee of Novartis with stock/stock options. T. Sahmoud: Employee of Novartis with stock/stock options. M. Piccart: Board PharmaMar, consultant sanofi-aventis, Aman, BMS, GSK, Boehringer, Roche, & Bayer, & grant Pfizer, Amgen, BMS, GSK, Roche, & sanofi-aventis, honoraria Bayer, BMS, GSK, & Azee, Aze.
Background: Abiraterone irreversibly inhibits 17-hydroxylase/c-17-20 lyase (CYP17), reducing androgen and estrogen levels and improves overall survival from castration resistant prostate cancer. We hypothesized that: A) Postmenopausal ERα+ MBC continue to be ERα+ AR driven; and B) Postmenopausal ERα− AR+ MBC can be driven by AR.

Methods: This Phase I/II trial of AA with hydrocortisone evaluated tolerability, pharmacokinetic (PK)-pharmacodynamic (PD) profile and anti-tumor activity. Two parallel but non-randomized Phase II arms utilized a Gehan design (95% probability of detecting a 24wk overall survival rate benefit (PR) = 0.8; type II error probability (β) = 0.20; power = 0.80). Twelve patients entered the Phase II study: 11 were in the test arm and 1 in the control arm. The control arm was used to obtain a control series. The test arm was a 2:1 randomization of patients to the control arm. The primary endpoints were objective response rate (ORR) and progression-free survival (PFS).

Results: In the phase I study, daily dosing of AA was well tolerated with variable PK profile. In the Phase II trial, daily dosing of AA was well tolerated with variable PK-pharmacodynamic profile and anti-tumor activity. Two parallel but non-randomized Phase II arms utilized a Gehan design (95% probability of detecting a 24wk overall survival rate benefit (PR) = 0.8; type II error probability (β) = 0.20; power = 0.80). Twelve patients entered the Phase II study: 11 were in the test arm and 1 in the control arm. The control arm was used to obtain a control series. The test arm was a 2:1 randomization of patients to the control arm. The primary endpoints were objective response rate (ORR) and progression-free survival (PFS).

Conclusion: AA is well tolerated and merits further evaluation in MBC. Cancer Research UK (Drug Development Office) Sponsored and funded the trial. Johnson & Johnson provided AA.

Disclosure: M. Dowsett: The Institute of Cancer Research has a commercial interest in Abiraterone. Mitch Dowsett is an employee of the Institute of Cancer Research, which has a ‘Rewards to Inventors’ scheme and is a recipient of the scheme. J.S. de Bono: The Institute of Cancer Research has a commercial interest in Abiraterone. Prof de Bono is an employee of the Institute of Cancer Research, and recipient of a ‘Rewards to Inventors’ scheme. He is also a consultant for Johnson and Johnson. All other authors have declared no conflicts of interest.
absolute difference of median values. Linear regression analysis was also conducted to predict the effects of a new anticancer drug on OS based on the effects on PFS.

Results: A total of 5041 studies were identified and 144 fulfilled the eligibility criteria. Seven studies included 15 treatment arms, which represents 43,459 patients with mBC. There was a significant relationship between median PFS and median OS across included trials (r = 0.428, p < 0.01). The correlation between median PFS/TP and median OS was higher for studies evaluating chemotherapy alone (r = 0.575, p ≤ 0.01) or in combination (r = 0.632, p ≤ 0.01) compared with those evaluating hormone therapy (non-significant r). The correlation coefficient for the treatment effect on PFS and OS was estimated at 0.427 (p < 0.01). The linear regression equation was: ΔOS = −0.088 (95% CI, −1.347 to 1.172) + 1.753 (95% CI, 1.307 to 2.198) * ΔPFS, with a proportion of variation explained (R²) of 0.86. Results of the regression analysis predict that a difference in median PFS/TP of 5, 10, and 20 months would translate into a difference in median OS of 8.7, 17.4, 26.2, and 35.0 months respectively.

Conclusion: The present findings point toward a statistically significant correlation between median OS and median PFS in the context of mBC and support the surrogacy of PFS for OS in this cancer setting.

Disclosure: All authors have declared no conflicts of interest.

Keywords: median OS, median PFS, linear regression analysis, surrogacy, breast cancer, metastatic disease.

IMPACT OF RESPONSE SHIFT ON TIME TO QUALITY OF LIFE SCORES DETERIORATION IN BREAST CANCER PATIENTS: IS IT TIME TO MOVE FOR QOL RECIST CRITERIA?

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Background: Time to quality of life (Qol) score deterioration (TD) is a method of longitudinal Qol data analysis that has been proposed for breast cancer (BC) patients (Hamidou et al Oncologist 2011). As for RECIST criteria, the optimal definitions dealing with reference should be explored. This study aims to study the impact of changes in internal standards (CS) of response-shift (RS) and the influence of baseline Qol expectations on TD.

Methods: A prospective multicenter study including all women hospitalized for a primary BC was conducted. The EORTC-QLC-C30 and BR-23 questionnaires were used to assess the Qol at baseline, at the end of 1st hospitalization, and 3 and 6 months after. ALS was investigated by the then-test method. Qol expectancy was assessed at baseline using Likert scale. Determination was defined as a decrease in Qol scores reaching at least the mean difference identified as minimal clinically important difference (MCID) using Jaeschke’s transition question. Sensitivity analyses were done using the then-test score as reference score, and considering 5 and 10 points as MCID. TD was estimated using Kaplan-Meier method. Cox regression analyses were used to identify factors influencing TD.

Results: From February 2006 to February 2008, 381 women were included. For role functioning dimension, the median TD increased from 3 to 5 months after. ALS was investigated by the then-test method. Qol expectancy was assessed at baseline using Likert scale. Determination was defined as a decrease in Qol scores reaching at least the mean difference identified as minimal clinically important difference (MCID) using Jaeschke’s transition question. Sensitivity analyses were done using the then-test score as reference score, and considering 5 and 10 points as MCID. TD was estimated using Kaplan-Meier method. Cox regression analyses were used to identify factors influencing TD.

Disclosure: All authors have declared no conflicts of interest.
adjusting on CIS, sentinel lymph node biopsy became significantly associated with longer TD (HR: 0.64[0.43–0.94]) as compared to axillary lymph node dissection, radiotherapy to a shorter TD (HR: 0.63[0.42–0.93]) and the type of surgery had no effect on TD. For global health, cognitive and social functioning dimensions, patients expecting deterioration in their QoL had a significantly shorter TD. For fatigue and breast symptom scales, patients expecting no change had a significantly shorter TD, as compared to patients expecting an improvement. Sensitivity analyses using a MDCS of 0.5 or 10% confirmed these results.

Conclusions: Our results suggest that it would be more accurate to take into account CIS component of RS as well as QoL expectations to estimate TD of QoL scores in patient with BC.

Disclosure: All authors have declared no conflicts of interest.

HEALTH STATE UTILITY DETERMINATION IN ADVANCED STAGE BREAST CANCER PATIENTS

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Background: Quality adjusted Time Without Symptoms of disease and Toxicity (Q-TWiST) survival analysis method provides a comprehensive estimate of quality of life in cancer patients. AIMS: We assess women’s preferences for health states specific to advanced stage breast cancer including a baseline of survival responses, no treatment response but no disease progression, disease progression and hormonal therapy specific toxicities.

Method: Using FACT-B quality of life data from a randomized clinical trial in ABC univariate statistics were obtained for each item for each health state without regard to treatment. These item scores were paired to the actual narrative in the FACT-B to construct health state narratives consisting of physical, social, emotional, functional well-being and additional concerns content domains. The order of the content domains was varied to prevent order bias. One hundred and nine per- post-menopausal women were recruited and interviewed by a single woman in their age group using visual analogue and standard gamble techniques. Univariate and multivariate analyses were performed to control for age, marital status, menopausal status and whether the interviewer had had breast cancer or any other cancer.

Results: Of the 109 recruited 100 women completed the interview, mean age was 55.76 years. 64% were postmenopausal. 11% had breast cancer previously and 16% had another type of cancer previously. Multiple regressions results for the VAS scores yielded values of 51.8 (p < 0.01) for baseline ABC diagnosis, 82.5 (p < 0.01) for treatment response, 57.5 (p < 0.01) for no response no progression and 38.4 (p < 0.01) for disease progression. The SG results were 0.64 (p < 0.01), 0.76 (p < 0.01), 0.67 (p < 0.01), and 0.50 (p < 0.01), respectively. Women who previously had breast cancer related the health states consistently higher (p < 0.05) in the VAS and SG analyses. The trade-off between a chance of treatment response yet the possibility of toxicity yielded a utility score of 0.34 (p < 0.01).

Conclusion: These VAS and SG scores can be used to better assess women’s preference for treatment options in ABC.

Disclosure: W.R. Simons: This research was conducted independent of Eisai Inc.

COST EFFECTIVENESS OF ADJUVANT CYCLOPHOSPHAMIDE CONTAINING REGIMES TO AT IN THE TREATMENT OF BREAST CANCER IN GERMANY

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Objectives: 58,000 women in Germany are diagnosed with breast cancer each year. Anthracycline-containing regimes - in addition to other treatment options - have been standard adjuvant breast cancer regimens. The purpose of this analysis was to estimate the cost-effectiveness of AT (doxorubicin, docetaxel) compared with AC (doxorubicin, cyclophosphamide), CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and FEC (5-fluorouracil, epirubicin, cyclophosphamide) administered as adjuvant therapy to women with node-positive breast cancer in Germany.

Methods: We developed a multi-country Cost-Utility-Model to simulate the long-term consequences from initiation of adjuvant chemotherapy over 10 years. Markov modelling techniques were used to estimate incidence of complications during chemotherapy (fibrile neutropenia, chemotherapy induced nausea/vomiting, dose-reduction, dose-delay, other grade 3/4 adverse events) and long-term consequences like local or distant relapse, secondary acute myelogenous leukaemia, chronic heart failure and death. Monte-Carlo-simulation accounted for uncertainty. Probabilities were derived from clinical and epidemiological studies; direct costs from published sources from the payer’s perspective. QALYs, life years and costs were discounted at 3% p.a.

Results: Over a 10 year timeframe, costs and outcomes associated with AT amounts to 21,055.91 € and 6.3 QALYs (7.5Ys). Costs associated with AC are 17,018.04 €, while outcomes are comparable to AT. The cost saving potential associated to AC vs. AT amounts to 4,937.87 € per patient. Costs and outcomes associated with CMF are 17,790.42 € and 6.3 QALYs (6.9Ys), leading to a cost saving potential of 6,326.49 € with CMF vs AT. FEC associated total costs are 18,471.84 €.

Quality-adjusted life expectancy increases to 6.5 years, which represents a QALY gain of 0.2 QALYs over 10 vs 10 years. AT. The increase in life expectancy without quality adjustment amounts to 7.4 years and leads to 0.4 LYs gained with FEC versus AT. Accordingly, FEC dominates AT.

Conclusion: Cyclophosphamide-based regimens (FEC, AC and CMF) demonstrate a better performance from cost-effectiveness perspective vs. AT (doxorubicin, docetaxel).

Disclosure: All authors have declared no conflicts of interest.

HEALTH-RELATED QUALITY OF LIFE (QOL) IN METASTATIC BREAST CANCER PATIENTS TREATED WITH EVEROLIMUS AND EXEMESTANE VERSUS EXEMESTANE MONOTHERAPY

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Background: The phase 3 BOLERO-2 study randomized 724 patients with hormone-receptor-positive (HR+) advanced breast cancer and recurrence or progression during/after nonsteroidal aromatase inhibitor therapy to everolimus (EVE) plus exemestane (EXE) or EXE and placebo (PBO). Interim analysis after 12 months median follow up demonstrated that EVE + EXE significantly improved progression-free survival (PFS) vs EXE + PBO, with a higher rate of grade 3/4 adverse events but no deterioration in QOL. We report here on additional post hoc analyses of patient-reported QOL.

Methods: Using the EORTCQLQ-C30 questionnaire and QLQ-BR23 module, QOL was assessed at baseline and every 6 weeks thereafter until progression or discontinuation. The QLQ-C30 consists of 30 items combined into 15 subscales, including Global Health Status (GHS). The BR23 consists of 23 items specific to breast cancer combined into symptom and functioning subscales, including breast symptom (BS) and arm symptom (AS) scales. Average difference in change from baseline between treatment groups was evaluated using linear mixed models with several adjustment covariates. Sensitivity analysis was conducted using pattern-mixture models to examine the effect of study dropout on or before week 24. Treatments were compared using differences of least squares means (LSM) changes from baseline at each timepoint and overall.

Results: Linear mixed models indicated no statistically significant overall difference between EVE + EXE and EXE + PBO for GHS (LSM difference = −2.8; 95% CI = −4.8, 0.9), breast symptoms (LSM difference = 0.3; 95% CI = −2.8, 2.4), or arm symptoms (LSM difference = −0.2; 95% CI = −2.8, 2.4). Pattern-mixture models indicated that patients who dropped out early had worsening QOL over time in both treatment arms; EVE + EXE patients who did not drop out early had stable QOL, whereas EXE + PBO was associated with worsening QOL over time.

Conclusions: These additional analyses from the BOLERO-2 study confirm that compared with EXE alone, EVE + EXE improved PFS without adversely impacting QOL in patients with HR+ advanced breast cancer progressing despite nonsteroidal aromatase inhibitors.

Disclosure: J.T. Beck: Has received grant support from Pfizer and Novartis. H. Rugo: Has received grant support from Pfizer and Merck, and has received travel support from Novartis. J. Baselga: Is a consultant to Novartis, Roche, Merck, sanofi-aventis, Verastem, Bayer, Chugai, Euxlia, Onyx, and Constellation. T. Taran: Is an employee of Novartis with stock options. L. Bennett: Is an employee of RTI Health Solutions, which contracted with Novartis for data analysis services. J. Ricci: Is a consultant to Novartis. I. Sahmoud: Is an employee of Novartis with stock options. G.N. Hortobagyi: Members of Sci Ad Board of Allergan; consultant to Allergan, Novartis, Genentech, and sanofi-aventis; has received grant support from Novartis; travel expense reimbursement from...
Novartis, Genentech, and sanofi-aventis. All other authors have declared no conflicts of interest.

**335P DYSPHONIA AS A PREVIOUSLY UNREPORTED SIDE EFFECT OF BEVACIZUMAB TREATMENT IN PATIENTS WITH METASTATIC BREAST CANCER**

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**Introduction:** Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor and has been approved for the treatment of several metastatic tumours. There is considerable heterogeneity in the response to treatment with bevacizumab, both in effectiveness and in toxicity. Here we describe a previously unreported adverse drug reaction (ADR) in pts with MBC treated with bevacizumab.

**Methods:** In a teaching hospital in the Netherlands (from Sep 2009 to Jul 2011), 32 consecutive pts with MBC treated with chemotherapy and bevacizumab were registered in a retrospective database. TNM stage, comorbidities, concomitant medication, prior treatment for the primary tumour, date of metastatic disease, prior treatment for metastatic disease and toxicities were recorded. The WHO global individual case safety report database, Vigibase contains summaries of suspected spontaneous case reports summated by health care professionals and pts to national pharmacovigilance centres. As of May 2010, Vigibase contained >5 million case reports. We searched the Vigibase extraction of Dec 2011 for dysphonia. Reporting odds ratios (RO) were calculated for the occurrence of dysphonia compared with other ADR for bevacizumab and paclitaxel.

**Results:** In total, 9/32 pts (28%) reported dysphonia during treatment with bevacizumab and 5/9 pts underwent ENT examination. In several pts marked oedema of the vocal cords and/or chronic laryngitis were found. As of Dec 2011, 6,880,361 reports were available in Vigibase, of which 16,239 were related to dysphonia. For bevacizumab there were 51 reports for dysphonia and 46,041 reports for other ADR. Corresponding figures for all other drugs were 22,108 reports for dysphonia and 25,151,628 reports for other adverse effects: ROR of 1.26 (95% CI: 0.95-1.66). For paclitaxel there were 45 reports for dysphonia and 85,988 reports for other ADR. Corresponding figures for all other drugs were 22,114 reports for dysphonia and 25,111,681 reports for other adverse effects: ROR of 0.59 (95% CI: 0.44-0.80) meaning that the risk of angiooedema is significantly higher in bevacizumab users compared to paclitaxel users.

**Conclusion:** Dysphonia is a previously unreported side-effect in pts with MBC treated with bevacizumab and paclitaxel.

**Disclosure:** S.A. Radema: I am member of an advisory board for Roche. All other authors have declared no conflicts of interest.

**338P PATTERNS OF CLINICAL MANAGEMENT AND RESOURCE UTILIZATION FOR POSTMENOPAUSAL HORMONE-RECEPTOR-POSITIVE HER2-NEGATIVE (HR+ HER2-) ADVANCED BREAST CANCER (ABC) IN EUROPE**

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**Objective:** To understand treatment patterns and quantify resource utilization of HR+ HER2- ABC with the overall aim of comparing the burden as patients progress from hormonal therapy (HT) to chemotherapy (CT).

**Methods:** We conducted a chart audit in France, Germany, The Netherlands, Belgium, and Sweden of 375 living and deceased postmenopausal female patients (75 per country) diagnosed with ER- HER2- ABC in the past 4 years. Patients were required to have progressed on ≥2 line of prior HT either in the adjuvant or advanced setting and to have completed ≥1 line of CT treatment (minimum 2 full cycles) in the ABC setting. The chart audit was completed online using a standardized form developed with the assistance of European academic physicians, pharmacy directors, and hospital administrators. Participation was sought from 25 oncologists per country, except in Germany (15 oncologists and 10 gynecologists to reflect local clinical practice). Data collection was compliant with European and local clinical practice. Data collection was compliant with European and local clinical practice (except in Germany (15 oncologists and 10 gynecologists to reflect local clinical practice). Data collection was compliant with European and local clinical practice. Data collection was compliant with European and local clinical practice. Data collection was compliant with European and local clinical practice (except in Germany (15 oncologists and 10 gynecologists to reflect local clinical practice). Data collection was compliant with European and local clinical practice. Data collection was compliant with European and local clinical practice.

**Results:** Our report details the patient care pathway, CT side effects, and resource utilization in the inpatient and outpatient settings throughout the continuum of ABC treatment. Preliminary analyses indicate that 55% of HR+ HER2- ABC patients are first treated with HT and switch to CT after 1.5 lines of HT. This switch is primarily influenced by the extent (56%) and progression rate (36%) of metastases. The switch from HT to CT is associated with increased resource utilization and the associated costs of treating ABC. In addition to cost of drug therapies, the main drivers of cost are treatment for CT side effects (chiefly febrile neutropenia and diarrhea) and related hospitalization events. CT side effects that have the greatest impact on the overall disease burden of ABC include alopecia, nausea, vomiting, fatigue, and peripheral neuropathy.

**Conclusions:** Our results highlight the increased costs and disease burden for postmenopausal ER- HER2- ABC patients treated with CT versus HT.


**337P EFFICIENCY FRONTIER ANALYSIS (EFA) OF METASTATIC BREAST CANCER (MBC) TREATMENTS: A UK PERSPECTIVE**

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**Background:** As newer therapies for MBC become available, understanding the efficiency of these therapies will be important for HTA recommendations and treatment decisions. EFA may be a useful method of assessing the efficiency of newer interventions. The EFA displays the output (cost) and gains with technologies, and displays the next most efficient option going forward. This study was designed to evaluate whether EFA could be useful in identifying the efficiency of mBC therapies adopted by the NHS, and to identify the efficiency frontier for newer technologies.

**Methods:** A literature search was performed to identify mBC treatments that have undergone HTA in the UK. Reviews were reported to identify treatment efficacy and HTA recommendations. Costs were determined for a course of treatment. The incremental costs per patient were plotted on the horizontal axis and incremental median overall survival (OS) of each treatment was plotted on the vertical axis to construct the EFA line. Treatments below this line are considered inefficient options. Treatments above this line have better OS and may redefine the efficiency frontier. Treatments in the upper right quadrant beyond the frontier line are in an area where ceiling price has not been defined. Treatments in the lower right quadrant beyond the frontier line are inefficient due to higher cost for lower OS.

**Results:** Ten reports that evaluated efficacy in terms of median OS were included in the EFA. The therapies are paclitaxel albumin, gemcitabine, trastuzumab, bevacizumab, lapatinib, eribulin and fulvestrant. On the horizontal axis are paclitaxel albumin (DOS of 2.3 months at £2091), gemcitabine (DOS of 2.8 months at £6020) and trastuzumab (DOS of 4 months at £16939); all received positive recommendations. Lapatinib (DOS of 1.9 months at £10180), bevacizumab (DOS of 1.7 months at £36560), eribulin (DOS of 2.5 months at £4834) and fulvestrant (DOS of 2.3 months at £2481) are all below the frontier line and received negative recommendations.

**Conclusion:** EFA may be a useful method for assessing the efficiency of new mBC treatment options for clinical use. Further studies are needed to better understand value in terms of efficiency of treatments in other tumor types and disease areas.

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

**338P A CONJOINT ANALYSIS OF WILLINGNESS TO PAY TO AVOID METASTATIC BREAST CANCER SIDE EFFECTS**

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**Background:** Patients with metastatic breast cancer (MBC) are treated with a variety of regimens with differing side effect profiles. In addition to efficacy, side effect profile can be an important consideration in therapy choice. Conjoint analysis is a research method used to evaluate how trade-offs are made between different attributes. This study assessed the willingness to pay (WTP) to avoid side effects related to MBC treatment using conjoint analysis. The WTP thus informs clinicians of patients’ preferences and which side effects they are most or least concerned about.

**Methods:** An online, self-administered survey of MBC patients in the US was conducted. The survey was fielded with a sample of adult female patients with a diagnosis of MBC. Key variables (attributes) included in the analysis and with levels described in lay terms were: Alopecia, Diarrhoea, Fatigue, Pain, Nausea, Neutropenia, Neurotoxicity and Out of pocket costs. 12 scenarios (choice-based conjoint questions)
were presented where patients selected the most preferred therapy. Each therapy was described with three distinct variables. The choices of variables for each therapy included two side effects and an out of pocket price. The survey also collected information on prior treatment regimens, previous side effect history, and demographics.

Results: There were 298 responses. Most respondents were white (84%), married (57%) over 40 years of age (86%), and had private insurance (57%). MBC patients were willing to pay $3,894 to avoid severe diarrhea, $3,479 to avoid being nauseous, $1,458 to avoid severe pain. The most important attributes when selecting a therapy for MBC in terms of average utility were neuropathy, diarrhea and nausea.

Conclusions: Patients most highly value the avoidance of diarrhea, neutropenia, and nausea with MBC treatment regimens. These are common side effects seen in many regimens used for treatment of MBC. This information can aid in clinical decision making when selecting between MBC treatment options. Treatment regimens providing clinical efficacy while decreasing or eliminating key side effects would be an important consideration.

Disclosure: D. Lalla: Dr. Lalla is an employee of Genentech, which funded this analysis. A. Bramley: Dr. Bramley is an employee of Genentech, which funded this analysis. R. D’Souza: Dr. D’Souza is an employee of Genentech, which received funding from Genentech to conduct this analysis.

FULVESTRANT 500 MG AS FIRST-LINE TREATMENT IN HORMONE-POSITIVE (HR+) METASTATIC BREAST CANCER (MBC) PATIENTS (PTS): PROSPECTIVE EVALUATION OF ACTIVITY, SAFETY, QUALITY OF LIFE (QOL) AND TUMOUR MARKERS CHANGES

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Background: Fulvestrant 500 mg has been shown to have a biologically greater effect and to produce a clinical meaningful benefit over Fulvestrant 250 mg. We carried out an analysis to conduct this analysis. R. Carlton: Dr. Carlton is an employee of Xcenda, which received funding from Genentech to conduct this analysis. T. Bramley: Dr. Bramley is an employee of Xcenda, which received funding from Genentech to conduct this analysis. A. D’Souza: Dr. D’Souza is an employee of Xcenda, which received funding from Genentech to conduct this analysis.

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RESULTS:

There were 298 responses. Most respondents were white (84%), married (57%) over 40 years of age (86%), and had private insurance (57%). MBC patients were willing to pay $3,894 to avoid severe diarrhea, $3,479 to avoid being nauseous, $1,458 to avoid severe pain. The most important attributes when selecting a therapy for MBC in terms of average utility were neuropathy, diarrhea and nausea.

Conclusions: Patients most highly value the avoidance of diarrhea, neutropenia, and nausea with MBC treatment regimens. These are common side effects seen in many regimens used for treatment of MBC. This information can aid in clinical decision making when selecting between MBC treatment options. Treatment regimens providing clinical efficacy while decreasing or eliminating key side effects would be an important consideration.

Disclosure: All authors have declared no conflicts of interest.

ADJUSTED INDIRECT COMPARISON ANALYSIS DEMONSTRATES SIGNIFICANT BENEFIT IN PROGRESSION-FREE SURVIVAL FOR FULVESTRANT 500MG COMPARED TO ANASTROZOLE IN ADVANCED BREAST CANCER

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Objectives: Randomised controlled trials (RCTs) provide the highest level of evidence for comparing two treatments. However, with the increasing number of cancer drugs, direct comparison through RCTs is not feasible for all treatment indications and combinations. Bucher et al (1997) have developed a method for an adjusted indirect comparison analysis between RCTs. This method was used to compare the efficacies of fulvestrant 500mg and anastrozole 1mg in advanced breast cancer (ABC).

Methods: A systematic literature search on RCTs of fulvestrant 500mg or anastrozole 1mg in ABC was performed in June 2011, using CENTRAL, EMBASE and MEDLINE databases. Published data were used to perform a meta-analysis and an adjusted indirect comparison analysis (Bucher method). The primary endpoint was progression free survival (PFS).
Results: Three RCTs with 1023 patients were identified comparing fulvestrant 500mg (F500) with fulvestrant 250mg (F250), and two RCTs with a total of 851 patients were identified comparing anastrozole 1mg (Ana) with fulvestrant 250mg. Meta-analysis demonstrated a significant benefit in PFS for F500 compared to F250 (Hazard ratio (HR) 0.80 95% Confidence Interval (CI):0.69-0.93). There was no significant difference in PFS between Ana and F250 (HR 0.95, 95CI 0.82-1.1). Using F250 as common comparator, the adjusted indirect comparison analysis demonstrated a significant benefit in PFS for F500 compared to Ana (HR 0.70, 95CI 0.50-0.97).


Disclosure: P. Turner: Pauline Turner is a full-time employee of AstraZeneca and is a stockholder in AstraZeneca. M. Howlett: Matthew Howlett is a full-time employee of AstraZeneca and is a stockholder in Astrazeneca. All other authors have declared no conflicts of interest.

### FULL VENSTRAST (FUL) PLUS ENZASTATURIN (ENZA) VS PLUS PLACEBO (PBO) IN AROMATASE INHIBITOR (AI) RESISTANT METASTATIC BREAST CANCER (MBC): A RANDOMIZED, DOUBLE-BLIND, PHASE 2 TRIAL

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AIs are used as first-line treatment for postmenopausal women with hormone-receptor-positive MBC. Overexpression of PKC α has been linked to AI resistance in several studies. We examined whether Enza, a serine/threonine kinase inhibitor that targets PKC, could improve the effect of Ful in pts who progressed following first-line AI treatment for MBC. Postmenopausal pts with hormone-receptor-positive, HER2-negative, locally advanced or MBC who progressed on prior AI received a loading dose of Ful 500 mg IM on Day (D) 1 and 250 mg on D 15 of Cycle (C) 1 and D 1 of each cycle thereafter. Enza 500 mg or PBO was administered orally once daily (QD) or 250 mg twice daily (BID). Primary endpoint was the clinical benefit rate (CBR). Secondary endpoints were response rate (RR), duration of CB, progression-free survival (PFS), and overall survival. A total of 156 pts was randomly assigned to therapy: 152 received at least 1 dose of study drug (39 BID; 55 QD; 58 PBO). Baseline disease characteristics were balanced across arms. There was no statistically significant difference in CBR between pts in Ful + Enza vs Ful + PBO. There was not statistically significant difference in CBRs, RRs and PFS between pts on QD and BID dosing schedules. Pts on BID dosing had numerically more TEAEs vs those on QD and PBO (61.5%, 43.6%, and 43.6%, respectively) and numerically more Grade 3/4 TEAEs (17.9%, 9.1%, and 5.2%, respectively). Most frequent Grade 3/4 TEAEs in the BID arm were fatigue (n [%]) (4 [10.7%]), dyspnea (2 [5.1%]) and nausea (2 [5.1%]). 8 pts died; 5 due to disease, 3 due to AEs: 1 drug-related hepatic dysfunction (Enza arm), 1 non-drug-related myocardial infarction and 1 non-drug-related respiratory failure (both in the Enza BID arm).

### PHARMACOKINETICS (PK) OF PERTUZUMAB (P) WITH TRASTUZUMAB (T) AND DOCTAXEL (D) IN HER2-POSITIVE FIRST-LINE METASTATIC BREAST CANCER (MBC): RESULTS FROM THE PHASE III TRIAL CLEOPATRA

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Patients were homogeneous for tumor burden at diagnosis and received anthracycline-taxane and trastuzumab-based neoadjuvant treatment. 14 out of 3 patients achieved pathological complete remission. Ki-67 and HER2 H score were significantly higher in patients who achieved complete remission (medians were 45.5% versus 25%, p = 0.022; 100% versus 50%, p = 0.045 respectively. We found a correlation between age and HER2 H score (r = 0.13, p = 0.03) and an inverse correlation between age and HER2 H score (r = 0.03) and between PNR and ACT intensity (r = 0.01). Ki-67 and HER2 H score maintained significatively different medians in the group of patients who experienced pathological complete response versus the group on incomplete responders with multivariate analysis (p < 0.01).

Disclosure: All authors have declared no conflicts of interest.

### NEW IMMUNOHISTOCHEMICAL MARKERS PREDICTIVE OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY PLUS TRASTUZUMAB IN HER2-POSITIVE LOCALLY ADVANCED BREAST CANCER: A SINGLE CENTER EXPERIENCE

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We present the results of a prospective pilot study aimed to investigate the value of new immunohistochemical predictive markers of response to chemotherapy in locally advanced HER-2 breast cancer. pTN, loss, PAK and HER-2 overexpression cause PI3K activation and induce resistance to trastuzumab in vitro and in vivo, with poorer clinical responses in patients with advanced disease. We studied the expression of EGFR, HER-3, pTEN and PAK in 31 patients with locally advanced HER-2 positive breast cancer who received neoadjuvant chemotherapy plus trastuzumab. Mean age of patients was 55.7 years (median 55, 95% CI 42.4-63.5 years). Results of immunohistochemical staining are reassumed in the table.
for P were collected before and after infusion at Cycles 1, 3, 6, 9, 12, 15, 18, and at treatment discontinuation. Samples for T were collected before and after infusion at Cycles 1 and 3. Samples for D were collected at Cycle 1 at 8 serial time points during and following the infusion, at no greater than a 24 h period to allow calculation of C\text{max}, CL, V\text{ss}, t\text{1/2}, AUC\text{0-t}, and AUC\text{inf}.

Results: 37 pts (17 Pla arm, 20 P arm) were available for PK evaluation. Serum P C\text{max} exceeded the target of 20 mg/ml in >90% of pts and there was no impact of T and D on P PK, compared with historical data. Serum T C\text{max} and AUC\text{0-24 h} at Cycles 1 and 3 were similar in both arms. Ratios of geometric LS means of P + T + D/C\text{max} were 1.06, 1.07, 1.11, 1.04, 1.09, and 1.08 for serum T C\text{max} and AUC\text{0-24 h}.

Conclusions: PK parameters were consistent with previous studies, and co-administration of T and D appears not to influence P PK in HER2-positive MBC. There was no evidence of drug–drug interactions between P and T, or between P and D, which have different clearance pathways.

Disclosure: I. Cortes: I am an advisory board member for Roche, Celgene and Novartis. I have received research funding from Roche, Celgene, Cephalon and Ferrer. S. Swain: Advisory Board for Genentech/Roche for EMILIA study and Avastin - uncompensated. Research funding: Genentech/Roche. T. Patel: I have an advisory board membership for Genentech/Roche. I have no disclosures to make and am a speaker for Genentech/Roche. I have received research funding from Genentech/Roche. No. Mauser: I have honoraria to disclose received from Chugai Pharmaceutical Co., Ltd. V. McNally: I am a Roche employee and hold Roche shares. J. Visch: I am an employee of Genentech. J. Baselga: Dr Baselga reports the following relationships with relation to the topic of this abstract: Roche, Sanofi Aventis, Consulting/Scientific Advisory Board. Roche, Sanofi Aventis, Honoraria for speaking engagements. All other authors have declared no conflicts of interest.

PROGNOSTIC FACTORS INFLUENCING THE SELECTION OF BEVACIZUMAB COMBINED WITH CHEMOTHERAPY IN PATIENTS WITH HER2-NEGATIVE METASTATIC BREAST CANCER IN ROUTINE CLINICAL PRACTICE. ONCOSUR-AVALOX: OBSERVATIONAL CROSS-SECTIONAL STUDY


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Background: Combining bevacizumab (BEV) with chemotherapy (CT) improves survival in HER2-negative metastatic breast cancer (MBC). We investigated the influence of age, ECOC, hormonal status, number of sites and location of metastases and patient decision on the selection of BEV combined with CT in MBC.

Methods: Observational cross-sectional multicenter study in pts with HER2- negative MBC who have received first-line CT with BEV.

Results: From November 2010 to November 2011, 124 pts were included: median age 51 (45-64); yr; ECOC: 8 = 0%; 60% pre-menopausal; 23% triple-negative (TN); 77% hormone receptorpositive (HR+). Metastatic disease: ≥ 3 sites = 42% (TN: 32%; HR+ = 45%); location = 44% bone, 35% lung, 30% liver. Most frequent BEV-based combinations were paclitaxel/BEV (53%) and docetaxel/BEV (14.5%); median no. of CT cycles: 6 (5-8). A disease-free survival (DFS) ≥ 12 months was achieved by 73%; TN: 68%; HR+ = 76%. Overall response rate (ORR) was 58%: 51% partial response (PR); 7% complete response (CR); 28% stable disease (SD) and 10% disease progression. TN: ORR 44% (40% PR), clinical benefit 80% (36% SD); HR+ : ORR 62% (54% PR), clinical benefit 87% (25% SD). 58% presented at least one toxicity, mainly grade 1-2; 26% BEV-related: only 3 (2.4%) grade 3 toxicities; no grade 4. Receiving adjuvant hormonal therapy was associated to DFS ≥ 12 months (p < 0.05). ER+ tumors (OR: 0.215; 95% CI: 0.08-0.56; p = 0.002) and one metastatic site, vs. ≥ 3 sites (OR: 0.309; 95% CI: 0.12-0.83; p = 0.020) were independent factors associated with the selection of paclitaxel BEV therapy in the overall population (TN or HR+). Metastases in the liver were significantly related to paclitaxel-BEV administration (p < 0.01).

Conclusions: Our findings suggest that first-line CT with BEV is an active and tolerated treatment option for pts with TN and HR+ MBC. ER+ tumors and a single metastatic site were identified as independent factors for the selection of a paclitaxel-BEV therapy. The presence of metastases in the liver was significantly associated to the administration of a paclitaxel-BEV regimen.

Disclosure: All authors have declared no conflicts of interest.

THE ENCHANTTMTRIAL: AN OPEN LABEL MULTICENTER PHASE 2 WINDOW OF OPPORTUNITY STUDY EVALUATING GANETESPIB (STA-9090) MONOTHERAPY IN WOMEN WITH PREVIOUSLY UNTREATED METASTATIC HER2 POSITIVE OR TRIPLE NEGATIVE BREAST CANCER (TNBC)

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Background: Hsp90 is a molecular chaperone required for proper folding and activation of many cancer-promoting oncoproteins. Several Hsp90 clients are oncoproteins known to play a key role in the pathobiology of breast cancer, including HER2, p95, ER, HER2, EGFR, ER, PI3K, AKT, and VEGFR. The inactivation of these oncoproteins by Hsp90 inhibition is a promising approach for breast cancer therapy. Ganetespib is an Hsp90 inhibitor which has shown anti-tumor activity in heavily pretreated patients with lung, breast, and other cancers. Ganetespib is well tolerated without severe liver or common ocular toxicities. In a phase 2 trial, 22 breast cancer patients with HER2+ disease, the objective response rate (ORR) was 15% (2/13) and the SD rate was 46% (6/13). Only 3 patients presented with TNBC, one of those patients achieved SD with substantial tumor shrinkage on treatment.

Methods: This is a single arm international open-label Phase 2a study in patients with HER2 amplified, or triple negative breast cancer. Patients must not have received any prior therapy for aBC or mBC Pts, no specific profile in terms of clinical or histological characteristics have been observed. Thus, the exploratory biomarkers analysis will be useful to identify such a profile.

Disclosure: O. Tredan; Roche consultant. P. Beuzeboc; Roche consultant. D. Coefic; Roche consultant. M. Fellous; Roche employee. L. Arnould; Roche Consultant. All other authors have declared no conflicts of interest.
collected from all patients for determination of predictors of response and mechanisms of resistance to treatment. Patients are treated with ganetespib 150 mg/m² is given twice weekly for a 4-week cycle for up to 12 weeks. A total of 70 patients are planned for accrual. At the time of submission, the study is receiving IRB approvals in several centers.

Disclosure: All authors have declared no conflicts of interest.

Background: Breast cancer metastasis to bone represents a devastating complication of advanced breast cancer, frequently resulting in significant increase in morbidity and mortality. An understanding of the mechanisms that govern breast cancer metastasis at the molecular level should lead to more effective therapies. Recently, the kringe 1 domain of human hepatocyte growth factor (HGFK1) was identified as a candidate metastasis suppressor gene.

Methods: Here, we investigated whether HGFK1 is a key regulator of breast cancer bone metastasis.

Results: Of the 193 human breast carcinoma tissue samples examined, HGFK1 expression was positive in 82 (42.4%). The positive expression of HGFK1 was significantly associated with a better prognostic value (P < 0.001) and inversely correlated with bone metastasis (P = 0.003). The efficacy of adeno-associated virus carrying HGFK1 (AAV-HGFK1) in osteolytic bone metastasis was then evaluated using an in vivo bone metastasis model. AAV-HGFK1 significantly inhibited osteolytic bone metastasis and prolonged the survival of mice in this model (P < 0.01). In vitro, HGFK1 expression resulted in significant anti-invasion effects, enhanced the phosphorylation of TAK1, p38 MAPK and MAPKAPK2, and decreased the expression of receptor activator of NF-κB (RANK), which was abrogated by the p38 MAPK inhibitor SB203580.

Conclusions: This study shows for the first time that HGFK1 significantly inhibits the metastasis of breast cancer to bone by activating the TAK1/p38 MAPK signaling pathway and inhibiting RANK expression. Thus, AAV-HGFK1 treatment represents a potential therapy for bone metastasis in breast cancer.

Disclosure: All authors have declared no conflicts of interest.

Background: Clinical experience and previous studies suggest that women with diabetes and breast cancer have worse outcomes than their non-diabetic counterparts. The purpose of this study was to examine the impact of diabetes and hyperglycemia on cancer-specific survival of patients with metastatic or recent breast cancer.

Methods: We performed a retrospective analysis of patients with advanced breast cancer receiving palliative chemotherapy from 2006 to 2011 at the National Cancer Institute in Mexico, and compared breast cancer-specific mortality in diabetic and non-diabetic patients, as well as in patients that presented hyperglycemia during palliative treatment.

Results: A total of 265 patients receiving palliative therapy were eligible for inclusion. Previous diagnosis or detection of diabetes at recurrence was recorded in 40 patients (15%). No difference was observed between diabetic and non-diabetic patients in terms of OS. A statistically significant difference in OS was observed between patients without diabetes and diabetic patients who had hyperglycemia (p = 0.003). OS in diabetic patients with proper metabolic control was shown to be superior compared to diabetics with hyperglycemia (p = 0.01). Hyperglycemia was identified in 14% of non-diabetics at some point while receiving palliative treatment. For patients that experienced hyperglycemia during treatment or who had a mean glucose level above 130, either in the diabetic or non-diabetic subgroups, a worse outcome was noted compared to normoglycemic patients, with a HR of 1.2 (p = 0.029) and HR of 2.04 (p = 0.006) for death, respectively.

Conclusions: Elevated glucose levels confer a poor outcome in diabetic and non-diabetic patients in contrast with patients with normoglycemic levels, conferring an elevated risk of death. According to these results, clinicians must monitor glucose levels during treatment for advanced breast cancer disease, and should take action in order to maintain normal glucose levels.

Disclosure: All authors have declared no conflicts of interest.

Background: The phosphoinositide 3-kinase (PI3K) pathway, either by receptor tyrosine kinase overexpression or PI3K/Akt/mTOR axis dysregulation, has been implicated in endocrine therapy resistance, prompting combination of PI3K inhibitors and antiestrogen therapy in the clinical setting such as in the recent BOLERO-2 study. We hypothesize that dissecting the molecular crosstalk between the PI3K and estrogen receptor (ER) pathways will help define the subset of patients most responsive to combined PI3K/antiestrogen therapy.

Methods: ER+ cell lines MCF7, MCF7-long term estrogen deprived (LTED), MCF7-fus3vinter resistant clones Fdx64 and Fdx70, T47D, ZR75-L, CAMA1, MDA361, KPL-1, BT474, EFM19, HCC11428, UACC812, were treated with the ER degrader, fulvestrant, and the p110α-specific PI3K inhibitor BYL719 in vitro. Cell viability was measured by CellTiter-Glo and Crystal Violet. MCF7 and ER+ patient-derived xenografts were treated with fulvestrant, BYL719 or the combination in vivo. Protein expression was measured by Western blot and immunohistochemistry.

Results: Fulvestrant or BYL719 treatment resulted in variable inhibition of cell viability in all ER+ cell lines. Combination treatment was significantly superior to monotherapy in MCF7, MCF7-LTED, MCF7-Fdx64 and MCF7-Fdx70. While MCF7 clones Fdx64 and Fdx70 were resistant to >1 µM of fulvestrant, they were exquisitely sensitive to BYL719. Moreover, PI3K inhibition led to ER upregulation in ER+ cell lines, including those most sensitive to combination treatment. Total ER levels also increased in MCF7 xenografts treated with therapeutic doses of BYL719.

Conclusions: Combined treatment with BYL719 and fulvestrant in vitro was superior to single-agent treatment in 4 of 13 ER+ cell lines. Importantly, dual PI3K/ER blockade was effective in cells resistant to ER deprivation and/or degradation. Induced ER levels following PI3K suppression may represent a feedback mechanism by which ER+ cells escape PI3K inhibition. We are currently studying whether this phenomenon predicts sensitivity to dual PI3K/ER blockade in ER+ breast cancer models.

Disclosure: J. Baselga: J. Baselga is a consultant/advisory board member for Aragon, AstraZeneca, Sanofi, Bayer, Onyx, Chugai, Constellation, Exelixis, Intrakine, Merck, Novartis, and Roche Genentech. All other authors have declared no conflicts of interest.

Background: Hormone-receptor-positive (HR+), breast cancer (BC) refractory/ resistant to nonsteroidal aromatase inhibitor (NSAI) may be treated with the steroidal AI exemestane (EXE), although there is no approved treatment standard. The BOLERO-2 trial showed that adding everolimus (EVE) to EXE significantly improved clinical benefit beyond that of EXE alone (Hortobagyi et al, SABCS 2011, Abstract 53-7). As many women with advanced BC are elderly (>65 years), the efficacy and tolerability of EVE + EXE in this population are of interest.

Methods: BOLERO-2 is a phase 3, randomized trial comparing EVE (10 mg once daily) versus placebo (PBO), both plus EXE (25 mg once daily) in postmenopausal women with advanced HR+ BC, progressing or recur after NSAI.

Results: Baseline disease and prior treatment characteristics were balanced between study arms (N = 724). At 18 months’ median follow-up, adding EVE to EXE significantly improved progression-free survival in patients < 65 years (HR = 0.38; 95% CI = 0.30, 0.47) and ≥ 65 years (n = 275; 6.8 vs 4.0; HR = 0.59; 95% CI = 0.43, 0.80). Overall incidence of adverse events (AEs) was marginally higher in patients ≥ 65 years (n = 272, safety population) compared with those < 65 years. Grade 3–4 AEs occurred in 50% of patients ≥ 65 years and 44% of patients < 65 years (P = 0.03). Overall, 49% of patients ≥ 65 years and 44% of patients < 65 years experienced hyperglycemia in EVE-treated patients ≥ 65 years and those < 65 years were similar. Additional analysis using an age cutoff of 70 years also showed no meaningful differences in the efficacy/safety profile of EVE. Grade 3/4 AEs in patients ≥ 65 years...
reported among patients receiving EVE (n = 192) but not in those receiving PRO included anemia (9%), hyperglycemia (7%), stomatitis (9%), dyspepsia (8%), pneumonitis (5%), neutropenia (3%), and hypertension (2%). These AEs were also reported at similar frequency in EVE-treated patients < 65 years.

**Conclusions:** Adding EVE to EXE was effective and well tolerated overall and, in elderly patients with advanced BC, grade 3/4 AEs were uncommon and manageable. Overall, AEs were consistent with the known safety profile of EVE.

**Disclosure:** M. Grant: Research support from GSK, Sanofi-Aventis, Novartis, and Roche, consultant to Merillon and Novartis, and received honoraria & travel support from Amgen, Pfizer, Novartis, GSK, Bayer, Sandoz, AstraZeneca, and GenomicHealth. S. Noguchi: S. Noguchi received grant support from AstraZeneca, BMS, Chugai, GSK, Novartis, Pfizer, Sanofi-Aventis, and Takeda, and honoraria (speaking, advisory boards, etc.) from AstraZeneca, Chugai, GSK, Novartis, Pfizer, Sanofi-Aventis, and Takeda. M. Piccart: Board for PharmaMar, consultant Sanofi-Aventis, Amgen, BMS, GSK, Boehringer, Roche, & Bayer, grant support Pfizer, Amgen, Bayer, Boehringer, BMS, GSK, Roche, & Sanofi-Aventis, honoraria Bayer, BMS, GSK, Boehringer, Roche, Amgen, & AstraZeneca. J. Baselga: J. Baselga is a consultant to Novartis, Roche, Merck, Sanofi-Aventis, Verastem, Bayer, Chugai, Exelixis, Onyx, and Constellation. A. Panneerselvam: Employee of Novartis with stock/stick options. T. Taran: Employee of Novartis with stock/stick options. T. Sancar: Employment of Novartis G. H. Hortobagyi: Member of the Scientific Advisory Board of Allergan, is a consultant to Allergan, Novartis, Genentech, and Sanofi-Aventis, has received grant support from Novartis, and has received travel expense reimbursement from Novartis, Genentech, and Sanofi-Aventis. K. Pritchard: Consult: sananv AZE, Roche PFE NVR ARR AMG GSK & OrthoBio honoraria & Spkr B SanAven AZE PFE Roche NVR & AMG paid expert test SanAven AZE & GSK AdCom SanAven AZE Roche PFE NVR GSK & AMG. All other authors have declared no conflicts of interest.

**Results:** Loss of PTNP 12 expression was observed in 35.5% of the patients in this study. No significant differences were found in the clinicopathological characteristics and expression status of ER, PR, EGFR, HER-2 were compared according to PTNP 12 expression status. The prognostic significance of PTNP 12 expression on disease-free survival (DFS) and overall survival (OS) was analyzed and the prognosis was also assessed in subgroups defined on the basis of major prognostic factors and ER, PR, HER-2, EGFR expression status.

**Conclusions:** PTNP 12 expression loss was observed in 35.5% of the patients in this study. No significant differences were found in the clinicopathological characteristics and expression status of ER, PR, EGFR, HER-2 were compared according to PTNP 12 expression status. The prognostic significance of PTNP 12 expression on disease-free survival (DFS) and overall survival (OS) was analyzed and the prognosis was also assessed in subgroups defined on the basis of major prognostic factors and ER, PR, HER-2, EGFR expression status.

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

**RESULTS:** MTOR expression in basal-like breast cancer and the ability of Everolimus to inhibit the invasion cancer cell capacity

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

**RESULTS:** The introduction of high-throughput technologies in breast cancer enabled the recognition of groups with prognostic value, in which target-therapies can be applied. However, a relevant percentage of patients show no clinical benefit or incur in the development of acquired resistance. A possible solution could be the inhibition of pathways that are common in all tumor subtypes that have a proven role in carcinogenesis. Alterations of the serine-threonine kinase mammalian target of rapamycin (mTOR) signaling pathway are common in cancer and thus mTOR is being pursued as a therapeutic agent. Everolimus, a rapamycin analog, has already an established activity in the treatment of renal cell carcinoma. In this study, we proposed to evaluate the expression of activated mTOR in a large series of invasive carcinoma samples and cell lines, and its association with the four main molecular subtypes (Luminal A, Luminal B, HER2-overexpressing and Basal-like). We also aimed to evaluate the ability of Everolimus to inhibit mTOR expression and function in basal cancer cells. p-mTOR expression was found in 66.7% (231/348) of the invasive breast carcinoma cases analysed. Considering the molecular subtypes of breast carcinomas, p-mTOR expression was more frequently observed in basal-like breast carcinomas (80.6%). All breast cancer cell lines, representative of distinct molecular subtypes, showed expression of total and activated mTOR. These cells have been treated with RAD001, in order to assess their sensitivity to this drug, and all cell lines showed a decrease of p-mTOR expression after everolimus treatment. Due to the higher prevalence of p-mTOR in basal-like tumors, we treated three basal-like cell lines with Everolimus to assess the effects on cell invasion and aggregation. Cell invasion was significantly inhibited in response to Everolimus. The results revealed that there is a significant higher frequency of p-mTOR in basal-like tumors, compared with the other subtypes. In addition, Everolimus is able to significantly decrease mTOR expression and activity, inhibiting invasion of cell lines of basal-like breast cancer cells, thus opposing the anti-tumour activity of mTOR inhibitors in breast cancer models.

**Disclosure:** All authors have declared no conflicts of interest.
BACKGROUND: First-line BEV combined with weekly paclitaxel, docetaxel or other chemotherapy significantly improves progression-free survival (PFS) in HER2-negative metastatic breast cancer (mBC), as shown in E2100, AVADO and RIBBON-I trials. In the ATINIA study, 21% of pts continued BEV for ≥1 year with no new safety outcome and a time to progression of 19.9 months (95% CI 18.9-21.8 months). To further understand and provide insight into the efficacy and safety of long-term responders to first-line BEV, we conducted a descriptive study of 2 different cohorts of pts with mBC: HR+ and TN, treated in routine oncology practice with at least 1 year of first-line BEV.

METHODS: Pts who had received first-line BEV (≥1 year) associated to chemotherapy were retrospectively included in the 2 independent cohorts and followed up, if they were alive at inclusion, for 18 months. Clinico-pathological characteristics, treatment received, efficacy and safety data were collected.

RESULTS: The recruitment of the TNBC cohort was just completed (n = 80) and received, efficacy and safety data were collected. In multivariate analysis, prognostic factors significantly related to longer OS from initial first-line therapy with 3 HER2 diagnosis, and more than 1/3 of the patient had lung and/or liver involvement. In the initial phase (N = 284), 284 pts were included, 17% were aged ≥65 y, 53% had ECOG PS 0 and 30% had triple-negative mBC. Maintenance therapy was administered in 183 pts (64%). Key safety results are below.

CONCLUSIONS: Most grade ≥3 AEs during BEV-DOC were typical DOC-related AEs. Apart from hypertension and proteinuria, BEV AEs occurred predominantly in early cycles, suggesting that long-term BEV is well tolerated. Efficacy results are expected in 2013. Disclosure: J. Gligorov; RG has sat on Advisory Boards and received speaker honoraria from Roche. J. Bines; JB has served on Advisory Boards for Roche. P.A. Cortes; PC has served on Advisory Boards for Roche, RBS and Sanofi-Aventis. U. Freudensprung; UF works as a Consultant for F Hoffmann-La Roche Ltd. G. Mustacchi; GM has acted as a Consultant for Roche, Agenda, Celgene, Novartis, Merck, Glaxo, Eisai. All other authors have declared no conflicts of interest.

Table: 356P

<table>
<thead>
<tr>
<th>Pts, n (%)</th>
<th>Initial BEV-DOC phase (N = 284)</th>
<th>Maintenance BEV ≥ CAP phase (N = 183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD AE Other/unknown</td>
<td>99 (35)</td>
<td>134 (73)</td>
</tr>
<tr>
<td>Grade ≥3 AEs, n (%)</td>
<td>41 (14) 31 (11) 27 (10)</td>
<td>101 (55) 15 (8) 18 (10)</td>
</tr>
<tr>
<td>Neopterin Febrile neutropenia Diarrhoea Mucosal inflammation</td>
<td>138 (49)</td>
<td>63 (34)</td>
</tr>
<tr>
<td>Grade ≥3 BEV AEs of special interest</td>
<td>44 (15) 30 (11) 3 (1) 9 (3) 6 (2) 6 (2) 2 (1) 0 (2) 2 (1) 1 (1) 25 (14)</td>
<td></td>
</tr>
<tr>
<td>Hypertension Proteinuria Bleeding Arterial TE Venous TE Wound-healing complication GI perforation</td>
<td>5 (2) 1 (&lt;1) 9 (3) 2 (1) 2 (1) 5 (1) 5 (9) 3 (2) 2 (1) 2 (1) 0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

AE = adverse event; TE = thromboembolic event
Schedule 1 (n = 19) and Schedule 2 (n = 15) MTDs were 1.6 and 1.4 mg/m² on Day (D) 1) or Schedule 2 (0.7, 1.1 or 1.4 mg/m² on D1 and D8) in combination with twice-daily oral capecitabine 1000 mg/m² on D1 – 3, D8 and D15. Correlation of eribulin metabolites was variable and independent of schedule. Co-administration had no effect on exposure. No accumulation occurred upon multiple dosing; at each dose, Δ QTc was increased and independent of schedule. Non-compartmental analysis, and cardiac repolarization by 12-lead ECGs at and 6 h post-capecitabine; Schedule 2: pre-dose). PK was examined by non-compartmental pharmacokinetics (PK) of eribulin in combination with capecitabine in pts with locally advanced (LA)/metastatic breast cancer (MBC) who have received ≥2 prior chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and taxane. This Phase Ib, open-label dose-escalation study assessed maximum tolerated dose (MTD), safety and pharmacokinetics (PK) of eribulin in combination with capecitabine in pts with advanced/metastatic cancer. Results: Schedule 1 (n = 19) and Schedule 2 (n = 15) MTDs were 1.6 and 1.4 mg/m² eribulin mesilate, respectively. Dose-limiting toxicities (all n = 1) were: Grade (G) 4 neutropenia, G3 febrile neutropenia, G3 fatigue, G3 lethargy (Schedule 1); G4 neutropenic sepsis, G3 neutropenia (Schedule 2). There were no unexpected toxicities. Eribulin PK was independent of schedule and had dose-related increases in exposure. No accumulation occurred upon multiple dosing; at each dose, eribulin PK was comparable in Cycles 1 and 2. Exposure to capecitabine and metabolites was variable and independent of schedule. Co-administration had no effect on Δ QTc.

Conclusions: No drug-drug interaction of eribulin and capecitabine was observed. From these results, the combination appears to be tolerated without effect on cardiac repolarization. A Phase II LA/MBC study evaluating Schedule 2 MTD is ongoing.

Disclosure: C.J. Twelves: The author declares the following conflicts of interest: employee (Eisai Ltd). C. Savulsky: The author declares the following conflicts of interest: employee (Eisai Ltd). C. Johnston: The author declares the following conflicts of interest: employee (Eisai Ltd). L. Ryderman: The author declares the following conflicts of interest: employee (Eisai Inc.). J. Wanders: The author declares the following conflicts of interest: employee at the time of study (Eisai Ltd). R. Plummer: The author declares the following conflicts of interest: research funding (Eisai Ltd). T.R.J. Evans: The author declares the following conflicts of interest: research funding (Eisai Ltd). All other authors have declared no conflicts of interest.
**361P** A RETROSPECTIVE ANALYSIS OF PLATINUM-BASED NEOADJUVANT CHEMOTHERAPY FOR LATNBC TO COMPARE SURVIVAL OUTCOMES BETWEEN PATIENTS WITH PCR AND WITH NON-PCR. FURTHERMORE, THE FREEDESEASE FREE SURVIVAL OF LATNBC PATIENTS WITH PCR CONTINUOUSLY RECEIVING PRIMARY REGIMEN AS ADJUVANT SETTING HAD COMPARATIVE ADVANTAGE CONCERNING THAT OF “PCR” PATIENTS SWITCHING TO OTHER REGIMENS AS ADJUVANT SETTING AS WELL AS THOSE WITHOUT ANY CHEMOTHERAPY AFTER SURGERY.

**Patients and methods:** 124 women with stage II or III TNBCs experienced platinum-based regimes as neoadjuvant chemotherapy from Nov 1, 2007 to Dec 31, 2011. All patients were divided into the two groups, who were with and without PCR in the pathological reports after surgery. According to the adjuvant settings for LATNBC patients with PCR, the three arms were determined as continuous primary regimen (the same as neoadjuvant) arm, no more chemotherapy arm and switching arm. Disease free survival was computed using the Kaplan-Meier product limit method.

**Result:** We presented a retrospective chart review of 124 LATNBC patients who underwent platinum-based neoadjuvant chemotherapy in our hospital. Fifty (40.32%) of those patients receiving neoadjuvant chemotherapy had PCR when they underwent surgery. After controlling for covariates associated with survival, patients undergoing neoadjuvant chemotherapy with platinum tumor had significantly worse survival than patients with PCR (HR = 0.37; P < 0.05). Of 50 patients with PCR confirmed by surgery, the disease free survival of 24 cases switching to other regimens in the adjuvant setting was significantly better than that of 24 cases continuously receiving primary regimens in the adjuvant setting (HR= 0.51, P = 0.025) and that of 2 cases with no more chemotherapy (HR= 0.58, P = 0.017)

**Conclusion:** Patients with PCR had statistically significantly better clinical survival than those with non-PCR after platinum-based neoadjuvant settings. So far, if LATNBC patients with PCR after platinum-based neoadjuvant chemotherapy, they might have better clinical survival if they receive switching regimens than to receive primary regimens and to continue with no additional chemotherapy after surgery. A randomized prospective study needs to be carried out to strengthen the results because of statistical bias.

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

**365P** MIGHT EARLY METABOLIC RESPONSE BY 18F-FDG-PET/CT BE USEFUL TO SELECT PATIENTS (PTS) WITH BREAST CANCER (BC) WHO WILL NOT OPTIMALLY RESPOND TO PREOPERATIVE CHEMOTHERAPY (PCT)?

**Purpose:** To evaluate 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) changes between baseline and after 2 cycles of PCT in pts with locally advanced BC, with the aim to verify whether early metabolic assessment of response during PCT may have a role in clinical practice to enable early changes in the therapeutic strategy.

**Patients and methods:** Sixty pts with newly diagnosed E/ LA BC received 6-8 cycles of anthracycline and taxane-based PCT. Fifty-eight pts underwent surgery, which consisted in breast conserving surgery or radical mastectomy; axillary node dissection was performed in all cases. Optimal pathologic response (pR) to PCT was defined as breast cancer lesions at and after 2 cycles of PCT that were locally advanced at baseline (LA) BC, with the aim to verify whether early metabolic assessment of response during PCT may have a role in clinical practice to enable early changes in the therapeutic strategy.

**Conclusions:** PET assay after 2 cycles of PCT correctly predicted pNR in 32% of ER +/HER2- pts, identifying a subgroup of BC pts with worse prognosis who might benefit from an early change of the therapeutic strategy.

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

**363P** BREAST CANCER RECURRENCES AT THE CHEST WALL (BCRCW) WHEN STANDARD TREATMENTS (TX) HAVE FAILED: LYSO-THERMOSENSITIVE LIPOSOMAL DOXORUBICIN (LTLTD) + MILD LOCAL HYPERERTHMA (MLH)

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**Background:** BCRCW has a poor prognosis, with disfigurement, pain, and restriction of movement. Study treatment consisted of LTLTD that releases high concentrations of doxorubicin (Dox) in areas treated with mild hyperthermia at > 39.5°C. MLH kills tumor cells, selectively increases liposomal permeability in tumor microvasculature, releases Dox from LTLTD, and promotes Dox tumor uptake.

**Methods:** We conducted a phase I study of LTLTD + MLH in patients (pts) with BCRCW tumors < 3 cm deep who had failed all standard Tx including surgery, radiation, and chemotherapy (CTx). Pts received up to 6 LTLTD/MLH Ttx every 21 days. Dosing cohorts started at 40 mg/m² and stopped escalation at 50 mg/m². LTLTD was infused IV over 30 minutes; then MLH was given by microwave or ultrasound. The thermal dose goal was 40°C–42°C for 60 min. Pharmacokinetic samples for total plasma Dox and doxorubicinol (Doxol) were taken at 0.5, 5, 10 and 24 hours after starting infusion.

**Results:** Eleven pts with a median of 4 prior CTxs (range 2 – 12) were enrolled; 10 had recurred after prior anthracycline (AC). All pts received > 2 cycles. The within subject variability in Dox and Doxol exposure was small with mean Cycle 2 vs Cycle 1 ratios ranging from 0.99 to 1.06. Two types of grade 3/4 toxicity were seen in > 5% of 42 cycles given: reversible neutropenia in 17 (40.9%) and reversible leukopenia in 9 (21.4%). One case (each) of mucositis (grade 1), chest wall thermal burn, and chest wall cellulitis (both grade 4) occurred, and no cases of cardiomyopathy or hand-foot toxicity were seen. The rate of clinically significant (≥ 6 point) QoL improvement on the FACT-B after 2 cycles was 54.5% (95% CI: 25.1% - 83.9%), including 1 lasting > 3 months. The local objective response rate was 45.5% (95% CI: 16.1% - 74.9%), with 1 complete and 4 partial local responses.

**Conclusion:** LTLTD + MLH is safe and active in BCRCW pts with prior radiation and AC exposure. A phase II study is underway.

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

**364P** IMMUNOHISTOCHEMICAL PREDICTORS OF THE CLINICAL AND PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

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**Purpose:** To determine predictive immunohistochemical characteristics of the tumor correlated with the response to neoadjuvant chemotherapy in patients with locally advanced breast cancer.

**Material and methods:** A prospective study of 87 breast cancer patients (T2-4N0-M0) treated in N.N.Blokhin Russian Cancer Research Center 1997 - 2009. Tumor samples were taken prior to neoadjuvant chemotherapy (cor-biosy).

Pathological criteria assessed were: histological variant, tumor grade, HR and HER-2/ neu status, Ki67 expression and glycoprotein Pgp-170 status. After 4-6 cycles of chemotherapy all the patients underwent radical surgery. We quantified the response
clinically and pathologically (Lavrnikova’s system of therapeutic pathomorphism evaluation).

Results: The experimental results showed the following response rates: complete response - 11 (12.6%), partial response - 54 (62.1%), stable disease - 21 (24.1%) patients. One patient had progression of the disease. Stable disease correlated significantly with positive Pgp-170 status (41.7% vs. 17.7%, p = 0.04), whilst negative Pgp-170 – with objective response (82.4% vs. 54.2%, p = 0.02). Pathomorphism was achieved follows: lack of pathomorphism - 10 (11.5%), first-degree pathomorphism 17 (19.5%), second-degree – 28 (32.2%), third-degree – 18 (20.7%), fourth-degree – 14 (16.1%). Rare histological variants had more often third-degree pathomorphism than ductal carcinoma (p = 0.02); G1 had more often fourth-degree pathomorphism than G2 (p = 0.002); high-degree pathomorphism was observed more frequently in males and younger patients with N2 status than with N0 (p = 0.006) and N1 (p = 0.009). Her-2/neu + tumors showed lower degree of pathomorphism that those with HR status (23.7% vs. 45.6%, p = 0.03). Pgp-170 + tumors had significantly more often no (p = 0.004) or first-degree pathomorphism (p = 0.004), and as a result – lower rate of high degree pathomorphism than in Pgp-170 negative tumors (12.5% and 47.1%, respectively).

Conclusions: Some pathological and immunohistochemical characteristics of the tumor can be assessed preoperatively and predict the likelihood of the clinical and pathological response to neoadjuvant chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

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publications and aggregated in a meta-analysis. A meta-regression weighted for extent of disease, ER/HER2 status, age, visceral or bone disease, rate of radiotherapy, and systemic therapies offered was also performed.

Results: 15 articles were included in this meta-analysis (all retrospective case series), for a total of 15,378 patients. Surgery of the primary breast cancer appeared to be an independent factor for an improved survival in the multivariate analyses from the individual studies, with an HR of 0.69 (p < 0.00001). According to meta-regression, the survival benefit was independent of age, extent, site of metastatic disease and HER2 status, but was directly proportional to rate of patients exposed to systemic therapies and radiotherapy and inversely correlated to ER+ status of the population included.

Conclusions: Our pooled-analysis, reveals that surgery of an intact primary tumor, although associated with distant metastases, reduces the risk of death by 30%. This results are particular significant if local surgery is associated with systemic therapy and radiotherapy into a multimodality strategy. The surgical excision of a primary breast cancer in patients with stage IV disease – if feasible – should be discussed with and proposed to patients.

Disclosure: All authors have declared no conflicts of interest.
INCIDENCE OF BONE METASTASES AND SURVIVAL AFTER A DIAGNOSIS OF BONE METASTASES (BM) IN BREAST CANCER PATIENTS

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Objectives: To measure crude and cumulative incidence of BM and cumulative survival after diagnosis of BM. BM were grouped by (i) BM only (ii) BM followed by visceral metastases (iii) visceral metastases followed by BM.

Methods: Kaplan-Meier and Cox regression database analysis of women with breast cancer diagnosed 1975-2006 and treated at Guys Hospital London, whose details were prospectively updated regularly till end 2010.

Results: Of 7064 women, 1589 (22%) developed BM by end follow-up (mean 8.4 years); 2254 (32%) were diagnosed with breast cancer < 50 years, and 4810 (68%) were diagnosed within 10 years of breast cancer treatment, 25% were diagnosed within 1 year, 50% within 2.5 years and 75% within 4.7 years. Median survival after BM diagnosis was highest in 1975-1982 (0.25 [95% CI 0.23-0.27]), falling to 0.22 (0.20-0.24) in 1983-1988, 0.18 (0.10-0.14) in 1990-1997 and 0.095 (0.08-0.12) in 1998-2006.

Conclusion: Incidence of BM has decreased in recent years and risk of BM is significantly affected by clinical tumour characteristics. Women with bone only metastases survive longer with their disease. BM remain an important target for prevention, treatment and palliation in breast cancer.

Disclosure: A. Taylor: I own shares with Amgen and work at Amgen. All other authors have declared no conflicts of interest.

PREGNANCY-ASSOCIATED BREAST CANCER: CHEMOTHERAPY DURING PREGNANCY

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Background: Pregnancy-associated breast cancer is a rare disease and treatment for these patients is a challenging problem. There are limited data about diagnosis and treatment for this disease, and outcome of fetuses who were exposed to chemotherapy during pregnancy.

Patients and methods: Forty-two pregnancy-associated breast cancer patients were treated from November 1999 to May 2012. We reviewed the data, including clinicopathological characteristics, therapeutic management, and fetal outcome of twenty-eight patients who received chemotherapy during pregnancy.

Results: Twenty-eight of the 42 patients (66.6%) were treated with chemotherapy during pregnancy. Patients’ age ranged from 27 to 44 years (a mean age, 35 years). Fetal gestation age at diagnosis ranged from 6 to 28 weeks (a mean gestation age, 17.1 weeks). All of the patients had invasive carcinoma. Thirty-six of the patients (46%) had ER-positive (ER+) and HER2-negative (HER2-) tumors, 3 (10.7%) had ER + HER2+ tumors, 3 (10.7%) had ER-/HER2+ tumors, and 10 (35.7%) had ER-/HER2- tumors. At diagnosis, 6 of the 28 patients (21.4%) were classified as having stage I, 14 (50%) as stage II, 6 (21.4%) as stage III, and 2 (7.1%) as stage IV. All patients started to receive chemotherapy at second and third trimesters. Ten patients received fluorouracil, doxorubicin, and cyclophosphamide (FAC), 16 patients received doxorubicin and cyclophosphamide (AC). Two patients with stage IV disease received taxane chemotherapy (Paclitaxel). For one of the two patients with stage IV disease, trastuzumab was added with careful monitoring for occurrence of oligohydramnios. Twenty-six of the 28 patients had delivered at a gestation age of at least 35 weeks (a mean gestation age, 37.6 range, 35-42 weeks). Two patients have not delivered yet up to this period. No congenital malformations or delay of fetal development were observed.

Conclusion: Our data revealed that breast cancer can be treated with AC/PAC chemotherapy during the second and third trimesters without significant complications for the fetus. Further study is needed to confirm the safety use of taxanes and trastuzumab for these populations.

Disclosure: All authors have declared no conflicts of interest.

ASSOCIATION OF CYP1A1 A4889G AND T6235C POLYMORPHISMS WITH INCREASED RISK AND AGGRESSIVENESS OF BREAST CANCER

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Background: Estrogen and its metabolites, activated by cytochrome P450 enzymes (CYP1A1), participate in the origin and progression of breast cancer (BC). The CYP1A1 gene is highly polymorphic in humans. G and C variant alleles of CYP1A1 A4889G and T6235C polymorphisms encode enzymes with increased activity in activation of these compounds than the respective wild alleles. This study aimed to clarify the biological characteristics of the above-mentioned polymorphisms and their roles in the risk of BC.

Materials and methods: CYP1A1 A4889G and T6235C genotypes of 742 BC patients (median age: 52 years, 638 Caucasians, 104 non-Caucasians) and 742 healthy women (median age: 40 years, 638 Caucasians, 104 non-Caucasians) were obtained in genomic DNA by PCR and enzymatic digestion. The differences between groups was tested by the χ2 test. Power of analysis (PA) was used to determine the effect of sample size on the results obtained in the study.

Results: Patient and control samples were in Hardy-Weinberg equilibrium at CYP1A1 A4889G (p2 = 0.15, P = 0.70; p2 = 1.15, P = 0.28) and T6235C (p2 = 2.65, P = 0.10; p2 = 1.93, P = 0.16) loci. The frequency of CYP1A1 A4889AG + GG genotypes was higher in patients than in controls (29.0% versus 23.2%, P = 0.04; PA = 93.0%). Carriers of the variant G allele were under a 1.50-fold (95% CI: 1.14-1.97) increased risk for BC than those with the wild AA genotype. CYP1A1 A4889AG + GG genotypes was higher in patients than in controls (29.0% versus 23.2%, P = 0.04; PA = 93.0%). Carriers of the variant G allele were under a 1.50-fold (95% CI: 1.14-1.97) increased risk for occurrence of histological grade III tumors than with those with grades I + II tumors. The CYP1A1 A4889AG + GG genotypes was more also common in BC patients with histological grade III tumors than in controls (80.1% versus 23.2%, P = 0.04; PA = 72.0%). Carriers of the variant G allele were under a 1.35-fold (95% CI: 1.01-1.82) increased risk of occurrence of histological grade III tumors than others.

Discussion: Our data suggest that CYP1A1 A4889G and T6235C polymorphisms alter the risk and aggressiveness of BC in Brazilian women. We believe that women with variant alleles of the above-mentioned genes should receive additional medical attention for disease prevention and early diagnosis.

Disclosure: All authors have declared no conflicts of interest.

TARGETING BREAST CANCER STEM CELLS FOR TREATMENT FAILURE CASES OF LATE STAGE BREAST CANCER

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Targeting breast cancer stem cells (BCSCs) present in bone marrow and breast tissues is an attractive alternative for ‘event-free survival’ in breast cancer as it is an extremely heterogeneous disease. The invasive and mesenchymal properties of BCSCs with CD44 + /CD24low/ALDH1+ phenotype has made them a promising target for eliminating the metastatic capacity of primary tumors. We hypothesize that the ability to therapeutically attack stem cells will be decisive for the development of specific target therapies. Ten chemotherapy failure late stage patients with biopsy-proven triple-negative metastatic breast cancer were selected randomly. Breast cancer cells were isolated from whole tumor and cultured for in vitro drug sensitivity towards platinum, anthracycline and docetaxel and correlation was drawn between cell differentiation and drug response. Accordingly chemotherapy was designed for a particular patient. BCSCs were also isolated from the whole tumor, cultured and chemotherapy was designed. We detected chemo-failure in 65% cases for whole cell chemo-predictive assays, while BCSCs isolated from those non-responders responded to chemosensitization. Among positive 89% of patients showed platinum sensitivity and rest were found to be anthracycline sensitive. No sensitivity towards docetaxel was observed. In lieu of this, cisplatin was applied ex vivo and percentage of BCSCs came down to 6.58% from an initial 11.16% (for a representative case).
All authors have declared no conflicts of interest.

376 GENETIC POLYMORPHISM IN AURORA-A AS A RISK FACTOR IN EGYPTIAN WOMEN WITH BREAST CANCER
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Introduction: Although many risk factors have been identified, the cause of any individual breast cancer (BC) is most often unknown. Aurora A, the gene, encoding serine/threonine kinase, has been shown to be over expressed in many tumors, noticeably in BC. The aim is to study the single nucleotide polymorphism in Aurora-A, and compare the frequency distributions of different genotypes between patients with BC and those with fibroadenoma to define its tumorigenic contribution to BC development.

Patients and methods: This study was conducted on 60 pathologically confirmed BC patients, 20 patients with fibroadenoma and 40 frequency matched controls. There were no age, stage or histology restrictions. Serum CA-15-3 & estradiol were measured. DNA was isolated from peripheral blood lymphocytes for genotyping of Aurora A at the T91A (Phe31Ile) site and were analyzed by PCR & RFLP assay.

Results: This study showed that women carrying the Ile/Ile genotype had an increased risk of developing BC (P = 0.04). Logistic regression analysis showed that subjects having Ile/Ile genotype had a 9.3 fold increased risk of developing BC compared with those with the Phe/Phe genotype (OR 9.35% CI 1.12–77.67). The heterozygous Phe/ Ile genotype was significantly associated with the risk of survival, suggesting a possible recessive effect of the polymorphism. No significant association was observed between the polymorphism and the risk of fibroadenoma. Patients with negative ER &PR were more likely to carry the IIe/IIe genotype compared with positive ER &PR.

Results: This study showed that women carrying the Ile/Ile genotype had an increased risk of developing BC (P = 0.04). Logistic regression analysis showed that subjects having Ile/Ile genotype had a 9.3 fold increased risk of developing BC compared with those with the Phe/Phe genotype (OR 9.35% CI 1.12–77.67). The heterozygous Phe/Ile genotype was significantly associated with the risk of survival.

Conclusion: This study provides the evidence that the Aurora-A Ile/Ile genotype is associated with an increased risk for the occurrence but not progression of BC. Logistic regression analysis showed that subjects having IIe/IIe genotype had a 9.3 fold increased risk of developing BC compared with positive ER &PR.

Conclusion: This study provides the evidence that the Aurora-A Ile/Ile genotype is associated with an increased risk for the occurrence but not progression of BC

Disclosure: All authors have declared no conflicts of interest.

377 CLINICAL, MOLECULAR PROFILES AND RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER: AN INDIAN EXPERIENCE
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Background: Breast cancer is now the most common cancer in many parts of India and Locally advanced breast cancer (LABC) accounts for nearly one third of cases. Advanced stages at presentation are attributed to late diagnosis and biologically aggressive disease in Indian women.

Materials and methods: Patients diagnosed with inoperable LABC at the Gujarat Cancer and Research Institute, Ahmedabad, India were included in the study.

Baseline evaluation included clinical assessment, testing for Estrogen Receptor(ER), Progesterone Receptor (PgR), Her2Neu and serum Vascular Endothelial Growth Factor (S. VEGF). First line NACT was FAC or FEC. Patients were assessed clinically and radiologically at the end of 3 cycles for response evaluation (mass reduction on ultrasonography of breast). S. VEGF levels were repeated at the end of 3 cycles of NACT or before surgery. All resectable patients underwent a Modified Radical Mastectomy. Unresectable patients were offered taxanes based chemotherapy or supportive care.

Results: Fifty seven patients with LABC were included. Fifty Four patients (95%) received NACT. Mean age at diagnosis was 49 years. ER was positive in 51%, PgR in 35% and Her2Neu in 47%. Mean baseline S. VEGF was 463.4pg/ml Baseline S. VEGF was higher in patients who were hormone receptor or Her2Neu positive. The overall clinical response rate (complete response (CR) + partial response (cPR)) to the initial anthracycline based chemotherapy was 63%, cPR was 0%. Resectability rate after 1st line NACT was 77%. Pathological CR (pCR) was 4%. There was no significant reduction in S. VEGF levels after NACT, irrespective of clinical or pathological responses. Nearly 17% of patients were lost to follow up at various stages of treatment including three patients who refused any kind of treatment.

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Conclusion: This study analyzes clinical and molecular profile of patients with LABC in India which differs from that seen in developed nations. High treatment drop-out rates may reflect treatment related toxicities, socio-cultural and logistical issues in a big developing country. Responses to anthracycline based NACT are comparable to the results reported from similar centers.

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Disclosure: All authors have declared no conflicts of interest.

378 RESPONSE TO NEOADJUVANT THERAPY AND DISEASE FREE SURVIVAL AND OVERALL SURVIVAL IN PATIENTS WITH TRIPLE-NEGATIVE BREAST CANCER (TNBC): SINGLE CENTER EXPERIENCE
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Background: Triple negative breast cancer (TNBC) is a distinct subtype of BC which is characterized by the absence of expression of estrogen receptor (ER), progesterone receptor (PR) or HER2/neu. TNBC is a very heterogeneous disease, that accounts for 15 to 20% of breast cancers. Despite initial chemosensitivity, patients with TNBC had a poorer outcome in terms of disease-free and overall survival, compared to non-triple-negative breast cancers. Neoadjuvant chemotherapy is commonly used for the initial treatment for TNBC, allowing for a higher rate of breast-conserving surgery and giving clues about the individual responsiveness of a particular cancer to chemotherapy.

Methods: We retrospectively reviewed 66 TNBC patients treated with neoadjuvant chemotherapy at our institution between 2001-2011. They were divided into three subgroups: complete pathological response after neoadjuvant chemotherapy (group A), residual tumor smaller than 1 centimeter wide (group B), and residual tumor bigger than 1 centimeter wide or involving lymph nodes.

Results: (One patient died before surgery and another patient refused it. Twenty (31%) of the other 64 patients achieved a complete pathological response. Mean DFS was 2.15 years; recurrent disease was higher for C (30.64%) vs B (2 pts, 10%) (p = 0.003). Most common recurrent sites were local (18) and bone (9). Mean OS was 4.5 years (95% IC 3.6 – 5.4); 1 (15%) pts died in A, 3 (23%) in B vs 16 (51%) in C (p = 0.03).

Conclusions: The pathologic complete response rate seen in our series is consistent with the one reported in other studies involving neoadjuvant chemotherapy for TNBC. The pathologic response after a neoadjuvant therapy correlates with disease-free and overall survival rates.

Disclosure: All authors have declared no conflicts of interest.

379 ULTRASOUND ESTIMATION OF THE BLOOD FLOW IN BREAST CARCINOMAS AS A PREDICTIVE FACTOR OF EFFICIENCY OF NEOADJUVANT POLYCHEMOTHERAPY (NPCT)
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Objective: Using ultrasound (US) techniques to determine the role of the intensity of the blood flow (BF) of breast tumors as a criterion of efficiency of NPCT.

Methods: 30 patients aged 50-62 years with verified BC, who were candidates for 3 courses of AC–nPTC, were carried out color-coded US in the triplex mode scanning and power doppler.

Results: ACBFV is increased and corresponds to the malignant process, whereas the higher rates were observed in patients with the triple-negative breast cancer (16.2 ± 2.8 cm/sec) and luminal A type (15.9 ± 3.9 cm/sec). While luminal A type had ACBFV 14.2 ± 2.6 cm/sec and HER2+ had 14.6 ± 2.5 cm/sec. IR in all subgroups was 0.73 ± 0.12, that matches the sharply increased values, and shows an increase peripheral resistance in vessels. IP was 12.35 ± 1.75, that reflects the amplified elastic and flexible properties of the newly formed blood vessels. Effect of AC–nPTC was higher in patients with the luminal A type (CR – 5, PR – 3). In patients with triple-negative BC effect of nPTC was worse, despite the high rate of BF in the tumor (PR – 1, stabilization – 6, support care).

Conclusions: This study analyzes clinical and molecular profile of patients with LABC in India which differs from that seen in developed nations. High treatment drop-out rates may reflect treatment related toxicities, socio-cultural and logistical issues in a big developing country. Responses to anthracycline based NACT are comparable to the results reported from similar centers.

Disclosure: All authors have declared no conflicts of interest.
progression – 2). In patients with low rate of BF in the tumor (luminal A, HER2(+) type) effect was the worst (PR – 2, stabilization – 7, progression – 4 patients in both groups). The correlation coefficient was statistically significant for BF as increased ABCP/VP, IB, and the frequency of CR + PR to nCCT of luminal B type.

Conclusions: There is a correlation between the velocity of BF and degree of destruction of tumor by cytostatics. While the rate of BF depended on the molecular type of the tumor and did not depend on the size of the primary tumor.

Disclosure: All authors have declared no conflicts of interest.

380 IMPACT OF BODY MASS INDEX (BMI) ON DISEASE FREE SURVIVAL AND LIKELIHOOD OF PATHOLOGIC COMPLETE RESPONSE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Background: The BMI is a clinical parameter that although not perfect is often used to measure adiposity. In breast cancer there are multiple studies indicating that overweight/obesity is related with lower survival and increased risk of relapse. It has been also reported less likely to achieve a pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) in O/O patients.

Methods: We retrospectively reviewed the records of 108 patients diagnosed with invasive locally advanced breast cancer (ILABC) who had been treated with NAC (anthracycline + taxane ± trastuzumab). The aim of our study was to review the impact of BMI on the pCR and the possibility of recurrence. pCR was defined as the criterion of strict pCR breast radio.

Results: From 2004 to 2011, 108 patients received NAC. Based on their weight and height, patients were divided into two groups: group 1: underweight/normal (BMI <25 kg/m2) and group 2: O/O (BMI ≥25 kg/m2). Fifty one (47.2%) patients were in group 1 and 57 (52.8%) were in group 2. Median age was 46 years in group 1 and 52 years in group 2 (p = 0.012). There were no differences at cTNM stage in both groups (p = 0.269). The NAC dose intensity was not different between groups (p = 0.399). Hormonal receptor negative tumors were more frequent in group 2 (71.1%) than in group 1 (28.9%) (p = 0.005). Likewise the triple negative receptor status was more frequent in group 2 (83.3%) than in group 1 (46.7%) (p = 0.001). Sixty-four patients had HER2 overexpression but was not different in both groups (p = 0.695). There was a pCR in 18 patients (35.3%) from group 1 vs 11 patients (20%) from group 2 (log rank 0.14). In an adjusted Cox regression analysis the BMI ≥25 kg/m2 was an independent factor for disease recurrence (HR 5.3 CI 95% 1.1-26.1).

Conclusions: Despite the retrospective nature of this study we can conclude that the patients with ILABC and O/O have a high risk for relapse and decreased response to NAC. It requires well-designed prospective studies to control confounding factors (dose intensity, chemotherapy regimens, changes in BMI) to get clear answers of these associations.

Disclosure: All authors have declared no conflicts of interest.

382 WHICH IS YOUR CHOICE?: NEOADJUVANT ADRIAMYCIN AND DOXETAXEL (AD) VERSUS ADRIAMYCIN, CYCLOPHOSPHAMIDE AND PACLITAXEL(AC-T) IN LOCALLY ADVANCED BREAST CANCER

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Background: It is well known that neoadjuvant chemotherapy is acceptable for women with locally advanced breast cancer. However, it is not achieving consensus that what kind of regimen is most effective and tolerable, although lots of regimens and dosages were clinically used.

Materials and methods: We compared the patients who were received adriamycin and doxetaxel (AD) and adriamycin, cyclophosphamide followed by paclitaxel (AC-T) as neoadjuvant chemotherapy and then received operation from 1 January 2006 to 30 September 2011. The group of AD regimen was scheduled for 3 cycles of AD (50mg/m2 and 75mg/m2, respectively) with 3 weeks interval and then completes resection. The group of AC-T was scheduled for 4 cycles of AC regimen (50mg/m2 and 500mg/m2, respectively) and then 4 cycles of paclitaxel (175mg/m2) with 3 weeks interval and then completes resection. The patients who were enrolled in this study were totally 78 (AD and AC-T were equally 39). The significant differences of patients’ characteristics between two groups were not observed. However, the significant differences were identified in hematologic toxicity including neutropenia more than grade 3 (p < 0.001), neutropenic fever (p < 0.001), dose reduction rate due to hematologic toxicity (p = 0.012) and chemotherapy induced anemia (p = 0.012), although chemotherapy induced thrombocytopenia (p = 1.0) was not different between two groups. No differences were identified in non-hematologic toxicity including hepatitis toxicity, gastrointestinal toxicity of CR and peripheral neuropathy. The response of chemotherapy was no difference between two groups, which was estimated by conversion rate of breast conserving surgery, clinical response of chemotherapy (p = 0.148), clinically downstaging rate (p = 0.464) and pathologic complete response rate (p = 1.0). There is no factor to predicting pathologic complete response or conversion to breast conservation in this study.

Conclusions: The neoadjuvant AC-T regimen is more tolerable with similar clinical outcome compared to AD regimen.

Disclosure: All authors have declared no conflicts of interest.
384 WHY DO WOMEN WITH BREAST CANCER IN SARAWAK, MALAYSIA PRESENT LATE?

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Introduction: Breast cancer (BC) is the most common cancer in Sarawak. We explore the reasons of late stage presentation in this study.

Methods: Based on a 175 questions questionnaire, information on barriers to late presentation were collected as a prospective study on 626 cases (2009 to 2011). Descriptive statistics and statistical tests were performed using the SPSS ver 17.0.

Results: The stage at diagnosis differed significantly with 71% of the Chinese being diagnosed at early stage compared to only 50% in Malay and 45% in Natives (p < 0.0004). The delay between first symptom and first medical consultation (DELAY 1) was more than one month in 57% of the patients and it differed significantly among ethnic groups (50% for Chinese, 64% for Malay and 65% for Natives, p < 0.0002). The highest delay were: women aged <30 years (75%) vs >50 years (53%, p < 0.037); from rural area (65%) vs urban areas (55%, p < 0.04). The main variables affecting this delay were knowledge about BC (p < 0.004), lack of interest in one's health (p < 0.0005) and choice of first professional consulted (doctor/nurse vs traditional healer, p < 0.03). The delay between first medical consultation and effective diagnosis (DELAY 2) for >1 month was 14% of the patients and it differed significantly among ethnic groups (14% for Chinese, 23% for Malay and 13% for Natives, p < 0.0008). The main reasons: the number of doctors consulted before diagnosis (less the better, p < 0.0003); Malays (66.4%) and natives (64.4%) consulted more than two doctors when compared to Chinese (42.6%, p < 0.0001) and were less likely to follow the recommendations given by the doctors (p < 0.06). The impact of teaching breast self-examination (BSE) on DELAY 1 and 2: Seventy-eight percent of patients were taught BSE and by 80% of government nurses. The age group (30-40 years) had been taught BSE more than other age groups. For DELAY 1, 72% were not taught BSE, p < 0.0001. There was no difference for those with DELAY 2. However for both DELAY 1 and 2, 42% were not taught BSE, p < 0.0001.

Conclusions: More than 50% of the patients had DELAY 1 and 14% for DELAY 2. Learning BSE had an impact on DELAY 1 but not for DELAY 2. Those in age groups (>40 to 60 years) had less BSE taught and this finding is crucial for public education on breast cancer.

Disclosure: All authors have declared no conflicts of interest.

384 THE ROLE OF ANTIESTROGENS IN BREAST CANCER CELLS’ INVASIVENESS

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Aim: The current study investigates the effect of two selective antagonists of the estrogen receptor (ER), fulvestrant (FL) and tamoxifen (Tam), on the invasive ability of breast cancer cells. ER blockage using anti-estrogens is associated with a small induction of invasion. Moreover, matrix metalloproteinases (MMPs) contribute to this procedure by cleaving components of the extracellular matrix, forming a path for the migrating cells. In addition, the focal adhesion kinase (FAK) plays a central role in invasiveness.

Methods: We used two ER+ breast cancer cell lines, MCF7 and T47D. Cells were stimulated by estradiol (E2) and then treated with FL, Tam and the metabolites of tamoxifen (4OHT and endoxifen (End)) and tamoxifen (4OHT). The invasiveness was evaluated using the matrigel assay and MMPs expression with gelatin zymography assay. Using immunofluorescence, we study the expression and localization of phospho FAK and its correlation with F-actin.

Results: We found that E2 exerts a protective role in invasiveness. On the contrary, the anti-estrogens, as well as their metabolites reversed the effect of E2, a finding that was more obvious with Tam. The effect of the agents on MMP expression was more pronounced at 48 h, when Tam and 4OHT were found to reduce the levels of both MMP-2 and MMP-9 compared to FL. Following E2 exposure, the maximum auto- phosphorylation of FAK (Y397) was observed at 10 min. At the same time point we assessed the effect of our agents, regarding the spatial organization of actin fibers. The concurrent administration of E2 with FL, Tam or End was associated with rearrangement of cytoskeleton, a finding that was not observed in untreated cells, as well as after the use of 4OHT and E2 or E2 alone.

Conclusions: Our results indicate that the metabolite 4OHT is superior to the pro-drug Tam as well as the pure anti-estrogen FL with respect to invasiveness, MMPs induction and actin rearrangement. Regarding the comparison of Tam with FL, the effect on MMPs and rearrangement was similar. However, FL was found to be slightly superior to Tam concerning invasiveness.

Disclosure: All authors have declared no conflicts of interest.

385 CANCER STEM CELL-LIKE CELLS: A THERAPEUTIC MODEL IN BREAST CANCER PATIENTS, WHERE ANY OTHER RECOMMENDED THERAPY FAILED

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Introduction: Nowadays, the difficulty to treat metastatic breast cancers is high. Many clinical therapeutic lines have failed and there is no suggested therapeutic approach (in literature) concerning this type of tumors. The last decades, circulating tumor cells (CTCs) are the state of the art in cancer therapy. In the present study, CTCs were isolated and identified. CSCs (cancer stem cells) were isolated from the above population of CTCs and their gene pattern was compared with those from the primary tumor as well as with those from the metastatic tumor. This study attempts to find a correlation between the CTCs and the metastatic regions in comparison with the primary tumor as well as to find out if all the CSCs have the same hallmark in the selected breast cancer stem cell populations.

Materials and methods: In order the protocol to be performed, CTCs from patient’s blood samples were isolated and then cultured in appropriate conditions. CTCs were isolated and isolated from the population of CTCs. mRNA was extracted and was used for Microarray hybridization assays. The same procedure was repeated for primary tumor as well for metastatic tumor samples. The expression pattern of primary tumor cells was compared with those in the metastatic tumor. Finally, the therapeutic approach which was based on the above findings, was designed.

Results: The results showed that the gene expression pattern of metastatic sites is similar to that of metastatic sites and less to that of the primary site. Then, the patients followed a therapeutic approach based on the data of the clinical results which were evaluated within a six-month period showing that the patients showed an objective response rate.

Conclusion: The results showed that the entity that determines the clinical outcome in breast cancer, is the sub-population of CTCs, the circulating CSCs. Moreover, there are various types of CSCs in one patient, and not only one, as they have different growth mechanisms in primary and secondary tumors.

Disclosure: All authors have declared no conflicts of interest.

386 BREAST CANCER PATIENTS WITH HER2NEU OVEREXPRESSION: RELATIONSHIP AMONG CLINICOPATHOLOGICAL CHARACTERISTICS AND LOCAL/DISTANT RECURRENCES AND SURVIVAL

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Objectives: The aim of this study was to correlate the overexpression of HER2 with clinicopathologic characteristics and its influence on local/distant recurrence and survival.

Methods: From 1998 to 2010, prospective data of 146 patients with invasive breast cancer with HER-2 overexpression was studied. The sample was divided into three groups: Negative hormonal receptors (NHR); Luminal B1 (Estrogen receptor +, Progesterone receptor -), Luminal B2 (Estrogen receptor +, Progesterone receptor +). Histological type (HT), size tumor (T), differentiation grade (DG), and nodal status were determined. Correlation with local and distant recurrence, and 5-year overall survival was done.

Results: NHR: 33.5%, luminal B1: 47.5%; luminal B2: 19% Clinical pathologic characteristics:

<table>
<thead>
<tr>
<th>Age (%)</th>
<th>Size(%)</th>
<th>HT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>50-69</td>
<td>&gt;70</td>
</tr>
<tr>
<td>T1</td>
<td>T2</td>
<td>T3</td>
</tr>
<tr>
<td>Ductal</td>
<td>Lobular</td>
<td></td>
</tr>
<tr>
<td>NHR</td>
<td>23</td>
<td>51</td>
</tr>
<tr>
<td>Luminal B1</td>
<td>33</td>
<td>51</td>
</tr>
<tr>
<td>Luminal B2</td>
<td>22</td>
<td>64</td>
</tr>
</tbody>
</table>

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Volume 23 | Supplement 9 | September 2012
Local and distant recurrence and overall survival at 5 years follow-up:

<table>
<thead>
<tr>
<th>Status</th>
<th>G1 (%)</th>
<th>G2 (%)</th>
<th>G3 (%)</th>
<th>Node Status</th>
<th>Nodal Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHR</td>
<td>0</td>
<td>21</td>
<td>79</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Luminal B1</td>
<td>11</td>
<td>37</td>
<td>52</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Luminal B2</td>
<td>0</td>
<td>28</td>
<td>73</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Conclusions: Patients with NHR and patients with PR had more aggressive differentiation grade, less axillary infiltration and increased risk of distant metastasis. At 5-year follow-up, overall survival was better in the PR+ group.

Disclosure: All authors have declared no conflicts of interest.

SURGICAL RESECTION OF LOCALLY ADVANCED PRIMARY TUMOR IN PATIENTS WITH DISTANT METASTATIC BREAST CANCER AT DIAGNOSIS: RESULTS OF A RETROSPECTIVE COMPARATIVE STUDY

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Background: Women with metastatic breast cancer (MBC) with intact locally advanced primary tumors (LAT) present aggressive local symptoms that may warrant palliative surgery to the breast. However, it is unclear if such surgery otherwise improves clinical outcome. The aim of this study is to demonstrate if surgery of the breast may avoid uncontrolled chest wall disease and may improve survival.

Methods: We reviewed the records of all MBC patients presented with intact LAT, treated at our institution between 2007 and 2011. We compared two groups of patients: surgical group versus nonsurgical group. Clinical outcome was assessed in the two groups. Prognostic factors affecting locoregional relapse, were evaluated.

Results: 75 patients were identified. The mean patient age was 49 ± 12.15 years. 52% were premenopausal women. 87.1% of tumors were hormone receptors positive. Her2 was assessed in 59 cases and was positive in 33.9%. Inflammatory breast cancer presented 16%. Clinical lymph node involvement was noted in 58.7% cases. 69.6% had visceral metastasis and 5.3% had brain metastasis. 89.3% had good Performance Status §1. All women received systemic therapy. First-line therapy consisted of anthracycline-based regimen (95.6%) and Taxane (39.7%). Among patients with HER2 positive 36.4% received Trastuzumab. Only 14% of patients with bone metastasis received bisphosphonate. 49.3% underwent mastectomy while 50.7% had intact LAT. The two groups were well balanced regarding demographics, clinicals, and tumors, characteristics. Among women who underwent mastectomy 48.5% had axillary lymph node dissection, and excision margins were positive in 25% cases. Locoregional radiotherapy (LRRT) was given to 8 women. pCR occurred in 7 patients among those who were operated. Local recurrence (LR) occurred in 9 patients (28.1%). Median time to local relapse was 3 months (2-19). LR was related to excision margin (p = 0.0001) and LRRT (p = 0.04). Median PFS was 10 months in nonsurgical group patients versus 16.5 months in surgical group.

Conclusions: MBC patients with locally advanced breast cancer who underwent mastectomy had improvement in locoregional symptoms when the excision margin was in-sano. However, the impact of this surgery in survival is not clear.

Disclosure: All authors have declared no conflicts of interest.

CISPLATIN, CYCLOPHOSPHAMIDE, METHOTREXATE, AND 5-FLUOROURACIL (PCMF) AS FIRST LINE THERAPY OF METASTATIC TRIPLE NEGATIVE BREAST CANCER (MTNBC) IN PATIENTS PREVIOUSLY TREATED WITH ADJUVANT ANTHRACYCLINES AND TAXANES: RETROSPECTIVE ANALYSIS

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Background: The purpose of this study was to evaluate the efficacy and toxicity of applied PCMF chemotherapy every four weeks (q4w) in the treatment of MTNBC patients (pts) previously treated with adjuvant anthracyclines and taxanes.

Methods: We administered cyclophosphamid 500mg/m² on day 1, 5-fluorouracil 500mg/m² on day 2, and methotrexate 30mg/m² on day 1, 3, and 5. The evaluation was performed after 4 cycles. We included 76 pts (median age 58 years, range: 32-71 years). PS medium was 1 (0-2): 21 pts (27.6%) were premenopausal and 55 (62.4%) postmenopausal. Adjuvant anthracyclines (AC or FAC x 4) and taxanes (paclitaxel x 2, or docetaxel x 3) x 4) therapy was applied in all patients. DFS <12 months was obtained in 47 patients (61.8%) and >12 months in 29 pts (38.2%). Adjuvant radiotherapy was applied in 48 pts (63.2%). Visceral metastases were observed in 51 pts (67.1%), bone metastases in 34 (44.7%), and soft tissue metastases in 11 pts (14.5%). Only one organ was affected in 15 pts (19.7%), in 41 (53.9%) two organs, and in 5 pts (6.6%) three or more.
Results: We evaluated 76 pts with MNTBC after 4 cycles of PCMF chemotherapy. CR was found in 3 pts (3.9%), PR in 16 pts (21.0%), SD in 11 pts (14.5%), and PD in 39 pts (51.3%); with ORR in 19 pts (24.9%) and TCR in 30 pts (39.5%). Hematological toxicity: grade 3 and 4 anemia was found in 4 pts (5.3%) and leukopenia in 9 pts (11.8%). Non-hematological toxicity: renal grade 3a was observed in 2 pts (2.6%). Not a single therapy was interrupted due to toxicity, but therapy prolongation was present in 15% of applied cycles.

Conclusions: The application of PCMF chemotherapy q4w in the treatment of patients previously treated with anthracyclines and taxanes as adjuvant treatment appeared to be effective with ORR in 24.9% and TCR in 39.5% and can be administered with good tolerance. It is today our standard treatment in this pts population.

Disclosure: All authors have declared no conflicts of interest.

**391** TRASTUZUMAB-BASED CHEMOTHERAPY (CT) FOR HER2-POSITIVE METASTATIC BREAST CANCER (MBC): WHICH OPTIMAL PARTNER BEYOND THE FIRST LINE? A SINGLE-CENTRE RETROSPECTIVE STUDY

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Background: The activity of trastuzumab-based chemotherapy (CT) in HER2+ MBC is well established, but the question of the optimal CT partner remains a relevant issue. We performed a retrospective comparison of the clinical outcomes associated with different trastuzumab-CT regimens.

Patients and methods: Patients (pts) for this analysis were selected from a non-institutional database of HER2+ MBC pts receiving trastuzumab-based CT for the metastatic disease (February 2005-December 2008). Treatment activity and safety were assessed by the WHO criteria, time to progression (TTP) and overall survival (OS) were calculated by the Kaplan Meier method.

Results: A total of 147 pts with measurable disease were evaluated: 57 received the metastatic disease (February 2005-December 2008). Treatment activity and safety were assessed by the WHO criteria, time to progression (TTP) and overall survival (OS) were calculated by the Kaplan Meier method.

Conclusions: These results confirm the high activity of the tested regimens as first-line therapy of HER2+ MBC, without significant differences in clinical outcomes, as also suggesting the benefit of multiple lines of trastuzumab-based CT in a significant subset of pts, since each subsequent line may contribute to a longer OS.

Disclosure: All authors have declared no conflicts of interest.

**392** PHASE II STUDY OF SINGLE AGENT ORAL VINORELBINE (OV) AS FIRST-LINE CHEMOTHERAPY (CT) IN PATIENTS (PTS) WITH HER-2 NEGATIVE METASTATIC BREAST CANCER (MBC): A SINGLE CENTER EXPERIENCE

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Background: Quality of life and pts preferences play an important role in treatment decision-making in the metastatic setting. Previous studies indicated that ORL CT is convenient and a preferred option by many pts. We hereby report the efficacy and safety of OV as first-line CT for MBC.

Patients and methods: 31 pts were enrolled between January 2007 and December 2010. All pts had measurable disease, a majority (84%) relapsing after anthracyclines (ANT) and/or taxanes (TNX) adjuvant treatment, WHO PS ≤ 2, adequate bone marrow, hepatic and renal functions and no adjuvant CT within the last 6 months. Pts were treated every 3 weeks with OV 60 mg/m2 D1 and D8 for the 1st cycle and thereafter 80 mg/m2 D1 and D8 every 3 weeks in the absence of G4 neutropenia and/or febrile neutropenia. Treatment was administered until disease progression or unexpected adverse event or pt refusal to continue. Primary endpoint (EP) was Objective Response Rate (ORR); secondary EPs were TTP, OS and safety. Follow-up results until April 2012 are reported.

Results: Median age was 42 years (range, 33-75); median WHO PS 1 (range, 0-2). Previous adjuvant therapy: ANT-based alone: 29%, TXN-based alone: 19%, ANT plus TXN: 36%, other: 16%. Median disease-free interval from end of previous CT was 7 months; 26 pts (84%) had 2 or more metastatic sites, liver (61%), bone (58%), lung (58%) being the most frequent sites. A median of 6 cycles were administered (range, 2-20). ORR was achieved in 9 pts (29%), including 1 complete and 8 partial responses. 12 pts (39%) had stable disease, resulting in a clinical benefit rate (CBR) of 68%. In pts pretreated by ANT, ORR was 35% and CBR was 70%. Median TTP was 3.7 months.

Conclusions: These results confirm the high activity of the tested regimens as first-line CT for HER-2 negative MBC pts. Similar activity was observed in the sub-group of pts pretreated by ANT.

Disclosure: All authors have declared no conflicts of interest.

**393** VINORELBINE WITH OR WITHOUT TRASTUZUMAB IN METASTATIC BREAST CANCER

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Background: Vinorelbine is one of the most widely used drugs in metastatic breast cancer. We report a single center experience with vinorelbine with or without trastuzumab in patients with metastatic breast cancer.

Patients and methods: All patients with metastatic breast cancer receiving vinorelbine with or without trastuzumab during a six years period were retrospectively reviewed. Demographic data and data on response, time to progression (TTP) and survival were collected. Patients received vinorelbine IV 25-30 mg/m2 PO 60-80 mg/m2, in days 1 and 8 of a 21 days cycle. In patients who received concomitant trastuzumab a standard dosing schedule with 8 mg/kg loading dose followed by 6 mg/kg in subsequent administrations every three weeks was used.

Results: Eighty seven women were included. The median age was 63 years (range 32 to 85). Sixty two patients received vinorelbine alone and 25 patients received vinorelbine with trastuzumab. In 67 patients this was the first line treatment for metastatic disease and in 20 patients it was 2nd or later line of treatment. Seventy patients were evaluable for response while the remaining seventeen patients were not evaluable due to early progression (n = 6) or early termination of treatment for adverse effects (n = 11). The response rate of evaluable patients was 37.1% (14.4% Complete Response (CR) and 35.7% Partial Response (PR)). Eighteen additional patients (25.7%) had Stable Disease (SD) for three or more months resulting in a Disease Control Rate of 62.8%. Twenty four of 54 (44.4%) patients receiving first line treatment had a response while in the second and subsequent lines setting two of 16 (12.5%) patients responded (x2 = 9.66, p = 0.001). A response was obtained in 63.6% of patients receiving concomitant trastuzumab and in 25% of patients receiving vinorelbine alone (x2 = 13.63, p = 0.0002). The median TTP was 6 months (range 1-45). Sixty six patients of the cohort have died and the median overall survival was 11.5 months (range 1-83). Adverse effects necessitating interruption of treatment were observed in 18.5% of patients.

Conclusion: This retrospective study of vinorelbine in metastatic breast cancer confirms a high disease control rate. Response rate is higher in first line treatment compared to subsequent lines and with the combination with trastuzumab.

Disclosure: All authors have declared no conflicts of interest.

**394** A RETROSPECTIVE STUDY OF CISPLATIN/VINORELBINE VERSUS CAPECITABINE/VINORELBINE AS SECOND-LINE OR THIRD-LINE TREATMENT IN ADVANCED BREAST CANCER


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Purpose: To compare the efficacy and safety of cisplatin or capecitabine, both with vinorelbine, as second-line or third-line treatment in advanced breast cancer previously treated with anthracyclines and taxanes.

Methods: From June 2004 to November 2011, 62 advanced breast cancer patients were eligible. Patients (38) enrolled in group NP received VIN 25mg/m2 on day 1 and 8 combined with Cisplatin 75mg/m2 on day 1 of a 21-day cycle. Patients (24) enrolled in group NX received VIN 25mg/m2 on day 1 and 8 of a 21-day cycle combined with CAP 1000mg/m2 twice daily for 14 consecutive days followed by 7 days of rest. Tumor assessment was performed every 2 cycles according to RESIST criteria. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (version 3.0).

Results: The overall response rate (ORR) in group NP was 47.4%, all were partial responses (PRs). In group NX, ORR was 33.3% (P = 0.275), with 4.2% CRs and...
29.2% PRs. Median time to progression (TTP) was 6.1 months (range, 3.2-9.0 months) in group NP and 6.3 months (range, 4.1-8.5 months) in group NXP (P = 0.783). COX regression showed no statistically significant difference (P = 0.782, OR = 0.95). Median NP survival (OS) was 28.8 months (range, 21.6-36.0 months) in group NP and 15.1 months (9.6-20.6 months) in group NXP (P = 0.027, OR = 0.495). COX regression showed a statistically significant difference (P = 0.045). Neutropenia was the most frequent hematologic toxicity, with 57.9% grade 3/4 neutropenia observed in group NP and 38.1% in group NXP (P = 0.145). 13.2% grade 3/4 vomiting was seen in group NP and no grade 3/4 vomiting in group NXP. No grade 3/4 nephrotoxicity or hand-foot syndrome was noted in both groups.

Conclusion: Better OS was seen in group NP than in group NXP. Treatment-related toxicity in both groups was manageable.

Disclosure: All authors have declared no conflicts of interest.

396 EFFICACY OF TRASTUZUMAB CONTAINING RETREATMENT AFTER PROGRESSION ON LAPATINIB THERAPY IN JAPANESE PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

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Background: Lapatinib has been approved for HER2 positive metastatic breast cancer patients with refractory to trastuzumab (T)-therapy in Japan. Currently, it has been proposed that lapatinib can reexpress trastuzumab-mediated antibody-dependent cellular cytotoxicity (ADCC). Recent clinical data suggest the efficacy of T containing retreatment after progression on lapatinib therapy in patients with HER2-positive metastatic breast cancer. Here, we present a retrospective review of data from 25 patients who received T containing retreatment after progression on lapatinib therapy.

Methods: We reviewed the data of 50 patients with HER2-positive metastatic breast cancer who received lapatinib therapy in our institution from August 2004 through March 2012. Of these, 25 patients received T containing retreatment after progression on lapatinib therapy. We retrospectively assessed the clinical benefit of this treatment regimen in these patients.

Results: Luminal-HER2 and HER2-enriched subtypes were identified in 13 (52%) and 12 (48%) of these cases, respectively. The median duration of lapatinib therapy was 5.9 months (range, 1.6-20.2 months). The median number of preceding regimens was 3 (range, 2-8) in metastatic setting. Seven patients (31.8%) responded to T containing retreatment; all 7 patients achieved PR and none achieved CR. There were no significant differences in subtype, number of preceding regimens and brain metastases; however, responders achieved higher clinical response from lapatinib therapy than non-responders (response rate of 84% versus 13%, respectively). The median time to progression of T containing retreatment was 3.0 months (95% CI, 2.4-3.5 months). Among seven responders to T containing retreatment, one patient responded to refractory T containing regimen. All patients tolerated T containing retreatment with no occurrence of Grade 3/4 toxicities.

Conclusion: T containing retreatment could be a favorable treatment regimen which can achieve clinical response in patients with HER2-positive metastatic breast cancer who experienced progression on prior trastuzumab and following lapatinib therapy.

Disclosure: All authors have declared no conflicts of interest.
more than 6 cycles of capecitabine. 65 (43%) patients commenced treatment at a dose less than 1250 mg/m² twice daily and 60 patients (40%) received a dose reduction during treatment. Median overall survival was longer in those patients who received more than 6 cycles of capecitabine treatment (20.9 months) compared to those who stopped at 6 cycles by clinical decision (16.3 months) although this did not reach significance (P = 0.088). PFS and OS were similar among patients who received lower vs. full-dose capecitabine (PFS P = 0.32, OS P = 0.71).

Conclusions: In this retrospective analysis, patients receiving more than 6 cycles of treatment had a better OS than those who stopped at 6 cycles (by clinical decision). Continuing capecitabine monotherapy beyond the standard 6 cycles if well tolerated, should be considered in patients with locally recurrent or metastatic breast cancer as this may allow for an improvement in survival. In addition, these data support the practice of dose reduction in under-dosing capecitabine, including the possibility of starting at a lower dose (<1250 mg/m² twice daily), to reduce the incidence of adverse events without compromising efficacy.

Disclosure: All authors have declared no conflicts of interest.

Method: Coming of 5 Spanish hospitals have been selected 129 consecutive patients who receive treatment with BVZ sec-line treatment or later. For the efficacy analysis were used tests of Wilcoxon signed-rank and sign test.

Results: When analyzing the data of 114 patients (88.4%) had progressed. The responses obtained with the previous line of treatment (without BVZ) were: RC: 4 (3.1%), RP: 31 (24.4%), EE: 54 (41.9%), PROG: 36 (27.9%) and NV: 4 (3.1%). The line obtained during treatment with BVZ: RC: 2 (1.6%), RP: 31 (44.2%), EE: 37 (28.7%), PROG: 28 (21.7%) and NV: 5 (3.9%). With respect to time to progression (TP), 76 patients achieved a TP longer than they had achieved with the previous line of treatment (p = 0.011). The overall median time to progression was also higher: 4.96 vs 5.83 months (p = 0.032).

Conclusion: Opposite to it is expected, treatment with bevacizumab in advanced lines improves the results obtained with previous treatment lines. This suggests that bevacizumab is active in advanced lines and produces favorable changes in the natural history of patients with metastatic breast carcinoma 1. Dufresne, A. et al. Impact of chemotherapy beyond the first line in patients with metastatic breast cancer. Breast Cancer Res Treat. 2010; 127(1): p. 227.

Disclosure: All authors have declared no conflicts of interest.

Method: Continuing capecitabine monotherapy beyond the standard 6 cycles of treatment was considered in patients with locally recurrent or metastatic breast cancer as this may allow for an improvement in survival. In addition, these data support the practice of dose reduction in under-dosing capecitabine, including the possibility of starting at a lower dose (<1250 mg/m² twice daily), to reduce the incidence of adverse events without compromising efficacy.

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CSP-Br is a self-reported tool which allows to assess the severity of 57 symptoms of Comprehensive Symptom Profile in Patients with Breast Cancer (CSP-Br). The tool can be used to evaluate treatment outcomes in breast cancer patients. One hundred and eighty-four patients with breast cancer were treated with conventional chemotherapy (CT) combining Epirubicin (60 mg/m²) and Cyclophosphamide (500 mg/m²). The patients were divided into two groups: the control group received Epirubicin (60 mg/m²) and Cyclophosphamide (500 mg/m²) as the standard treatment, while the experimental group received Paclitaxel in two different formulations: Cremophor-Formulated Paclitaxel and Albumin-Bound Paclitaxel. The feasibility of using standardized QoL and symptom assessment tools to determine benefits and risks of conventional chemotherapy (CT) in breast cancer patients was also evaluated.

Quality of life (QoL) and symptom assessment are of increasing importance to current treatments and to improve quality of life. We aimed to study the feasibility of using generic QoL questionnaires, the SF-36 and the EQ-5D; symptoms of using standardized QoL and symptom assessment tools to determine benefits and risks of conventional chemotherapy (CT) in breast cancer patients. One hundred and seven breast cancer patients (Stages I–IV) were included in the study (58% patients with metastatic breast cancer). Mean age/SD = 53/10 y.o. All the patients underwent taxane-based CT with the previous treatment including CT (89%), surgery (69%), and radiation therapy (65%). The following distribution of patients receiving taxane-based CT according to the grades of QoL impairment was observed: 23% of patients had no QoL impairment; 15% patients had mild QoL impairment, 33% had moderate or severe QoL impairment, and 19% had critical QoL impairment.

We identified breast cancer patients at high risk to develop MC. These patients may benefit from an early diagnosis of MC to obtain better results with current treatments and to improve quality of life. All authors have declared no conflicts of interest.

## Results

A total of 4 patients have been treated with IT trastuzumab (Table 1). Table 1: Patient characteristics, previous treatment and survival. All HER2 positive, IDC invasive ductal carcinoma, ADC adeno-carcinoma, S surgery, RT radiotherapy, HT hormonal treatment, iT systemic trastuzumab. LM were confirmed by lumbar puncture in patients B, C, and D. In patient A LM was diagnosed by MRI (CSF cytology persistently negative). Patients A, B, and C received weekly IT trastuzumab 25 mg. Patient D received weekly IT trastuzumab 25 mg + melphalan 12 mg. Toxicity related to IT trastuzumab was not observed. The CSF cytology remained positive in patient D and became negative after 1 and 3 weeks for patient C and B, respectively. Patient A was still receiving treatment at last follow-up.

## Conclusions

In our group of patients, IT trastuzumab was well tolerated and had encouraging results. Ours is a small and somewhat heterogeneous population and we can not extrapolate on the efficacy of trastuzumab in this setting, but a study with a larger number of patients is warranted and may help identify patients appropriate for this therapy. All authors have declared no conflicts of interest.

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Background: Phase II clinical trials of HER-2-targeted agents in combination with cyclin-dependent kinase inhibitors or chemotherapy have shown promising results. However, the combination of pertuzumab and trastuzumab in the first-line setting has not been extensively studied.

Methods: PERTUZUMAB AND TRASTUZUMAB IN COMBINATION WITH VINOCEL IN HER2-POSITIVE STAGE IIIB-III METASTATIC BREAST CANCER: A SINGLE-ARM, TWO-COHORT, PHASE II STUDY (VELVET)

Results: The study is ongoing and will provide valuable insights into the clinical efficacy and safety of this combination therapy in HER2-positive metastatic breast cancer.

Conclusion: The combination of pertuzumab and trastuzumab in the first-line setting for HER2-positive metastatic breast cancer is a promising approach with the potential to improve outcomes for patients.
P is distinct from that bound by trastuzumab (H) and their complementary mechanisms of action lead to a more comprehensive HER2 blockade when combined. Data from the phase III trial CLEOPATRA showed significantly improved PFS in pts with HER2-positive 1L MBC given P + H + docetaxel (D). As H was not widely available in the (neo)adjuvant setting prior to CLEOPATRA recruitment, a relatively low proportion of pts in CLEOPATRA had previously received H. PERUSE will assess the safety and tolerability of P + H + one of a choice of taxanes (T) as 1L therapy for pts with HER2-positive metastatic or locally advanced BC. Efficacy endpoints will also be recorded in PERUSE, in a pt population likely to have experienced wider exposure to prior H therapy.

Methods: PERUSE is a phase IIIb, multicenter, open-label, single-arm study in pts with HER2-positive BC who have not been treated with systemic non-hormonal anticancer therapy for MBC. The planned sample size is 1500. Pts will receive, P: 840mg initial dose, 420mg q3w IV; H: 8mg/kg initial dose, 6mg/kg q3w IV, T: D, paclitaxel or nab-paclitaxel according to local guidelines. A planned protocol amendment will allow HR-positive pts to receive endocrine therapy in conjunction with P + H following completion of T in line with clinical practice. Treatment will be administered until disease progression or unacceptable toxicity. At baseline, pts must have an LVEF of ≥50%, ECOG PS of 0, 1 or 2 and must not have received prior anti-HER2 agents for MBC. Prior H and/or lapatinib in the (neo)adjuvant setting is allowed, provided there was no disease progression on-treatment. A disease-free interval of ≥6 months is required. The primary endpoint is safety and tolerability. Secondary endpoints include PFS, OS, ORR, CBR, duration of response, time to response and QoL. The final analysis will be carried out when pts have been followed up for ≥12 months. Interim analyses are planned after enrollment of ~350, 700 and 1000 pts. Regular interim safety assessments by a DSMB will take place.

Disclosure: D. Miles: I have an interest in relation with one organisation that could be perceived as a possible conflict of interest in the context of the subject of this abstract. I have served on Advisory Board Meetings for Roche/Genentech. F. Puglisi: I have an interest in relation with one organisation that could be perceived as a possible conflict of interest in the context of the subject of this abstract. I participate in Advisory Board Meetings for Roche. A. Schneeweiss: I have an interest in relation with one organisation that could be perceived as a possible conflict of interest in the context of the subject of this abstract. I serve on Roche Advisory Boards and am involved with corporate-sponsored research with Roche. L. Mitchell: I am currently an employee of F. Hoffmann-La Roche. A. Dünn: I have an interest in relation with one organisation that could be perceived as a possible conflict of interest in the context of the subject of this abstract. I am an employee of Hoffmann-La Roche. T. Bachelot: I have an interest in relation with one organisation that could be perceived as a possible conflict of interest in the context of the subject of this abstract. I am involved with Roche sponsored research and Roche advisory Board Meetings. All other authors have declared no conflicts of interest.