cancer, locally advanced and metastatic

**FIRST EFFICACY RESULTS FROM THE TURANDOT PHASE III TRIAL COMPARING TWO BEVACIZUMAB (BEV)-CONTAINING REGIMENS AS FIRST-LINE TREATMENT 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 capecitabine (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 mg d1+5 PAC 90 mg/m2 d1, 8 & 15 qw) or BEV-CAP (BEV 15 mg/kg d1 + CAP 1000 mg/m2 bid d1-14 qw) 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.

**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-CAP (E2100) and BEV-CAP (RIBO-1).

**Disclosure:** R. Greil: RG has received research support and honoraria from Roche. S. Beslila: SB has received research support and honoraria from Roche. D. Messinger: Employee of IST GmbH, CRC which provides 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 IB/II STUDY OF BKM120 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 impact of pathway inhibition on restoration of therapeutic sensitivity is being investigated. The RP2D of BKM120, an oral pan-class I PI3K inhibitor, plus T + pts is 100 mg/d. Here, we present PH IB results of BKM120 + T in pts with T-resistant advanced HER2+ BC.

**Methods:** Pts with HER+ locally adv/metastatic BC resistant to T (progression while on T, or within 4 weeks [metastatic] or 12 months [adjuvant] of last T dose) received daily BKM120 (100 mg) and the standard w/dose of T. Ph II eligibility criteria: ≥1 measurable lesion, ≥1 but ≤4 prior anti-HER2 regimens (incl. trastuzumab [required], lapatinib, and/or T-DM1), and ≥3 lines of prior chemotherapy for metastatic disease. Ph IB pts treated at the RP2D who met Ph II eligibility criteria were included in the analysis.

**Results:** As of 23 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 no. prior aneoplastic regimens 4 (1–10); 5 pts had a baseline brain mets (BM); 3 pts had a baseline lung mets (LM); 1 pt had a baseline moderate target lesion unsuitable for evaluation at study withdrawal; 2 pts had prior CNS 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:** BKM120 in combination with T has an acceptable safety profile, and has shown encouraging preliminary activity in heavily pretreated HER+ 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 ANTI TUMOR ACTIVITY OF E-8310, A NOVEL FGF 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 FGF pathway may be clinically relevant.
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. (Sponsored by Sanofi, ClinicalTrials.gov number, NCT00912444.)

Disclosure: All authors have declared no conflicts of interest.

**321PD IMPACT OF MULTIFOCAL OR MULTICENTRIC DISEASE ON SURGICAL, LOCOREGIONAL, AND DISTANT SURVIVAL AFTER NEOADJUVANT CHEMOTHERAPY IN 3562 BREAST CANCER PATIENTS**

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

Patients and methods: Participants of the GeparTrio and GeparQuattro trials with operable or locally advanced tumors received anthracycline-taxane (+/- anti-HER2-based neoadjuvant chemotherapy and were classified as having multifocal (one lesion detected by physical examination, sonography, and mammography ≤ 3 mm), multifocal (3 lesions in one lesion ≤ 20 mm), or multicentric (≥ 2 lesions in ≥ 2 quadrants) disease. Breast conservation was allowed when tumor-free margins were achieved.

Results: Tumors of 3,562 participants were classified as multifocal (N = 2793; 78.4%), multifocal (N = 429, 12.0%), and multicentric (N = 349, 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 pCR rate (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 fertility of the tumor. Overall survival was not statistically different through all glioblastoma 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.

**322PD A TREATMENT-INTERACTION ANALYSIS BALANCING PATHOLOGICAL COMPLETE RESPONSES (PCR) AND CARDIOXOTOXICITY OF SINGLE-(S)/DUAL-(D) HER2 INHIBITION AND NEOADJUVANT CHEMOTHERAPY (CT) BACKBONE IN OPERABLE/LOCALY ADVANCED BREAST CANCER (O/LABC) PATIENTS**

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Purpose: Given the toxicity drawbacks potentially related to the combination of anthracyclines and a D-HER2 inhibition, a treatment interaction analysis of the available randomized trials was accomplished.

Methods: pCR (breast + axilla), breast conserving surgery (BCS), grade 3-4 neuropenia/cardioxotoxicity, and febrile neutropenia (FN), events were extracted from papers/presentation and cumulated according to a random-effect model; 95% confidence intervals (CI) were derived. A sensitivity analysis according to S/D HER2 inhibition, hormonal receptors (HRs) and CT (anthracyclines-taxanes: antra-TAX; TAX alone was accomplished to test for interaction. Absolute differences (AD) with 95% CIs, and the number of pts needed to treat/harm (NNT/NNH) for 1 to benefit were calculated to derive the likelihood of being Helped or Hurt (LHH).
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>HER2-Inhibition</th>
<th>Rates (95% CI)</th>
<th>Interaction (p)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthra-TAX S</td>
<td>37.0 [34.0, 40.0]</td>
<td>0.22</td>
<td>2.7</td>
</tr>
<tr>
<td>D</td>
<td>44.3 [33.5, 55.2]</td>
<td>0.2</td>
<td>-</td>
</tr>
<tr>
<td>TAX</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>0.2</td>
<td>-</td>
</tr>
</tbody>
</table>

pCR rates were significantly higher in the HR 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 favour of adding Anthra to TAX was found in the context of S-HER2 inhibition subgroup with regard to pcCR (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 likelihood 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 a that everolimus (EVE), an oral mammalian target of rapamycin (mTOR) 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). To report the efficacy and safety of EVE + EXE in patients with visceral involvement, the primary endpoints were PFS and overall response rate (ORR).

Methods: BOLERO-2 is a phase 3, double-blind, randomized study that compared EVE (10 mg/d) + EXE (25 mg/d) ± 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 known 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 the end of the 18th month of follow-up, 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, 0.55]). 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 AstraZeneca, Chugai, Pfizer, sanofi-aventis, GSK, Taiho, Novartis, and Takeda. K. Pritchard: Consult sananave AZE Roche PFE NVR AR AMG GSK res funding NCICT Grp contracted AS NVR in AZE AZE PFE Peche NVR & AMG paid expert test SanAve AZE & GSK AdCom SanAve AZE Roche PFE NVR GSK & 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. Taran: Employee of Novartis with stock/stock options. T. Sahnoum: An employee of Novartis with stock/stock options. M. Piccart: Board PharmaMar, consultant sanofi-aventis, Amgen, BMS, GSK, Boehringer, Roche, & Bayer. R.& grant Pfizer, Bayer, & grant Boehringer, Roche, GSK, Boehringer, Roche, & Amgen, sanofi-aventis, & 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 ER+ MBC continue to be ER+ /AR driven; and, B) Postmenopausal ER+ AR+ MBC can be driven by AR.

Methods: This Phase II/III 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 each arm achieving a 40% reduction in time to failure rate (PR) at stable disease of >20%; 14 patients [pts] in the first stage; 11 in the second stage for each arm).

Prior therapy with ≥ 2 lines of endocrine therapy (for ER+ arm); ≥ 1 line of chemo (for AR+ ERs- arm); and prior trastuzumab if HER2-positive was required. Eros and AR positive women were defined as immunoreactivity ≥ 1%. Results: In the phase I study, daily dosing of AA was well tolerated with variable PK at all dose levels. PD studies of CYP17 blockade demonstrated suppression of circulating estradiol and androgen levels below the limit of assay detection with 1000mg and 250-2000mg AA respectively; 1000mg was selected for Phase II evaluation. In the ER+ arm, 6 pts (Phase I) and 25pts (Phase II) received 1000mg AA, of whom 4 were HER2-positive. The median age (range) was 60 (46-80), prior lines of hormonal and chemotherapy were 3 (2-4) and 2 (0-5) respectively. There was 1 partial response (PR) lasting 14m in a pt who had received 4 and 5 lines of circulating estradiol and androgen respectively. Median progression-free survival was 11wk. CRR at 24wk was 21%. In the AR + ERTs- arm, recruitment is ongoing. Hypokalaemia easily managed by hydrocortisone administration, was the most common adverse event (AE).

Conclusion: AA was well tolerated and merits further evaluation in MBC. Cancer Research UK (Drugs Development Office) Sponsered 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. I.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.

References:

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Results: Seven eligible trials involving 1694 patients with MBC were selected. Our meta-analysis results showed that paclitaxel-based regimen was comparable to docetaxel-based regimen in terms of OS (HR: 0.87, 95%CI: 0.60-1.27, p = 0.476), DFS (HR: 0.92, 95%CI: 0.58-1.00, p = 0.032), TTP (HR: 1.13, 95%CI: 0.81-1.58, p = 0.450), and ORR (RR:1.01, 95%CI: 0.88-1.15, p = 0.915), but less grade 3 or 4 adverse events including anemia(RR:6.64,95%CI:0.44-0.94 p = 0.023), neurotoxina (RR:0.74,95% CI:0.58-0.93, p = 0.011), febrile neutropenia (RR:0.38, 95% CI:0.15-0.96, p = 0.041), thrombocytopenia (RR:62.86, 95%CI:0.41-0.96 p = 0.033)mucositis (RR:0.082, 95% CI:0.025-0.27 p = 0.000),diarthea(RR:0.19,95%CI:0.81-0.47 p = 0.000) and fatigue (RR:0.434,95%CI:0.20-0.96 p = 0.039) were observed in paclitaxel-based regimen.

Conclusion: The present systematic review and meta-analysis demonstrate that both taxane-based regimens show comparable efficacy for patients with MBC, and paclitaxel-based regimen is associated with less toxicity and better tolerability, especially in older patients and when used in weekly regimens.

Disclosure: All 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 basis of its effects on PFS.

**Results:** A total of 3041 studies were identified and 144 fulfilled the eligibility criteria. Selected studies included 315 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 0.42 (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, 15, 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 PFS and OS 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.
Results: Over a 10-year timeframe, costs and outcomes associated with AT amounts to 21,055.91 € and 6.3 QALYs (7.1 LYs). Costs associated with AC are 17,818.04 €, while outcomes are comparable to AT. The cost saving potential associated to AC vs. AT amounts to 4,237.87 € per patient. Costs and outcomes associated with CMF are 17,790.42 € and 6.3 QALYs (6.9 LYs), 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 years vs 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.

### 333P

**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) analysis is increasingly common in health technology assessments of cancer treatments. AIM: We assess women's preferences for health states specific to advanced stage breast cancer including a baseline utility weight is increasingly common in health technology assessments of cancer treatments. AIM: We assess women’s preferences for health states specific to advanced stage breast cancer including a baseline utility weight.

**Method:** Using FACT-B quality of life data from a randomized clinical trial in ABC unicentric utilities 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 peri- or post-menopausal women were recruited and interviewed by a single woman in their age group using visual analogue and standard gamble tasks. Univariate and multivariate analyses were performed to control for age, marital status, menopausal status and whether the interviewee 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 VS 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 VS and SG analyses. The trade-off between a change in treatment response yet the possibility of toxicity yielded a utility score of 0.34 (p < 0.01).

**Conclusion:** These VS 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.

### 334P

**HEALTH-RELATED QUALITY OF LIFE (QOL) IN METASTATIC BREAST CANCER PATIENTS TREATED WITH EVEROLISMUS 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 EORTC QLQ-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 scales, 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 evaluate the effect of study dropout on or before week 24. Treatments were compared using differences of least squares mean (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 = –2.5, 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, Enealia, 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. T. Sahmoud: Is an employee of Novartis with stock options. G.N. Hortobagyi: Member of the Sci Ad Board of Allergan; consultant to Allergan, Novartis, Genentech, and sanofi-aventis; has received grant support from Novartis; travel expense reimbursement from Sanofi-Aventis.

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**COST EFFECTIVENESS OF ADJUVANT CYCLOPHOSPHAMIDE CONTAINING REGIMENS 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. Adjuvant therapy 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 due to chemotherapy (fibril neupenia, 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 (7.1 LYs). Costs associated with AC are 17,818.04 €, while outcomes are comparable to AT. The cost saving potential associated to AC vs. AT amounts to 4,237.87 € per patient. Costs and outcomes associated with CMF are 17,790.42 € and 6.3 QALYs (6.9 LYs), 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 years vs 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.
**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 A 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 summed by health care professionals and pts to national pharmacovigilance centres. As of May 2010, Vigibase contained 35 million case reports. We searched the Vigibase extraction of Dec 2011 for dysphonia. Reporting odds ratios (ROR) were calculated for the occurrence of dysphonia compared with other adr for bevacizumab and paclitaxel.

**Results:** In total, 9,323 pts (28%) reported dysphonia during treatment with bevacizumab and 5,909 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 25,111,681 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 angioedema 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.

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**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 innovations. The EFA displays the trade-off (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 had undergone HTA in the UK. Reports were reviewed 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 (ΔOS) 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 frontier line are paclitaxel albumin (ΔOS of 2.3 months at £20,201), gemcitabine (ΔOS of 2.8 months at £60,201) and trastuzumab (ΔOS of 4 months at £169,369); all received positive recommendations. Lapatinib (ΔOS of 1.9 months at £108,180), bevacizumab (ΔOS of 1.7 months at £36,560), eribulin (ΔOS of 2.5 months at £48,343) and fulvestrant (ΔOS of 2.3 months at £24,801) 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.

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**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/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, Diarrhea, Fatigue, Pain, Nausea, Neupathry, Neuropenia 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 hospitalized due to infection, $3,211 to avoid severe nausea, $2,764 to avoid severe tingling in hands and feet, $2,652 to avoid severe fatigue, $1,853 to avoid obvious hair loss and $1,456 to avoid severe pain. The most important attributes when selecting a therapy for MBC in terms of average utility were neutropenia, 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 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 to choose.

Disclosure: D. Lalla: Dr. Lalla is an employee of Genentech, which funded this analysis. M. Bramley: Dr. Bramley is an employee of Genentech, which funded this analysis. R. Carlson: Dr. Carlson 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.

# 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 a prospective phase II trial to evaluate the activity and safety of such an option as 1st line treatment of HR+ MBC, an analysis of QoL, patient compliance, and prognostic value of tumour markers monitoring was also performed.

Patients and methods: Pts with HR+ MBC relapsing after Tamofoxen and/or Aromatase Inhibitors adjuvant therapy received Fulvestrant 500 mg i.m. on day 0, then 500 mg on days 14-28 and every 28 days thereafter, until disease progression or unacceptable toxicity or patient refusal. Changes in cancer antigen 15.3 (CA 15.3) and carcinoembryonic antigen (CEA) were monitored monthly after treatment; QoL and treatment tolerability were assessed every 2 cycles.

Results: Forty-eight consecutive pts were enrolled and treated. The overall clinical benefit rate was 68%, with 3 (6%) complete (CR) and 12 (25%) partial responses (PR), and 18 (48%) stable diseases (SD) lasting ≥24 weeks. The median PFS was 11 months, median duration of treatment was 9 months. Toxicity was manageable, also in pts given long-duragion therapy (>18 months). Analysis of QoL by QLQ-BR23 showed a deterioration over treatment, while the tumour assessment documented an improvement of tolerability of treatment compared with their previous adjuvant hormone therapy. In pts achieving a CR or PR both CA 15.3 and CEA serial levels decreased significantly over the first 4 months of treatment, while in long-lasting SD a statistically significant difference from baseline was reached within a median of 8 months.

Conclusions: Our results confirm the known activity and tolerability of Fulvestrant 500 mg as 1st line therapy for HR+ MBC, with good patient compliance over long-term treatment and preservation of QoL. Of interest, changes in tumour markers resulted significantly predictive of treatment activity in responding pts, in contrast with previously reported data with Fulvestrant 250 mg, reflecting and additional difference between the two drug dosages.

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 efficacy 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, 95%CI 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 0.67, 95% CI 0.62-0.94).


Disclosure: P. Turner: Pauline Turner is a full-time employee of AstraZeneca and is a stockholder in Astra Zeneca. 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.

FULVESTRANT (FUL) PLUS ENZASTAURIN (ENZA) VS FUL 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 PCK 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 Fuls 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 CR, progression-free survival (PFS) and safety. 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 no 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 41.5%, respectively) and numerically more Grade 3/4 TEAES in the Enza arm were more frequent (17.9%, 9.1%, and 5.2%, respectively). Most frequent Grade 3/4 TEAES in the BID arm were fatigue (n [%]) (4 [10.3%]), dyspnea (2 [5.1%]) and nausea (2 [5.1%]).

Number of responders, CBR = complete response + partial response + stable disease Addition of Enza to Ful does not improve disease outcome in pts with locally advanced or MBC after progression on AI.

Disclosure: K. Mansouri: K. Mansouri is an employees of Eli Lilly and Co. L. Cirri: L. Cirri is an employees of Eli Lilly and Co. P. Shi: P. Shi is an employees of Eli Lilly and Co. O. Hamad: O. Hamad is an employees of Eli Lilly and Co. All other authors have declared no conflicts of interest.

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

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Introduction: P is a humanized mAb that inhibits heterodimerization of HER2. P and T bind distinct HER2 epitopes, and due to their complementary mechanisms of action they provide a more comprehensive blockade of HER2 signaling. Based on preclinical efficacy models, a steady-state trough P concentration (Cthest) of 20 μg/ml was selected as target in pts. CLEOPATRA is a Phase III study comparing P+T vs D placebos (D) in HER2-positive IIL MBC (Baselga NEJM 2012). The objectives of the substudy reported here are to characterize the PK of P in the presence of T and D, and to explore potential drug – drug interactions.

Methods: P/Pla (840 mg loading, 420 mg maintenance) was administered on Day 1 of each cycle; T (8 mg/kg loading, 6 mg/kg maintenance) was administered on Day 2 of Cycle 1 following T and on Day 2 of Cycle 2 or D, and to explore potential drug – drug interactions. P is a humanized mAb that inhibits heterodimerization of HER2. P and T bind distinct HER2 epitopes, and due to their complementary mechanisms of action they provide a more comprehensive blockade of HER2 signaling. Based on preclinical efficacy models, a steady-state trough P concentration (Cthest) of 20 μg/ml was selected as target in pts. CLEOPATRA is a Phase III study comparing P+T vs D placebos (D) in HER2-positive IIL MBC (Baselga NEJM 2012). The objectives of the substudy reported here are to characterize the PK of P in the presence of T and D, and to explore potential drug – drug interactions.

Patients were heterogeneous for tumor burden at diagnosis and included anthracyclinc-taxane and trastuzumab-based neoadjuvant treatment. 14 out of 31 patients achieved pathological complete remission. Ki-67 and HER2 Ki score of 500 mg 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 Ki score (p = 0.03) and an inverse correlation between age and HER2 Ki score (p = 0.03). The Ki-67 and HER2 Ki score maintained significantly 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.

Mean Median 25% CI 75% CI

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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. pTEN loss, pAKT and HER-3 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 pAKT 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 44-63.5 years). Results of immunohistochemical staining are reassembled in the table.

Disclosure: All authors have declared no conflicts of interest.
Background: For more than ten years, treatment of HER2-positive mBC patients (Pts) is based on T plus taxane in 1st line therapy. So far, in numerous studies, we have observed few subsets of Pts (long-term responders) who have not experienced disease progression for several years after T-based regimen in 1st line treatment. This study aims to characterize these Pts in the daily practice from a clinical and biological perspective.

Material and methods: This is an ambispecifich French multicentre non-interventional study. Eligible Pts were women aged ≥18 years with HER2-positive mBC or ABC treated with T at 1st line and who were progression-free for at least 3 years after starting T. The primary objective was to describe the clinical and tumor characteristics of these Pts. Progression Free Survival (PFS), OS, treatment discontinuation and safety were also collected. An exploratory biomarkers analysis is planned on tumor tissue samples. Here we present some preliminary results based on the interim analysis performed at the end of inclusions.

Results: 159 Pts were enrolled in 2011 and 110 Pts were eligible for data analysis. Median age was 59 years [34-95]. Tumor characteristics were: invasive ductal carcinoma for 96 Pts (88%), positive hormonal receptors in 63 Pts (58%). At initial diagnosis, presenting stages were I-II for 52 Pts (50%). 36 Pts (33%) had a mBC de novo or an aBC. The main metastatic localisations were bone, liver and lung in 51 (47%), 35 (32%) and 22 (20%) Pts respectively. Median T treatment duration was 4.1 years [0.8 - 11.0] in 1st line. T was associated with a taxane-based chemotherapy in 86 Pts (78%). Median PFS was 6.4 years [4.9 - 11.0]. Median OS was not reached. 13 retrospective adverse events related to T (cardiac or leading to discontinuation) were reported. None of these were serious.

Conclusions: In this long PFS population treated with a T-based treatment in first line 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 consultant. P. Beuzeboc: Roche consultant. D. Coëffet: 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 gancitabine 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.

346P
HGFK1 INHIBITS BONE METASTASIS IN BREAST CANCER THROUGH THE TAK1/P38 MAPK SIGNALING PATHWAY

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Background: Breast cancer metastasis to bone represents a devastating complication of advanced breast cancer, frequently resulting in significant increases 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 (HGF/K1) 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).

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.

349P
IMPACT OF DIABETES AND HYPERGLYCEMIA ON SURVIVAL IN ADVANCED BREAST CANCER PATIENTS

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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 recurrent 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 = 0.001). 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 1.5 (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.
MTOR EXPRESSION IN BASAL-LIKE BREAST CANCER AND THE ABILITY OF EVEROLIMUS TO INHIBIT THE INVASION CANCER CELL CAPACITY

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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 breast 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 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 aggressiveness. 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 basal-like breast cancer cells thus antagonising the antitumour activity of mTOR inhibitors in breast cancer models.

Disclosure: All authors have declared no conflicts of interest.

THE PROGNOSTIC MEANING OF PROTEIN TYROSINE PHOSPHATASE NON-RECEPTOR TYPE 12 (PTPN 12) EXPRESSION LOSS IN BREAST CANCER PATIENTS

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Background: Recent preclinical studies showed that protein tyrosine phosphatase non-receptor type 12 (PTPN 12) appears to be an important tumor suppressor in breast cancer. However, the clinical and prognostic significance of PTPN 12 expression in breast cancer patients has not been elucidated yet.

Methods: PTPN 12 expression status was assessed for 183 patients who underwent curative surgery for operable breast cancer between May 2000 and August 2003, using immunohistochemical (IHC) assay of tissue microarray. Clinicopathologic characteristics, and expression status of ER, PR, EGFR, HER-2 were compared according to PTPN 12 expression status. The prognostic significance of PTPN 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.

Results: Loss of PTPN 12 expression was observed in 35.5% of the patients in this study. No significant difference were found in the clinicopathological characteristics, and expression status of ER, PR, EGFR, HER-2 were compared according to PTPN 12 expression status. The prognostic significance of PTPN 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.

Conclusion: PTPN 12 expression loss was associated to poor disease free survival in HER2 negative and EGFR negative breast cancer patients in this study. Our findings suggests that PTPN 12 may have a prognostic meaning predicting recurrence in HER2 negative and EGFR negative breast cancer patients, and future validation is warranted.

Disclosure: All authors have declared no conflicts of interest.
FIRST REPORT OF LONG-TERM RESPONDERS TO FIRST-LINE BEVACIZUMAB (BEV) COMBINED WITH CHEMOTHERAPY IN TWO INDEPENDENT COHORTS OF HER2-NEG METASTATIC BREAST CANCER PATIENTS (PTS) WITH HORMONE RECEPTOR –POSITIVE (HR+) AND TRIPLE-NEGATIVE (TN) TUMORS

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1Breast Cancer Unit, Department of Medical Oncology, Institut de Canc, Villejuif Cedex, FRANCE; 2Gérontologie, Centre Français Baclesse, Caen, FRANCE; 3Service Oncologie Médicale, C.H.U. Jean Minjoz, Besancon Cedex, FRANCE; 4Oncologie, Poit Saint Rémy, Clermont Ferrand, FRANCE; 5Department of Medical Oncology, Clinical Trial Unit, Institut Curie, Paris, FRANCE; 6Oncologie, Centre de Radiothérapie Saint-Vincent, Saint-Germain, FRANCE; 7Oncologie Médicale, Hôpital Augustin Morvan, Brest, FRANCE; 8Oncologie Médicale, Hôpital Saint-Louis, Paris, FRANCE; 9Medical Affairs, Roche SAS, Boulogne Billancourt, FRANCE; 10Oncologie Médicale, Clinique Hartmann, Neudorf-Seine, FRANCE

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-1 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 results will be presented at the meeting. In the HR+ cohort (n = 132), 28.1% of the pts had a disease-free interval <12 months, 46.7% had >3 metastatic sites at diagnosis, and more than 1/3 of the patients had lung and/or liver involvement. In association to 1st line BEV, 93.2% had received a taxane as initial 1st line chemotherapy, 76.2% had received previous endocrine therapy and 4.2% had received previous chemotherapy (capecitabine). Best response obtained in 1st line was a complete response or partial response for 84,6%. With a median follow-up of 33 months, median PFS was 27.4 months (95% CI [23.2-33.8]). Overall survival data were immature as at 84.8% of the pts were alive at inclusion. The most common BEV related grade 3/4 adverse events were hypertension (7.5%), bleeding (1.9%), proteinuria (1.3%) and congestive heart failure (1.3%).

Conclusion: Prolonged BEV-containing therapy in this HR+ cohort is of interest and suggests that some pts achieve sustained disease control with limited side effects.

Disclosure: V. Déras: Advisory boards and Symposium participation. H. Simon: Member of an advisory board: Roche Maitology Group. N. Mesnard: Roche employee. E. Antoine: Membership of an advisory board. All other authors have declared no conflicts of interest.

NON PEGYLATED LIPOSOMAL DOXORUBICIN BEYOND THE FIRST LINE TREATMENT OF METASTATIC BREAST CANCER PATIENTS: A RETROSPECTIVE ANALYSIS

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Background: The aim of this retrospective study was to access the benefit of a non-pegylated liposomal doxorubicin (NPLD) treatment beyond the first line therapy in patients with metastatic breast cancer (MBC) after previous exposure to an anthracycline containing regimen.

Patients and methods: A pharmacy prospectively collected database in the Franche-Comté region, was used to identify a cohort of patients with MBC treated by NPLD regimen between 2003 and 2010. In total, 140 patients were included in the analysis. Progression-free survival (PFS) was chosen as the primary efficacy endpoint. Cox proportional hazard models were fitted to identify factors that could influence both PFS and overall survival (OS) length. Survival data were computed according to Kaplan Meier method.

Results: Primary tumours characteristics were oestrogen receptor-positive, progesterone receptor positive and HER2 positive in 77%, 63% and 20% respectively. Median PFS length was 4 months [95% CI: 2-5] and 33% of patients experienced a PFS longer than 6 months. Overall response (OR) was observed in 27 patients (19.3%, 95%CI [10.2-28.4]). Median OS after NPLD was 13 months [95% CI: 10-14]. In multivariate analysis, prognostic factors significantly related to longer OS from NPLD first exposure were age younger than 50 years old (HR = 0.57 [0.35-0.93], p = 0.02) and HER2 positive tumour (HR = 0.53 [0.30-0.95], p = 0.03). 17 patients

Table: 356P

<table>
<thead>
<tr>
<th>Tissue, n (%)</th>
<th>Initial BEV–DOC phase (N = 284)</th>
<th>Maintenance BEV + CAP phase (N = 183)</th>
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<tr>
<td>Discontinued therapy</td>
<td>99 (35)</td>
<td>134 (73)</td>
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<td>Grade ≥ 3 AEs, n (%)</td>
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AE = adverse event; TE = thromboembolic event

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Research Centre, New Delhi, INDIA; 3Department of Breast Cancer, Affiliated Hospital of Academy of Military Medical Sciences, Beijing, CHINA; 4Global Medical Affairs Biometrics, F Hoffmann-La Roche Ltd, Basel, SWITZERLAND; 5Oncoteca DI Oncologia Medica, Centro Oncologico ASST Trieste, Università di Trieste, Trieste, ITALY

BACKGROUND

Combining BEV with 1st-line chemotherapy (CT) significantly improved progression-free survival (PFS) and response rate (RR) vs CT alone in 3 randomised phase III trials (E2100, AVADO, RIBBON-1). In AVADO, DOC 100 mg/m² was given for a median of 5.5 months (maximum 9 cycles), after which BEV 15 mg/kg was continued as a single agent. IMELDA was designed in the context of BEV–DOC approval to determine whether efficacy is improved by adding CAP to BEV maintenance therapy after discontinuing DOC.

Methods: Eligible pts had HER2-negative measurable mBC, ECOG PS 0/1, had received no prior CT for mBC and were eligible for taxane-based CT. After initial 1st-line therapy with 3–6 cycles of BEV–DOC, pts free of progressive disease (PD) were randomised to BEV alone or BEV–CAP (BEV 15 mg/kg q3w; CAP 1000 mg/m² bid d1–14 q3w) until PD. The primary endpoint is PFS; secondary endpoints include safety, RR and overall survival.

Results: Between June 2009 and March 2011 (when enrolment to the study was terminated prematurely after withdrawal of BEV–DOC regulatory approval), 284 pts received BEV–DOC. Median age was 52 years (range 24–80), 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. Gilgoror: 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, BMS and Sanofi-Aventis. U. Freudensprung: UF works as a Contractor for F Hoffmann-La Roche Ltd. G. Mustache: GM has acted as a Consultant for Roche, Agenda, Celgene, Novartis, Merck, Glaxo, Eisai. All other authors have declared no conflicts of interest.

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(12.1%) discontinued NPLD treatment due to toxicity. In those, 9 (6.4%) patients experienced cardiac toxicity (grade 2 or 3). There were 2 (1.4%) deaths related to cardiac toxicity.

Conclusion: Re-challenge by an anthracycline-containing regimen should be considered in patients with MBC taking into account this encouraging ORR and the length of PFS and response duration. However cardiac safety of patients must be carefully investigated during the treatment taking into account the number of treatment cessation due to cardiac damage. Of interest the subset of patients with HER2 positive tumour seemed to highly benefit from the NPLD. This finding emphasizes the sensitivity to anthracycline in this subset of HER2 positive tumours and oncologist should not forget anthracycline containing regimens as a possible option in MBC after failure to numerous lines including chemotherapy and HER2 targeted agents.

Disclosure: All authors have declared no conflicts of interest.

PHARMACOKINETICS OF ERIBULIN MESILATE IN COMBINATION WITH CAPECITABINE IN PATIENTS WITH ADVANCED/METASTATIC CANCER: RESULTS FROM A PHASE IB DOSE-ESCALATION STUDY

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Background: Eribulin is a microtubule dynamics inhibitor EMA approved for certain patients (pts) with locally advanced and metastatic breast cancer (MBC) who have received ≥2 prior chemotherapy 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.

Methods: Pts received eribulin mesilate (2–5–min IV) by Schedule 1 (1,2,1.6 or 2.0 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-D4 followed by 14 days. To assess PK and drug-drug interaction of eribulin, capecitabine and capecitabine metabolites in Cycle 1 and 2, samples were taken on D1 (pre-, 0.25, 0.5, 1, 4, 6 and 8 h post-dose), any time on D2–3 and D4–6, and D8 (Schedule 1: pre-, 0.5–1.4 and 6 h post-capecitabine; Schedule 2: pre-dose). PK was examined by non-compartmental analysis, and capecitabine by 2-lead ECGs at screening, D1 (pre- and 4 h post-dose), D2–3, D8 and D15. Correlation of eribulin and capecitabine plasma concentrations with change from baseline (Δ) QTc was explored.

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 3 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, exposure to eribulin and metabolites was variable and independent of schedule. Co-administration had no effect on 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: consultant/advisory role (Eisai) and honoraria/speakers bureau (Eisai). 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. Reyderman: 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.

ACTIVITY AND SAFETY OF A COMBINATION OF EPIRUBICIN, DOCETAXEL AND CISPLATIN AS NEOADJUVANT TREATMENT FOR LOCALLY ADVANCED BREAST CANCER (LABC): A PRELIMINARY REPORT

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Purpose: This study compared six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) with a sequential regimen of three cycles of FEC followed by three cycles of docetaxel (FEC-D) as adjuvant treatment for women with node-positive or T3 or T4 breast cancer.

Patients and methods: Between January 2006 and January 2010, 657 patients with operable breast cancer were randomly assigned to either FEC every 21 days for six cycles, or three cycles of FEC followed by three cycles of docetaxel (FEC-D) as adjuvant chemotherapy. The most common side effect was myelotoxicity. WHO grade 4 neutropenia developed in 30 (73%) patients. No recurrence was observed in any patient after a mean follow-up of 17 months (13-21 months).

Conclusion: Although our study group was small and the follow-up period relatively short-term, the considerably high rates of CR in this preliminary series suggest that ETC regimen may be a promising option in neoadjuvant treatment of LABC.

Disclosure: All authors have declared no conflicts of interest.

SEQUENTIAL DOCETAXEL AS ADJUVANT CHEMOTHERAPY FOR NODE-POSITIVE OR/T3 OR T4 BREAST CANCER: CLINICAL OUTCOME (MANSOURA UNIVERSITY)

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Purpose: The aim of this study was to evaluate activity and safety of a combination of epirubicin, docetaxel and cisplatin (ETC) in the neoadjuvant setting.

Patients and methods: Forty-two patients with LABC (T2-T4, N0-N2, M0) were enrolled the study from March 2010 to April 2011. These patients received epirubicin (60 mg/m² intravenously [I.V.] day 1), docetaxel (60 mg/m² I.V. day 1) and cisplatin (60 mg/m² I.V. day 1) every 21 days for at least 4 cycles, plus a final 2 additional cycles. Upon completion of therapy, the primary tumor was resected when not contraindicated. The primary endpoint was the pathological complete response (pCR) rate; secondary endpoints included response rate and toxicity.

Results: Median patient age was 48 years (range, 23-73 years). Median tumor size was 3.2 cm. Thirty-seven patients (88%) received 6 cycles of ETC. The overall clinical response rate was 78.6%. Twenty of 42 patients (47.6%) achieved a complete pathological response (pCR). All tumors became operable after neoadjuvant chemotherapy. Although our study group was small and the follow-up period relatively short-term, the considerably high rates of CR in this preliminary series suggest that ETC regimen may be a promising option in neoadjuvant treatment of LABC.

Disclosure: All authors have declared no conflicts of interest.
Conclusions: PET assay after 2 cycles of PCT correctly predicted pN0 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. Discourse: All authors have declared no conflicts of interest.

363P BREAST CANCER RECURRENCES AT THE CHEST WALL (BCRW) WHEN STANDARD TREATMENTS (TX) HAVE FAILED: LYSO-THERMOSSENSITIVE LIPOSOMAL DOXORUBICIN (LTD) + MILD LOCAL HYPERTHERMIA (MLH)

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Background: BCRCW has a poor prognosis, with disfigurement, pain, and restriction of movement. Study treatment consisted of LTD that releases high concentration 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 LTD, and promotes Dox tumor uptake. Methods: We conducted a phase I study of LTD + 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 LTD/MLH Tx every 21 days. Dosing cohorts started at 40 mg/m² and stopped escalation at 50 mg/m². LTD was infused IV over 30 minutes (min); 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 anthracyline (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 (49.5%) 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 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: LTD + 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.
clinically and pathologically (Lavrikova’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 as 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 more frequently observed in patients with N2 status than with N0 (p = 0.006) and N1 (p = 0.009). Her-2 + tumors showed lower degree of pathomorphism than 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.
papers 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.

BEING THERE FOR WOMEN WITH METASTATIC BREAST CANCER: A PAN-EUROPEAN PATIENT SURVEY

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Background: This two-part European patient survey was designed to help identify needs of women with metastatic breast cancer (MBC), through understanding their experiences of diagnosis, treatment and care.

Material and methods: The survey, initiated in March 2011, was conducted using a two-stage methodology. The first stage collected views on standards of MBC care and unmet needs of patients from 47 MBC-related patient groups in 8 European countries. This information was used to develop the second stage patient survey. The patient survey was designed to capture personal experiences of MBC diagnosis, treatment, information provision and to determine insights into the ‘trade-off’ between extending overall survival and side effects associated with MBC treatment.

This online survey was open to women with locally advanced or MBC or their carers. All data were collected using anonymised local language questionnaires with responders recruited through local patient groups.

Results: A total of 230 responses were received from 17 identified European countries (94% of whom had locally advanced or MBC, and 6% of whom were adult carers). Although the overall experience of care was generally good to excellent (77%), there were still gaps in terms of treatment choice and information provision. Specifically, findings indicate that 32% of patients perceived treatment choice to be lacking. Overall, results showed that 67% of women with locally advanced or MBC believed life-extending treatment to be important so that they could spend more time with their family and friends; the same proportion judged their treatment worthwhile if it prolonged survival, irrespective of potential side effects. Additionally, 68% of responders would have liked more information about future medical treatments and research, with 57% wishing to receive this information from their oncologist.

Conclusions: These new survey findings highlight the unmet needs of women with MBC in Europe with respect to treatment choice and provision of information. Prolonging survival is a priority for most women, even if associated with toxicity.

Disclosure: All authors have declared no conflicts of interest.

CNS METASTASES, SUBTYPES AND SURVIVAL IN BREAST CANCER: A POPULATION BASED STUDY IN EASTERN SWITZERLAND

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Purpose: To examine tumor characteristics and outcomes associated with central nervous system (CNS) metastases in patients with metastatic breast cancer (MBC).

Methods: Patients listed in the regional cancer registry of St. Gallen-Appenzell with MBC between 2003-2009 were included. Estrogen- (ER), progesterone receptor (PR) and HER2 status were collected from pathology reports. Biologic subtypes were approximated using standard immunohistochemical markers.

Survival status was assessed in January 2012. Multivariate logistic regression models were used to identify factors associated with the risk of developing CNS metastases and with survival >12 months (mt) after the diagnosis of CNS involvement.

Results: Overall, CNS metastases were observed in 170 (22%) of 773 patients with MBC included in the study. In the multivariate model, factors associated with CNS metastases were age <65 (odds ratio (OR) 3.40; 95% confidence interval (CI) 2.32-4.98) and biologic subtype. Compared to patients with ER- and/or PR-positive and HER2-negative tumors, the risk to develop CNS metastases was two-fold higher for patients with triple negative (TN) tumors (OR 2.10; 95% CI 1.17-3.76) and 72% higher for patients with HER2-positive tumors (OR 1.72; 95% CI 1.14-2.61). CNS involvement occurred rarely as first metastatic manifestation. In most patients (n = 137, 81%), CNS metastases were observed metastochronally: in TN disease after a median time of 12 mt, and in the other subtypes after a median time of 19 mt (p < 0.01). Median survival of all patients after diagnosis of CNS metastases was 6 mt (interquartile range 2-14 mt) with no significant differences among subtypes (log-rank test p = 0.28). After diagnosis of CNS metastases, 48 patients (28%) lived longer than 12 mt and 14 (8%) longer than 24 mt. Age <65 (OR 3.50), surgical excision (OR 3.30) and radiotherapy of CNS (OR 4.10) were independently associated with survival >12 mt.

Conclusion: Patients with TN or HER2-positive tumors showed increased risk for CNS metastases. However, after diagnosis of CNS metastases only surgery and radiotherapy favorably influenced survival. New approaches to control CNS disease in young patients with these subtypes need to be developed.

Disclosure: All authors have declared no conflicts of interest.

MALE BREAST CANCER: THE EXPERIENCE OF AN ONCOLOGICAL CENTER

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Background: Male Breast Cancer (MBC) is a rare condition comparing to Female Breast Cancer (FBC). Because of that, its understanding is weak and its treatment has often been extrapolated from FBC in spite of many important differences already suggested by many studies. Objective: To evaluate risk factors, recurrence and survival in male breast cancer.

Material and methods: Review of clinical files of 115 male patients diagnosed with breast cancer and treated in the IPO- Porto from 1976 to 2011. Evaluation of demographic, tumor- related variables, treatment and survival were done. Survival curves were calculated by the Kaplan-Meier method and compared using the log-rank test. Statistical significance was set at p < 0.05.

Results: The median age of the treated patients was 63 years-old (33-94 years-old). Prior or active tobacco use was observed in 36,1% and alcohol use 44,8%. Over-weight or obesity was registered in 66,7% of the cases. 48,8% of the patients reported a positive family history of cancer (17,4% of breast or ovarian cancer in a first-degree member), 8,3% were BRCA2 positive and 12,5% developed secondary malignancies. Most tumors were located in left breast (55,7%), were ductal carcinomas (91,2%), G2 (54,6%), stage III (46,4%) or II (26,8%), with positive hormonal receptors (90,6%) and with lymphovascular invasion (67,4%). The majority of patients underwent surgery (95,6%), followed by chemotherapy, radiotherapy and hormone therapy (26,1%) or radiotherapy and hormone therapy (26,1%). 32,4% relapsed, in visceral non-hepatic sites (32,4%) or hepatic (17,6%). Median recurrence-free survival was 27,3% at five years. 5-years cancer- specific survival was 71,3%. In univariate analysis were prognostic factors the advanced stage (p < 0.001) and hepatic recurrence versus other sites (p = 0.014). The last factor was the only independent prognostic factor. 33,9% of the patients died for breast cancer.

Conclusions: This study confirmed many differences between MBC and FBC namely: older age at diagnose, high prevalence of family history, BRCA2 mutations and second malignancies. Cancer-specific survival is similar when adjusted to other factors such as stage and local of recurrence.

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 analyses of women with breast cancer diagnosed 1975-2006 and treated at Guy’s Hospital London, whose details were prospectively updated regularly till end 2010.

Results: Of 7064 women, 1599 (22%) developed BM by end follow-up (mean 8.4 years); 2254 (32%) were diagnosed with breast cancer <50 years, and 4810 (68%) ≥50 years; 735 (14.4%) were classified as grade I, 2303 (45.3%) grade II and 2049 (40.3%) grade III. Grade III, 37.8% were estrogen receptor (ER) -ve and 3982 (72.2%) ER +ve. Of all BM, 535 (33.7%) patients were in group i; 871 (54.8%) in group ii and 183 (11.5%) in group iii. Incidence of all BM within 0-3 years from breast cancer diagnosis was highest in 1980 (64/1000 person years) and lowest in 2006 (11/1000 person years), with the decline most pronounced 1985-1990. Cumulative incidence of BM after 5 years follow up was highest in 1976-1982 (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.Risk of BM was significantly influenced by: calendar period of breast cancer diagnosis, HR was 0.77 (0.68-0.86) 1983-1988; 0.46 (0.40-0.54) 1990-1997 and 0.33 (0.28 0.40) 1998-2006, all vs 1975-1982; tumour grade, HR 1.23 (1.08 - 1.40) grade 3 vs 1-2; nodal status, HR 1.88 (1.60-2.21) 1-3 nodes vs 0 nodes and 3.95 (3.36-4.64) 4+ nodes vs 0 nodes; and tumour size, HR 2.00 (1.75-2.29) 2-5 cm vs <2cm and HR 3.21 (2.73-4.01) 5+ cm vs <2cm. Amongst women with BM 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 2.3 years in group i compared with 0.96 years in group ii and 0.91 years in group iii.

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.

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 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 were tested by the χ2 and Fisher’s exact 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 (p= 0.15; P= 0.70; y2= 1.15; P= 0.28) and T6235C (y2= 2.65; P= 0.10; y2= 1.93; P= 0.16) loci. The frequency of CYP1A1 A4889G + GG genotypes was higher in patients than in controls (29.0% versus 23.2%, P= 0.043; PA= 93.0%). Carriers of the variant G allele were under a 1.5-fold (95% CI: 1.14-1.97) increased risk for BC than those with the wild AA genotype. CYP1A1 4889AG + GG genotypes were more frequent in BC patients with histological grade III tumors when compared with those with grades I + II tumors. The CYP1A1 4889AG + GG genotypes was also more 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.

Conclusion: 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 chemo-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, anthraccline 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 chemotherapy. Among positive samples, 89% of patients showed drug sensitivity and rest were found to be anthraccline 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 5.16% (for a representative case).
Thus the primary aim to target BCSCs to control metastasis and relapse of disease was somewhat obtained. We further plan to correlate ratio of selected markers present in patients in pre- and post-chemotherapeutic condition with time to recurrence, mortality and progression of survival.

Disclosure: 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 unknowable. 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 and estradiol were measured. DNA was isolated from peripheral blood lymphocytes for genotyping of Aurora A at the (Phe)208Tyr, (Phe)246Tyr 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 9.9fold increased risk of developing BC compared with those with the Phe/Phe genotype (OR 9.95% CI 1.12-77.69). 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 Ile/Ile genotype compared with positive ER &PR patients (34.8% vs 5.4%). Serum estradiol showed significant increase in the positive patients (34.8% vs 5.4%).

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 thirds 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 (mammography or 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 (PR)] to the initial anthracycline based chemotherapy was 63%, CR was 0%. Resectability rate after 1st line NACT was 77%. Pathological CR (pCR) rate 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.

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.

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 wich 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 (3pts, 23%) vs A (2 pts, 10%) (p = 0.0003). Most common recurrent sites were local (18) and bone (9). Mean OS was 4.5 years (95% IC 3.6 – 5.4); 3 (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-nPCT, were carried out color-coded US in the triplex mode scanning and power doppler.

3 courses of AC-nPCT

Luminal A Luminal B HER2(+) Triple-negative

| T2N0M0 | 3 | 1 | - | 2 |
| T2N1M0 | 3 | 2 | 2 | 2 |
| T3N0M0 | 3 | 4 | 1 | 3 |
| T3N1M0 | 1 | 1 | 2 |
| Average systolic blood flow velocity, ACBF (cm/sec) | 14.2 ± 2.6 | 15.9 ± 3.9 | 14.6 ± 2.5 | 16.2 ± 2.8 |

Measurements were made of resistance index (IR), pulsating index (IP).

Results: ACBFV is increased and corresponds to the malignancy process, higher rates were in patients with the triple-negative breast cancer (16.2 ± 2.8 cm/sec) and luminal B 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-nPCT was higher in patients with the luminal B type (CR – 5, PR – 3). In patients with triple-negative BC effect of nPCT was worse, despite the high rate of BF in the tumor (PR – 1, stabilization – 6, 1, stabilization –
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 ACBFV, IR, IP, and the frequency of CR + PR to NCT 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 (O/O) 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 neoad.

Results: From 2004 to 2011, 108 patients received NAC. Based on their weight and height at baseline we divided them 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 in group 2 (p = 0.012). There were no differences at cTNM stage in both groups (p = 0.695). There was a pCR in 18 patients (35.3%) from group 1 vs 11 patients (20.3%) from group 2 (p = 0.399).

Hormonal receptor negative tumors were more frequent in group 2 [27 (71.1%) vs group 1 [11 (28.9%)] (p = 0.005). Likewise the triple negative receptor status was more frequent in group 2 [20 (63.3%)] vs group 1 [4 (16.7%)] (p = 0.001).

Thirty-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 (19.3%) from group 2 (p = 0.061). O/O patients were less likely to have pCR (OR 0.43 CI 95% 0.18-1.0). Median follow-up was 26 months (7-84). Twelve patients relapsed (3 local, 8 systemic or both 1). There were more relapses in group 2 (p = 0.012). There were no differences at cTNM stage in both groups (p = 0.695). There was a pCR in 18 patients (35.3%) from group 1 vs 11 patients (20.3%) from group 2 (p = 0.399).

Conclusions: O/O is related with lower survival and increased risk of relapse. O/O patients contain a significantly high number of Lymph node metastases (p = 0.001), O/O patients have a high risk for relapse and decreased response to NAC.

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 adriamycine and doxetaxel (AD) and adriamycine, 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 2 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.

Results: 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 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 hepatic toxicity, gastrointestinal toxicity of CR + PR to NCT of luminal B type. 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.
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 < 0.003). 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 and by 80% of government nurses. The age group (>60 years) had less BSE taught and this finding is crucial for public health education as most BC occur after 45 years.

Conclusion: More than 50% of the patients had DELAY 1 and 14% for DELAY 2, 42% were not taught BSE, p < 0.0001. 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 DELAY2. Those in age groups (>40 to 60 years) had less BSE taught and this finding is crucial for public health education as most BC occur after 45 years.

Disclosure: All authors have declared no conflicts of interest.

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 invasiveness. 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 endoxifen (End) and 4OH tamoxifen (4OHMT). 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 MMPs expression was more pronounced at 48 h, when Tam and 4OHMT were found to reduce the levels of both MMP-2 and MMP-9 compared to FL. Following E2 exposure, the maximum autophosphorylation 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 4OHMT and E2 alone.

Conclusions: Our results indicate that the metabolite 4OHMT 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.

Why do women with breast cancer in Sarawak, Malaysia present late?

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CANCER STEM CELL-LIKE CELLS: A THERAPEUTIC MODEL IN BREAST CANCER PATIENTS, WHERE ANY OTHER RECOMMENDED THERAPY HAS 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 hallmarks 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. 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. 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.

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 clinical pathologic 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:

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DIAGNOSIS OF BREAST CANCER METASTASES WITH PET/TC IN PATIENTS WITH ELEVATION OF TUMOR MARKERS: FINAL DATA

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Background: Breast cancer is one of the most common cancers worldwide. PET / CT is more accurate than traditional methods for the detection of distant metastases or local recurrence and enables for early assessment of treatment response in patients after surgery for breast cancer undergoing primary chemotherapy. PET/CT is not considered a conventional examination during follow-up of patients with breast cancer, but recent data indicate its usefulness both in cases of asymptomatic increase of tumor markers that uncertain conventional imaging results. This study investigates the potential role of PET / CT to detect clinically occult metastases in patients with suspected recurrence of breast cancer during follow-up.

Methods: The authors studied 67 patients in breast cancer follow-up after primary surgery and chemotherapy and/or external radiotherapy. All patients were in remission without any other clinical or instrumental signs of relapses, except for the progressive elevation of CA 15.3 and/or CEA, tested during the follow-up. In 47 patients conventional imaging provided uncertain results and increase of CA 15.3 or CEA during follow-up. In 21 cases the anatomical distribution of metastasis sites was in the bone, 16 in the lymphnodes, 11 in the lung and 7 in the liver. We found 2 false-negative, 4 false-positive and 6 true-negative. Conclusions: PET/TC may be more sensitive than the serum tumor markers in detecting relapse of breast cancer. This study demonstrated the clinical utility of tumor marker-guided PET in the follow-up of breast cancer patients.

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 loco regional 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% have good Performans Status 0-1. 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. Loco regional 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 of local 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.
Results: We evaluated 76 pts with MTNBC 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 (39.1%). Hematological toxicity 3 and 4 grade was found in 4 pts (5.3%) and leukopenia in 9 pts (11.8%). Non-hematological toxicity: renal grade 3 awas 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 qIV 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 trastuzumab with weekly vinorelbine (T/VNR), 48 weekly or 3-weekly trastuzumab plus docetaxel (T/Doc), a triple combination of 3-weekly trastuzumab plus oral vinorelbine and capcitabine (T/OSVNR/Cape) as 1st line therapy. Objective RR was 36% (95% CI 25.2-48.2%); median (OS) were calculated by the Kaplan Meier method.

Conclusions: These results confirm the high activity of the tested regimens as 1st line treatment of HER2+ MBC, without significant differences in clinical outcomes, 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 Oral CT is better suited than parenteral CT, compared to subsequent lines and with the combination with trastuzumab.

Patients and methods: 31 pts were enrolled between January 2007 and December 2010. All pts had metastatic disease, a majority (84%) relapsing after anthracyclines (ANT) and/or taxanes (TXN) 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 (CRB) of 68%. In pts pretreated by ORT, ORR was 35% and CRB 70%; Median TTP was 3.7 months (95% CI: 2.2-5.2). Median survival was 16 months (95% CI: 11.4-20.6). 3 pts (10%) developed G 3-4 neutropenia. No events of febrile neutropenia, cardiac, renal toxicities or alopecia were recorded. G 3 thrombocytopenia were reported in 2 pts (6%). 5 pts (16%) developed G 3 nausea-vomiting.

Conclusions: Results show a good efficacy and tolerance profile of OV 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. 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 metastastic 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 adversary effects (n = 11). The response rate of evaluable patients was 37.1% (1.4% 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 testing of 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 CAPCITABINE/VINORELBINE AS SECOND-OR THIRD-LINE TREATMENT IN ADVANCED BREAST CANCER

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Purpose: To compare the efficacy and safety of cisplatin or capcitabine, 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 with 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 RECIST criteria. Toxicity was assessed according to 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 = 0.972). Median NLP 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 NLP and 38.1% in group NXP (P = 0.143). 12.3% grade 3-4 vomiting was seen in group NP and no grade 3/4 vomiting in group NX. 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 NX. 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 reseizitize 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, 1.8-20.2 months). The median number of preceding regimens was 3 (range, 2-8) in metastatic settings. Even 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 as 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.

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more than 6 cycles of capecitabine. 65 (43%) patients commenced treatment at a dose less than 1250mg/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 contribute to increased survival. In addition, these data further support the practice of dose-dense 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 received treatment with BVZ second-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 (88.6%) who progressed. The responses obtained with the previous line of treatment (without BVZ) were: RC: 4 (3.1%), RP: 31 (24.4%), 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: 38 (27.8%), 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 I. Dufrene, A. et al. Impact of bevacizumab therapy on the first line in patients with metastatic breast cancer patients of Breast Cancer Res Treatment 2007:105:1 p. 275

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CSP-Br is a self-reported tool which allows to assess the severity of 57 symptoms using generic QoL questionnaires, the SF-36 and the EQ-5D; symptoms taxane based CT with the previous treatment including CT (89%), surgery (69%), with metastatic breast cancer). Mean age/SD

seven breast cancer patients (Stages I-IV) were included in the study (58% patients FEDERATION Chemistry, Regional Clinical Oncological Center, Khabarovsk, RUSSIAN FEDERATION, 2Department of Biostatistics, National Progrov Medical Surgical Center, Moscow, RUSSIAN FEDERATION, 3Department of Oncology/ hematology, Multinational Center for Quality of Life, St. Petersburg, RUSSIAN FEDERATION)

Quality of life (QoL) and symptom assessment are of increasing importance to evaluate treatment outcomes in breast cancer patients. We aimed to study feasibility 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%), radiotherapy (39%), hormone therapy (24%) or biotherapy (9%). QoL was assessed using generic QoL questionnaires, the SF-36 and the EQ-5D; symptoms – by using Comprehensive Symptom Profile in Patients with Breast Cancer (CSP-Br). The CSP-Br is a self-reported tool which allows to assess the severity of 57 symptoms specific for breast cancer patients. Distribution of patients according to the grades of QoL impairment was analyzed using the SF-36. For comparison of means at different time-points Wilcoxon’s matched pairs test was used. The patients reported the usefulness of PROs tools to facilitate patient physician communication. 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 - mild QoL impairment, 33% - moderate or severe QoL impairment, and 19% - critical QoL impairment. Health index measured by the EQ-5D decreased during the CT cycle and improved by the next CT cycle. The most prevalent and disturbing symptoms were the following: hair loss (>90%), fatigue, feeling of constant tiredness (>80%) and psychological symptoms (>70%). Extreme deterioration of symptom profile and severity was observed in a week after CT cycle completion: the severity of 21 of out 47 symptoms increased significantly (p < 0.05). The usefulness of patient-reported outcome measures to distinguish patients in terms of QoL impairment as well as in terms of severity and number of symptoms experienced was demonstrated. The SF-36, EQ-5D and CSP-Br are robust and feasible tools to measure benefits and risks of breast cancer treatment from patient perspective.

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404 INTRATHECAL TRASTUZUMAB IN THE TREATMENT OF LEPTOMENINGEAL METASTASES FROM HER2-POSITIVE CANCER
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Introduction: Up to 8% of all cancer patients develop leptomeningeal metastases (LM). Median overall survival after diagnosis is approximately 1 month.

Trastuzumab, a monoclonal antibody against the HER2 receptor, is used in the treatment of HER2 positive breast cancer patients. It is still not clear if systemic trastuzumab can penetrate the intact blood brain barrier, because of its high molecular weight. Given intrathecally, trastuzumab could achieve higher concentrations in the cerebrospinal fluid (CSF).

Purpose: Determine safety, response and overall survival of patients treated with intrathecal (IT) trastuzumab, in a single centre population.

Patients and methods: Clinical data of patients treated with IT trastuzumab have been reviewed. Survival was defined as time since beginning of IT trastuzumab until death or last follow-up.

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 adenocarcinoma, S surgery, RT radiotherapy, HT hormonal treatment, sT systemic trastuzumab. LM were confirmed by lumbar puncture in patients B, C and D. In patient A LM were 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 + mehtrotrexate 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 D, 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 large number of patients is warranted and may help identify patients appropriate for this therapy.

Disclosure: All authors have declared no conflicts of interest.

405TIP A PHASE II STUDY OF ALBUMIN-BOUND PACLITAXEL COMBINED WITH EPIRUBICIN AND CYCLOPHOSPHAMIDE AS NEO-ADJUVANT THERAPY IN BREAST CANCER WOMEN
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Purpose: To observe whether the efficacy and safety of Albumin-Bound Paclitaxel has advantage over Cremorphor-Formulated Paclitaxel as neo-adjuvant therapy in breast cancer

Patients and methods: Twenty-six breast cancer patients were enrolled into Albumin-Bound Paclitaxel group. Albumin-Bound Paclitaxel 260mg/m², Epirubicin 60 mg/m², Cyclophosphamide 500mg/m² was administrated as neo-adjuvant therapy. Twenty-six patients who were treated with Cremophor Formulated Paclitaxel 175mg/m², Epirubicin 60 mg/m², Cyclophosphamide 500mg/m² as the control group. The objective observation include the pathologic complete response rates, clinical response rates, safety and toxicity. The PI3K, pAKT, mTOR, BAD protein were examined before and after chemotherapy in two groups.

Results: 34.6% patients (9/26) in Albumin-Bound Paclitaxel group achieved a clinical complete response, this rate was 11.5% higher than control group which rate was 23.1%(6/26). 15.4% patients (4/26) in Albumin-Bound Paclitaxel group achieved a pathologic complete response, this rate was 11.6% higher than control group which rate was 3.8%(1/26). None patients (0/26) in Albumin-Bound Paclitaxel group. Albumin-Bound Paclitaxel 260mg/m², Epirubicin 60 mg/m², Cyclophosphamide 500mg/m² as the control group. The objective observation include the pathologic complete response rates, clinical response rates, safety and toxicity. The PI3K, pAKT, mTOR, BAD protein were examined before and after chemotherapy in two groups.

Conclusions: In Albumin-Bound Paclitaxel group has advantage over Cremophor-Formulated Paclitaxel as neo-adjuvant therapy in breast cancer.
pertuzumab and trastuzumab plus docetaxel in combined treatment with hormone receptor-positive locally advanced or metastatic breast cancer (LABC/MBC): a single-arm, two-cohort, phase II study (VELVET)

Background: The humanised monoclonal antibody pertuzumab binds to the dimerisation domain of HER2, preventing heterodimerisation and downstream signalling. As pertuzumab is directed against a different epitope to trastuzumab, a combination with trastuzumab plus docetaxel, but pertuzumab with trastuzumab has not been tested in MBC. Trastuzumab plus vinorelbine (V) has comparable efficacy to trastuzumab plus docetaxel but with fewer adverse events. VELVET will assess the overall response rate (ORR) of pertuzumab with trastuzumab plus V in first-line treatment of HER2-positive MBC. Administration of pertuzumab and trastuzumab in the same infusion bag will also be assessed.

Methods: VELVET is a multicentre, open-label, two-cohort, Phase II trial in patients (pts) with HER2-positive LABC/MBC not previously treated in the metastatic setting with non-hormonal anticancer therapy. Pts must have LVEF ≥55% and ECOG PS 0-1. All pts will receive pertuzumab and trastuzumab sequentially, and Cohort 2 (next 105 pts) will receive pertuzumab and trastuzumab in the same infusion bag at Cycle 2 onwards assuming Cycle 1 was tolerated. Trastuzumab plus docetaxel will be administered for a maximum of 1 year unless pts discontinue or have disease progression. VELVET will include a treatment group variable and be stratified by whether pts were chosen to receive pertuzumab plus V or not. The primary endpoint is progression free survival (PFS); secondary endpoints include overall response of 70–80% and aiming at a distance from the estimated proportion to the CI limits of 8–11%, a total of 95 pts need to be evaluable per cohort (assuming withdrawal rate ~10%). Primary endpoint is ORR by independent assessment. Secondary endpoints include investigator ORR assessment, time to response, duration of response, PFS, TTP, OS, safety/ tolerability and QoL.

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pertuzumab in combination with trastuzumab and taxane for the first-line treatment of patients with her2-positive advanced breast cancer: a single arm phase IIIb study (PERUSE)

Background: Pertuzumab (P) inhibits downstream signaling of HER2 by preventing its heterodimerization with other HER family members. The epitope recognized by P is a conformational epitope on the external domain of HER2 that is found on HER2:HER2 homodimers in addition to dimeric HER2:HER3 complexes.
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.

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