

biomarkers

1290 CLINICAL RESPONSE TO THE MAGE-A3 IMMUNOTHERAPEUTIC IN METASTATIC MELANOMA PATIENTS IS ASSOCIATED WITH A SPECIFIC GENE PROFILE PRESENT PRIOR TO TREATMENT

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Objectives: Gene expressions profiling by microarrays are used to identify biomarkers predictive of the observed clinical activity of the MAGE-A3 Antigen-Specific Cancer Immunotherapeutic (ASCI) recorded in a Phase II study in metastatic melanoma (EORTC 16032-18031). Clinical activity to MAGE-A3 ASCI treatment in metastatic melanoma patients and a gene signature discriminating between clinical benefit and non clinical benefit patients were previously demonstrated (ASCO 2008). The predictive signature improved significantly the median time to treatment failure (2.3 months in the GS (-) and 10.3 months in the GS (+) population. Here we report on a new improved classifier to select patients with a higher likelihood of clinical response to treatment.

Methods: 75 patients with progressive, unresectable stage III or stage IV M1a MAGE-A3 (+) melanomas, were randomized as 1st line therapy between immunization with MAGE-A3 recombinant protein combined with GSK Adjuvant Systems AS15 or AS02B. Gene expression profiling was performed on tumor biopsies taken prior to any immunization.

Results: Supervised classification experiments were conducted on a subset of 62 patients. A multivariate gene selection process was embedded in the estimation of a mathematical predictive model (linear support vector machine). Using bootstrap resamplings, gene selection was repeated on 30 independent sample sets. A final gene signature of 33 probes was derived from genes appearing most frequently after the various resamplings. The vast majority of the identified genes are immune-related. The final classifier correctly predicts clinical response with 91% sensitivity, 95% specificity and 91% positive predictive value. These performances were estimated on new independent resamplings of the same data.

Conclusions: The gene signatures found in metastatic melanoma patients are strongly correlated with the response to the MAGE-A3 ASCI treatment, reflecting an immune microenvironment in the tumor present prior to any therapeutic intervention. Such signatures and associated classifier could be used to select patients with a higher likelihood of response to MAGE-A3 ASCI treatment.

1300 GENE EXPRESSION SIGNATURE IS A POTENTIAL PREDICTIVE FACTOR FOR EFFICACY OF MAGE-A3 ANTIGEN-SPECIFIC CANCER IMMUNOTHERAPEUTIC (ASCI) AS ADJUVANT THERAPY IN RESECTED STAGE IB/II NON-SMALL CELL LUNG CANCER (NSCLC)

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Objective: A phase II randomized trial in 182 NSCLC patients (pts) with completely resected stage IB or II MAGE-A3 positive tumors showed a strong positive signal for activity of postoperative MAGE-A3 recombinant protein combined with an Adjuvant System (q3w x 5, followed by q3m x 8), compared to placebo. Analysis of gene expression profiling of primary tumors was performed to identify a predictive signature that possibly correlates with clinical activity of MAGE-A3 ASCI treatment.

Methods: Microarray analysis (Affymetrix) was performed on 159 fresh-frozen tumor biopsies (MAGE-A3: 108; placebo: 51; stage IB: 109; stage II: 50). Clinical data on relapse are based on a median follow-up of 44 months.

Results: Study of tumor samples from pts in the placebo arm led to identification of a prognostic gene profile (GP) associated with a high risk of postoperative relapse. The absence of this profile correlated with a very low relapse rate in stage IB pts: placebo 0%; MAGE-A3 4%. In the MAGE-A3 treated pts with the high risk of relapse signature, we compared 10 stage IB pts with recurrence to 10 pts without recurrence. A 25-gene probe predicted benefit from MAGE-A3 treatment. The relevance of this signature was confirmed first on the remaining 139 stage IB and secondly on stage II biopsies. The hazard risk (HR) for disease-free interval in the ASCI arm was 0.57 and 0.78 in the GP+ and GP- groups, respectively, with no impact on relapse rate in the placebo arm. Immune related genes associated to the tumor microenvironment prior to treatment seem critical.

Conclusions: we identified prognostic markers associated with high risk of relapse. Stage IB pts with tumors not presenting this signature have a very low risk of relapse after surgery (<3%). We also described another gene expression signature that may predict clinical response to the MAGE-A3 ASCI treatment. Selection of pts with this signature results in a 2 fold increase in clinical efficiency. This signature is also associated to clinical activity of MAGE-A3 in a Phase II study in metastatic melanoma. Data will be validated in the ongoing NSCLC adjuvant phase III study (MAGRIT).

1310 TP53 AND KRAS MUTATIONS AS MARKERS OF OUTCOME OF ADJUVANT CISPLATIN-BASED CHEMOTHERAPY IN COMPLETELY RESECTED NON-SMALL-CELL LUNG CANCER (NSCLC): THE INTERNATIONAL ADJUVANT LUNG CANCER TRIAL (IALT) BIOLOGICAL PROGRAM

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Background: Adjuvant cisplatin-based therapy improves survival among patients with completely resected NSCLC, but there is a lack of biological predictors of the benefit. We have analysed mutations in TP53 (exons 5 to 8) and KRAS (codons 12 and 13) in archived specimens of patients enrolled in IALT, a randomized trial of adjuvant cisplatin-based chemotherapy against observation.

Methods: Genomic DNA was extracted from 783 paraffin-embedded sections. Mutations were detected by direct sequencing and independently confirmed by a second sequencing for TP53 or by Restriction Fragment Length Polymorphism (RFLP) for KRAS. Prognostic and predictive analyses were based on Cox models adjusted for clinical and pathologic variables.

Results: TP53 mutations were found in 240 of 524 patients (46%) for whom exons 5 to 8 could be entirely sequenced. TP53 mutation status had no prognostic or predictive value for survival in all NSCLC grouped together. However, in non-adenocarcinoma patients, there was a borderline significant interaction between TP53 status and treatment effect on disease-free survival (DFS) (test for interaction TP53 and treatment, p=0.05 and p=0.25 for overall survival (OS)). The effect of chemotherapy was not different in TP53 mutated and wild type patients (p=0.18 for OS and p=0.13 for DFS), but a trend of benefit in TP53 wild type and of harm in TP53 mutated patients were observed. The prevalence of KRAS mutation was 14% (98/718). The prognostic effect of KRAS on DFS was different among the 3 histology groups, adenocarcinoma, squamous cell carcinoma and non-adenocarcinoma/ non-squamous cell carcinoma (p=0.03 for DFS and p=0.31 for OS), with the worst prognostic effect in the latter. Mutation of KRAS was not predictive of the effect of chemotherapy.

Conclusions: Patients with non-adenocarcinoma and TP53 wild type might benefit from cisplatin-based adjuvant chemotherapy, whereas chemotherapy might be harmful in patients with mutated TP53. KRAS mutation might be a biomarker of poor prognosis factor in patients with non-adenocarcinoma. Mutation detection may help in assigning patients to appropriate treatment protocol.

1320 IGF-IR MARKERS IN NSCLC PATIENTS ON ANTI-IGF-IR THERAPY

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Background: The insulin-like growth factor type I receptor (IGF-IR) is potently and specifically inhibited by CP-751,871 (I), a fully human IgG2 subtype monoclonal antibody.

Methods: To assess the safety and efficacy of the combination of paclitaxel (T), carboplatin (C) and I as first-line treatment of advanced non-small cell lung cancer

(NSCLC) patients, blood and tissue markers of the IGF-IR pathway were comprehensively evaluated during the conduct of phase I/II studies. Expression of IGF-IR and its ligands was also assessed in archival samples using tissue arrays and AQUA[®] technology. IGFIR gene scanning was performed. Circulating tumour cells (CTCs) expressing the IGF-IR were enumerated using CellTracksTM. Serum markers investigated included cleaved circulating IGF-IR, total and free IGF-I, IGFBP-3 and acid-labile subunit (ALS). Glycaemia was evaluated using fasting glucose. Human growth hormone (hGH) and insulin levels were determined in a cohort of patients treated with single agent I.

Results: Blood and/or tissue samples were obtained from 190 NSCLC patients. Tissue markers were further investigated in 178 archival NSCLC specimens. Tumour IGF-IR expression was most pronounced in squamous cell carcinoma in concert with a high objective response rate (72%) to TCI in that histology. Two somatic mutations were identified in the beta subunit of the IGF-IR tyrosine kinase domain, one translated into blockade of ligand-induced receptor autophosphorylation in functional studies. CTCs expressing IGF-IR were cleared from blood on TCI treatment and in some patients reappeared on disease progression. Circulating IGF-IR decreased, and IGF-1, IGFBP3 and ALS levels increased in serum in response to I treatment in a dose-dependent manner. Importantly, sustained IGF-1 levels were observed at higher I doses, consistent with systemic IGF-IR downregulation. Manageable and reversible hyperglycaemia (glucose >250 mg/dL) that was independent of glucose levels at enrolment was seen in 11% of NSCLC patients receiving TCI. hGH and glucose oscillated in parallel suggesting that hGH may play a role in the pathogenesis of I-induced hyperglycaemia.

Conclusions: Biomarkers of the IGF-IR pathway are integral to anti-IGF-IR therapy development and monitoring.

breast cancer, advanced

1330 CAPECITABINE VS. CAPECITABINE + TRASTUZUMAB IN PATIENTS WITH HER-2 POSITIVE METASTATIC BREAST CANCER PROGRESSING DURING TRASTUZUMAB TREATMENT – THE TBP PHASE III STUDY (GBG 26 / BIG 3-05)

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Background: There is uncertainty, if trastuzumab treatment should be continued beyond progression (TBP).

Methods: Patients (pts) with HER-2 positive, locally advanced or metastatic breast cancer that progressed during treatment with trastuzumab with or without adjuvant and/or 1st-line metastatic chemotherapy were prospectively randomized to capecitabine (X; 2500 mg/m² on days 1-14, q21) or X plus continuation of trastuzumab (XH; 6 mg/kg, q3w). The primary end point was TTP. With registration of lapatinib, the slowly accruing trial was closed prematurely.

Results: Between 01/04 and 05/07 156 pts (X=78; XH=78) were randomized and stratified according to pre-treatment: taxane/trastuzumab as 1st-line therapy (111 pts), taxanes/trastuzumab as adjuvant therapy (3 pts), trastuzumab alone or without taxanes as 1st-line treatment (42 pts). 75 (48.1%) pts were pre-treated with anthracyclines. 119 (76.3%) showed visceral metastasis. The final analysis after a median follow-up of 15.6 months revealed a time to progression of 5.6 months with 65 events for X compared to 8.2 months with 62 events for XH (HR=0.69; CI: (0.49, 0.99), log-rank test p=0.0404). Brain metastases were observed in 5 (X) and 8 (XH) pts. Overall survival was 20.4 months with 38 events for X and 25.5 months with 33 events in XH (HR=0.77). Response rates were 26.7% (X) and 48.1% (XH) and primary progressions were observed in 22.7% (X) and 15.6% (XH) of patients. Grade III/IV toxicities were (%X / %XH): neutropenia (3.3/6.3), febrile neutropenia (0/0), vomiting (6.0 / 1.6), diarrhea (20.9 / 14.8), mucositis (3.0 / 1.6), hand-foot-syndrome (23.9 / 31.1), nail changes (0 / 4.9), sensory neuropathy (4.5 / 3.3), fatigue (6.0 / 4.9), allergic (3.0 / 3.3), and cardiac (2.9 / 4.9). No therapy related death occurred.

Conclusions: The final results of the TBP study demonstrate a significantly higher efficacy but similar toxicity for continuing trastuzumab beyond trastuzumab progression when 2nd line chemotherapy with capecitabine is initiated.

1340 RESULTS OF FDG-PET/CT AFTER FIRST CYCLE OF NEOADJUVANT CHEMOTHERAPY REFLECT TUMOR CHARACTERISTICS IN BREAST CANCER: POSSIBLE VALUE OF SUV CHANGES DURING CHEMOTHERAPY IN PREDICTION OF TUMOR BIOLOGY AND CHARACTER

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Background: Breast cancer is a heterogeneous disease that shows different biologic behavior according to its subtypes. We analyzed the clinical significance of FDG-PET/CT in terms of clinico-pathologic parameters in stage II and III breast cancer patients who received neoadjuvant chemotherapy.

Methods: Between July 2006 and December 2007, a total of 52 stage II and III breast cancer patients (median age: 46) who received neoadjuvant docetaxel/doxorubicin chemotherapy were enrolled in this prospective study. The patients received three cycles of neoadjuvant chemotherapy followed by surgery and received three more cycles of docetaxel/doxorubicin chemotherapy as an adjuvant. Quantitative FDG PET/CTs were acquired before chemotherapy and after the first cycle of chemotherapy for

early metabolic response prediction. Maximal standard uptake values (SUV_{max}) were compared with clinico-pathologic parameters.

Results: The median follow up duration was 8.6 months. The overall response rate to neoadjuvant chemotherapy was 78.9%. Mean SUV_{max}s were as follows: pre-chemotherapy 7.77 ± 4.45, post-chemotherapy 4.04 ± 2.65. Early metabolic response provided by FDG-PET/CT after one cycle of neoadjuvant chemotherapy was concordant with radiologic response provided by MRI and CT after three cycles of neoadjuvant chemotherapy (P=0.020). Estrogen receptor (ER) negative subtype showed higher pre-chemotherapy SUV_{max} (9.28 vs. 6.66, P=0.045) and change in SUV_{max} than ER positive subtype (5.00 vs. 2.80, P=0.043). In patients with high Ki-67 expression, similar phenomenon was observed that pre-chemotherapy SUV_{max} and change in SUV_{max} were higher than low Ki-67 expression group (9.53 vs. 6.38, P=0.002; 5.18 vs. 2.73, P=0.007, respectively). In triple negative breast cancer (TNBC), pre-chemotherapy SUV_{max} were higher than non-TNBC (10.44 vs. 6.97, P=0.027). Conclusion Early metabolic response using FDG-PET/CT has a predictive value for the assessment of response of stage II and III breast cancer after neoadjuvant chemotherapy. Furthermore, SUV_{max} change in PET after neoadjuvant chemotherapy reflects the subtype of breast cancer.

1350 A NOMOGRAM TO PREDICT SUBSEQUENT BRAIN METASTASIS IN METASTATIC BREAST CANCER (MBC) PATIENTS

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Background: The development of brain metastases (BrM) is usually a terminal event in the clinical course of breast cancer patients with metastatic disease other than brain (MDOB). We hypothesized that occurrence of BrM can be predicted in patients with MDOB, thus allowing preventive intervention such as prophylactic brain radiation.

Method: Patients with MBC treated between 2000 and February 2007 at M. D. Anderson Cancer Center were included in this retrospective analysis. We tested 20 variables and developed a multivariate model to predict occurrence of subsequent BrM and created a nomogram that could be used for individual prediction. The model was cross-validated by bootstrapping and tested in two independent cohorts consisting of 128 patients with MDOB treated at the Cross Institute, Edmonton, Canada, and 91 patients with BrM treated at the Hopital Tenon, France.

Results: Among 2136 patients with metastatic breast cancer, 362 subsequently developed BrM. Young age, histological characteristics, number of metastatic lymph nodes, short disease-free survival, and number of metastatic sites were significantly and independently associated with subsequent BrM. The Nomogram will be presented at the meeting. For each parameter, points are determined on a specific scale, added, and the probability of BrM is read along the Total Points scale. The cross-validation showed that the mean error was 0.8%. In the validation set, BrM probabilities were well predicted with less than 5% difference between the predicted and observed proportions for each quartile.

Conclusion: We developed a robust tool to predict subsequent BrM in patients with MBC. A prospective randomized study is in progress to confirm these results and test the effect of prophylactic treatment.

1360 DOCETAXEL PLUS EPIRUBICIN VERSUS DOCETAXEL PLUS CAPECITABINE AS FIRST LINE TREATMENT IN PATIENTS WITH ADVANCED BREAST CANCER. FINAL RESULTS OF A MULTICENTER PHASE III TRIAL

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Study objectives: To compare the efficacy and tolerability of Docetaxel plus Epirubicin versus (vs) Docetaxel plus Capecitabine as front-line treatment in patients with advanced breast cancer (ABC).

Patients and treatment: Previously untreated patients with locally advanced or metastatic breast cancer were randomized to receive either epirubicin 75 mg/m² plus

docetaxel 75 mg/m² (DE) on day 1 or docetaxel 75 mg/m² on day 1 plus capecitabine 950 mg/m² orally twice daily on days 1-14 (DC) in cycles every 21 days. Patients who had received anthracycline-based adjuvant or neoadjuvant chemotherapy more than one year before were allowed to participate. The primary end point of the study was to compare the time to disease progression (TTP).

Results: A total of 272 women were randomized to DE (n=136) and DC (n=136). All patients were evaluable for treatment toxicity and efficacy. Sixteen vs 18 patients were premenopausal, 15 vs 18 had stage IIIB disease, 3 vs 4 had performance status 2, 37 vs 50 had previously received (neo) adjuvant anthracycline-based treatment on DE vs DC arms, respectively. We observed 15(11%) vs 11(8%) complete responses and 55(40%) vs 61(45%) partial responses for an overall response rate of 51.5% vs 52.9% (p=0.8) in DE vs DC arms, respectively. The median duration of response was 10.4 vs 13.4 months (p=0.9) and the median TTP 10.4 vs 10.5 months (p=0.9) for DE and DC arms, respectively. A total of 803 DE vs 796 DC cycles were administered with 1 vs 0 toxic deaths (p=0.316) due to sepsis. Severe toxicity for DE and DC patients, respectively, included grade 3-4 neutropenia 57% vs 46% (p=0.07), febrile neutropenia 11% vs 8% (p=0.4), hand-foot syndrome 0% vs 3.6% (p=0.02), grade 2-3 anemia 20% vs 7% (p=0.001), diarrhea 6% vs 9% (p=0.2) and asthenia 13% vs 7% (p=0.09).

Conclusions: The DE and DC regimens have similar efficacy but different toxicity. Either regimen can be used as front-line treatment of women with ABC.

137P A RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF LAPATINIB IN COMBINATION WITH TRASTUZUMAB AND AS MONOTHERAPY AFTER PROGRESSION ON TRASTUZUMAB IN HEAVILY PRETREATED ERBB2+ METASTATIC BREAST CANCER (MBC)

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Purpose: Lapatinib (Tyverb/Tykerb®) an oral, small molecule inhibitor of ErbB2 and ErbB1 has a mechanism of action distinct from trastuzumab (T). L showed synergy with T in preclinical models and has established efficacy in patients (pts) with ErbB2+ MBC that progressed on T. Here L was studied alone and with T in pts with ErbB2+ MBC that progressed on T.

Methods: Eligible pts had prior anthracycline and taxane therapy, stage IV BC and progressed recently on prior T-containing regimens. Pts were stratified by hormone receptor and visceral disease status then randomized to receive L (1500 mg QD) or L (1000 mg QD) plus T (2 mg/kg weekly after 4 mg/kg loading dose). Crossover was allowed after progression on L arm. The primary endpoint was PFS; analyses were also conducted in pt subgroups based on metastatic site.

Results: 296 pts were randomized. All pts progressed on prior T; the median number of prior regimens was 6; 73% had visceral disease. PFS is summarized in Table 1. CBR was 24.7% in L+T arm and 12.4% in L arm (OR: 2.2; 95% CI: 1.2, 4.5; p=0.01); although data are not mature, a trend in improved OS was seen in pts treated with L+T (p=0.106). Grade 1/2 diarrhea was higher in the L+T arm; rash was more common in the L alone arm. Asymptomatic decline in LVEF was seen in 4% of L+T and 1.4% of L pts. 1 cardiac related death occurred in the L+T arm. PFS in ITT

Population (N)	HR L+T/L	95% CI	Stratified log-rank p-value
Overall (296)	0.77	0.6, 1.0	0.029
Visceral (211)	0.71	0.5, 0.9	0.014
Nonvisceral (80)	0.97	0.6, 1.6	0.894
Bone (156)	0.70	0.5, 1.0	0.035
Skin (52)	0.56	0.3, 1.0	0.037
CNS (34)	0.62	0.3, 1.2	0.132

Conclusions: L+T prolonged PFS in the overall and in several subgroup populations. This study represents the first randomized, phase III trial investigating the clinical benefit of 2 targeted agents in ErbB2+ MBC and supports the synergy observed in preclinical studies. Clinical benefit was meaningful with the combination and monotherapy despite pts progressing on prior T therapy. Both treatment arms were

generally well tolerated. The role of combined anti-ErbB2 therapy in pts with less advanced disease is tested in the ALTTO study.

138P LAPATINIB PLUS TRASTUZUMAB VERSUS LAPATINIB MONOTHERAPY IN TRASTUZUMAB-REFRACTORY ERBB2+ METASTATIC BREAST CANCER (MBC) PATIENTS (PTS): QUALITY OF LIFE (QOL) ASSESSMENT

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Purpose: Women with ErbB2+ MBC who had documented progression on at least 1 trastuzumab (T)-containing regimen in the metastatic setting were treated in a phase III randomized, open-label study with either lapatinib (L) plus T or L alone. Crossover was allowed after progression on L arm. This analysis focuses on impact of treatments on health-related QOL.

Methods: QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. Outcome measures included FACT-B total score, FACT-general (FACT-G) score and trial outcome index (TOI). Higher scores indicate better QOL. The questionnaire was completed at baseline, weeks (wks) 4, 12, 16, then every 8 weeks and at therapy discontinuation. Changes from baseline scores were analyzed in the ITT population using analysis of covariance with baseline value as a covariate. Analyses based on observed data and also using the last observation carried forward (LOCF) method was performed.

Results: Women with ErbB2+ MBC, a median of 6 previous chemotherapy regimens and who were treated with L+T had significantly prolonged PFS (HR: 0.77; 95% CI: 0.6, 1.0; p = 0.029). The clinical benefit rate (CR+PR+SD for 6 mths) with L+T was 24.7% (12.4% in L arm). Baseline QOL assessment in both arms (N=148/arm) was completed in >95% of patients. Approximately 40% of patients in the L+T arm (36% in L arm) completed the wk 12 assessment; 20% in both arms completed the wk 24 assessment. Differences in adjusted mean change from baseline for L+T vs. L alone for observed data are presented below. Results using the LOCF approach were comparable to results using observed data.

Score	Wk 4	Wk 12	Wk 16	Wk 24
FACT-B	0.4 (-2.9, 3.7)	4.1 (-0.4, 8.5)	0.0 (-6.7, 6.8)	2.5 (-4.9, 9.9)
FACT-G	1.0 (-1.8, 3.8)	4.0 (0.2, 7.7)*	1.6 (-4.2, 7.3)	1.4 (-4.9, 7.7)
TOI	0.5 (-1.8, 2.7)	2.3 (-0.8, 5.4)	0.4 (-3.9, 4.7)	2.7 (-2.4, 7.9)

*p = 0.037

Conclusions: QOL seems comparable for these heavily pre-treated pts receiving combination and monotherapy lapatinib. The addition of lapatinib to trastuzumab prolonged PFS and may improve or maintain near-term QOL, suggesting a meaningful clinical benefit to patients.

139P PAZOPANIB + LAPATINIB IS MORE ACTIVE THAN LAPATINIB ALONE: UPDATED RESULTS FROM A RANDOMIZED STUDY IN PATIENTS WITH ERBB2 POSITIVE ADVANCED OR METASTATIC BREAST CANCER

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Background: Evidence indicates a direct molecular link between ErbB2 amplification and up-regulation of VEGF in ErbB2+ breast cancer. Concurrent over-expression of ErbB2 and VEGF is associated with a poorer clinical outcome than over-expression of either alone. VEGF may also play a role in resistance to ErbB2-directed therapy. These

data provide the rationale for simultaneous blockade of both pathways. Pazopanib (P) is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-kit. Lapatinib (Tyverb / Tykerb[®]) (L) is an oral tyrosine kinase inhibitor of ErbB2 (EGFR) and ErbB2 (HER2). This study (VEG20007) evaluates the efficacy and safety of dual pathway inhibition in patients (pts) with ErbB2+ adv/met breast cancer.

Methods: Eligible pts received no prior chemotherapy or ErbB2-directed therapy for adv/met disease and had measurable disease per RECIST. Cohort 1 (C1) pts were randomized to receive P 400 mg/d + L 1000 mg/d or L alone (1500 mg/d) for 12 weeks. Cohort 2 pts received P 800 mg/d + L 1500 mg/d; this cohort is ongoing. Following disease assessment at week (wk) 12, pts with an objective response could continue on study following re-consent; those with stable disease could continue only where trastuzumab was unavailable. The primary endpoint was progressive disease rate (PDR) at wk 12 in ErbB2 FISH+ pts; these data have been reported elsewhere (ASCO 2008). Overall survival (OS) is a secondary endpoint.

Results: 69 PL and 72 L pts were included in Cohort 1 (77% stage IV, 23% stage III). Pts in the PL arm had a shorter time since initial diagnosis (294 vs. 380 days); baseline characteristics were otherwise well balanced. OS is immature (26 events) but favors PL (adjusted HR 0.56; p=0.1886). 8 C1 pts had received adjuvant trastuzumab: 5 PL pts had a response of SD and 3 L pts had PD by wk 12. The most common adverse events (all grades) (PL vs. L) were diarrhea (67 vs. 58%), rash (28 vs. 29%) and nausea (29 vs. 16%). ALT (61 vs. 37%) and bilirubin (39 vs. 15%) increases were more common on PL.

Conclusion: This is the first Phase II trial to evaluate the combination of 2 oral targeted agents in first-line ErbB2+ adv/met breast cancer. PL is tolerable and has improved activity vs. L. Updates on OS in C1 and activity in pts treated with adjuvant trastuzumab across cohorts will be presented.

140P A PHASE II TRIAL OF TRASTUZUMAB AND PERTUZUMAB IN PATIENTS WITH HER2-OVEREXPRESSION METASTATIC BREAST CANCER THAT HAD PROGRESSED DURING TRASTUZUMAB THERAPY: FULL RESPONSE DATA

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Background: Pertuzumab (P) is a humanised monoclonal antibody that binds to the specific dimerisation epitope of HER2, blocking both homo- and heterodimerisation, so inhibiting key HER signalling pathways that mediate cancer cell proliferation and survival. Trastuzumab (Herceptin[®], H) binds to a different HER2 epitope and xenograft studies indicate that the complementary mechanisms of action of P and H have a synergistic effect when combined. This single-arm, two-stage study evaluates the efficacy and safety profile of H plus P in previously treated patients with HER2-positive metastatic breast cancer (MBC) that had progressed during H as most recent treatment for metastatic disease.

Methods: Eligible patients with measurable disease had no decline in LVEF to <50% during previous H therapy and a baseline LVEF \geq 55% or local parameter \geq lower limit of normal. Patients received H at 2 mg/kg qw (4 mg/kg loading dose [LD]) or 6 mg/kg q3w (8 mg/kg LD) plus P at 420 mg q3w (840 mg LD) starting within 9 weeks of the last dose of H. LVEF was regularly assessed.

Results: 66 patients have been enrolled. Amongst all 66, the most frequent AEs (all grades) were diarrhoea (64%), fatigue (33%), nausea (27%) and rash (26%). There were 4 treatment-related grade 3 AEs (pruritic rash, central line infection and 2 events of diarrhoea), which resolved and treatment was continued; no grade 4 treatment-related AEs were observed. Three patients experienced a fall in LVEF of \geq 10%-points to <50% (1 based solely on local result [patient withdrawn for progressive disease]; and 2 based solely on central results [both LVEFs recovered and patients continued treatment]). Of 66 patients recruited, the overall response rate was 24.2% (CR 5 [7.6%]; PR 11 [16.7%]) and a further 17 patients achieved SD \geq 8 cycles to give a clinical benefit rate (OR and SD \geq 6 months) of 50%. The median PFS was 6 months.

Comment: The combination of H and P is active and well tolerated in patients with HER2-positive MBC that had progressed during prior H therapy. Additional studies are underway to further evaluate the use of P in breast cancer.

141P A PHASE II EVALUATION OF LAPATINIB (L) AND BEVACIZUMAB (B) IN HER2+ METASTATIC BREAST CANCER (MBC)

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Background: In a preclinical HER2+ BC model, combination anti-HER2 and anti-VEGF therapy was more effective than either treatment alone, and increased VEGF expression is associated with worse outcome in HER2+ disease. B plus trastuzumab (T) has shown promising activity in patients (pts) with HER2+ MBC, however the cardiac toxicity of this regimen requires further evaluation. L, an oral dual inhibitor of EGFR and HER2, is approved in combination with capecitabine after T-based therapy for HER2+ MBC. L may have less cardiac toxicity and may be a safer and more effective alternative to T+B. This hypothesis was evaluated in a phase 2 trial of L+B in HER2+ MBC pts.

Methods: This 50-patient single-arm study evaluated L (1500 mg PO daily) plus B (10 mg/kg IV q2wk). The primary endpoint is progression-free survival (PFS) at 12 weeks with 84% power to detect a clinically significant PFS rate of 60%; secondary endpoints include toxicity and response per RECIST. Efficacy was assessed at Week 6, 12, and q12wks thereafter. HER2+ status was locally defined as HER2 FISH amplified or IHC3+. Serial evaluation of circulating tumor and endothelial cells and HER2 extracellular domain was performed.

Results: Data are available on 31/49 pts enrolled; pts received median of 4 prior MBC therapies (range 0-13); 30/31 received prior T (median duration 84 weeks, 14-250 weeks). The most commonly-reported AEs included diarrhea (61%), muscle pain (48%), fatigue (39%), nausea (28%), and emesis (29%). Two grade 2 asymptomatic LVEF decreases and one grade 3 GI hemorrhage were reported. At week 12, 16/21 patients were evaluable for efficacy; 3 pts had a partial response (PR), 10 pts had stable disease (SD), and 3 pts had progressive disease (PD). The crude 12-week PFS rate was 62%. At week 24, 5/9 (56%) pts have shown clinical benefit (CR, PR, SD \geq 24 weeks); 2/2 pts remain in PR after 36 weeks. Conclusions: L+B is well tolerated and has shown promising activity in heavily pretreated HER2+ MBC pts. The trial has completed accrual; updated data will be presented.

142P THE USE OF TRASTUZUMAB IN METASTATIC BREAST CANCER PATIENTS BEYOND DISEASE PROGRESSION

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Although chemotherapy combined with trastuzumab in her2/neu positive advanced breast cancer patients is now the standard of treatment, there have not been any reported randomized trials to answer the question whether herceptin (HER) should continue or not beyond disease progression. In this retrospective analysis, we reviewed the characteristics and the clinical outcome of 85 patients (group A) who continued HER throughout the several lines of treatment for metastatic breast cancer and 34 patients (group B) who had it as part of a treatment course but HER was stopped and never restarted when there was PD. We compared the two groups (A/B) for differences in age (median, 56/54), ER status (+ve%:51/61, -ve%:47/35, nk%:2/4), PgR status (+ve%:14/9, -ve%:62/56, nk%:24/35), interval from 1st metastases to start HER (median, months:2/8), HER given as 1st line metastatic treatment (%:54/38), 2nd line (%:25/35), 3rd line or later (%:21/27), sites of disease at start of HER (local or soft tissue only, %:19/9), bone, %:13/6, visceral, %:32/35, visceral+bone, %:35/44, visceral+bone+CNS, %:1/6). The number of chemotherapies for metastatic disease was (median:2/2, range:0-5/1-5), all chemotherapy for metastatic disease including pre-Herceptin ones (taxanes, %:77/85, navelbine, %:62/21, anthracyclines, %:24/35, capecitabine, %:52/53) chemotherapy given concurrent with or subsequent to HER (taxanes, %:68/68, navelbine, %:62/21, anthracyclines, %:5/12, capecitabine, %:51/50), endocrine treatment for metastases (at any time, n:34/17, with HER, n:10/1, after HER, n:3/2). Analyzing the outcome the median OS from the start of HER for group A was 26 months (95%CI:21-31mn) and for group B was 16months (95%CI:13-19mn). The median survival from the date of diagnosis of metastatic disease was 40 months (95%CI:37-45mn) for group A and 25 months (95%CI:20-31mn) for group B. A multivariate survival analysis (Cox regression)

revealed a HR of 1.0 for group A and 3.4 (95%CI:1.9-5.8,p<0.001)for group B. Our analysis suggests that trastuzumab continuation may be useful but other biases are not ruled out. A trial could still be proposed comparing different durations of herceptin after disease progression.

143P LAPATINIB EXPANDED ACCESS PROGRAM (LEAP): UPDATED SAFETY DATA

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Enrollment in the Phase III trial of lapatinib and capecitabine vs capecitabine alone (EGF100151) was halted on 3 Apr 2006, after interim analysis data were evaluated by the IDMC and a marked improvement in time to progression, the primary endpoint, was found in the lapatinib and capecitabine arm. GlaxoSmithKline organized a global Lapatinib Expanded Access Program (LEAP) to provide pre-approval access to lapatinib for patients who presented with recurrent breast cancer after the study was halted. Design issues, enrollment, and updated safety data are presented. Design: LEAP is a worldwide program that was designed to provide access to lapatinib to a slightly broadened patient population compared with the EGF100151 clinical trial. A clinical trial study was chosen over a named patient format to assist with equal access. Unlike EGF100151, LEAP allows enrollment of patients without measurable disease, with ECOG PS 2, and with brain mets. As of 31 Mar 2008, 3709 patients were enrolled at 446 centres worldwide (836 patients in NA, 2204 in EU, and 669 in ROW).

Results: Only serious adverse events (SAEs) are reported in this study. To date, 37% (449) of 1206 reported SAEs were assessed by the investigator treatment related. The most frequently reported SAE was diarrhea (11%). Other SAEs included decrease in left ventricular ejection fraction (1.7%), pneumonitis/lung infiltration (0.4%), and hepatobiliary events (0.2%). Drug-related death was reported at an incidence rate of 0.3% (10/3709). A total of 2398 patients have been withdrawn from LEAP, mostly due to progressive disease.

Conclusion: To date, the safety profile of lapatinib in LEAP is consistent with that known for lapatinib. The LEAP design allows pre-approval access of lapatinib to patients who are likely to benefit from this treatment and have no other treatment options.

144P DISCORDANCES IN HER2 OVEREXPRESSION AMONG PRIMARY BREAST CANCER, AUTOLOGOUS METASTASES AND METACHRONOUS CONTRALATERAL BREAST CANCER

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Background: It is unclear to what extent primary breast cancer (PBC) is representative of metastases in terms of HER2 expression. Aims of the present study were to relate HER2 status of PBC with HER2 expression of the corresponding metastatic site as well as with HER2 expression of metachronous contralateral primary breast cancer (CLPBC).

Methods: Tissue microarrays constructed from surgical specimens of 157 PBC (134 ductal and 23 lobular), 80 corresponding metastases (11 visceral and 25 non visceral diseases, 44 breast recurrences) and 77 CLPBC were stained for HER2 (Dako HerceptTest). Median age of patients was 52 years (26-82), hormonal receptors (HR) were positive in 91 (58%) tumors. Ninety-two (58%) and 72 (46%) patients had undergone adjuvant chemo- and hormonal therapy respectively. No patients had received prior trastuzumab as adjuvant therapy.

Results: Discordance in HER2 expression between PBC and metastases was found in 12/80 cases (15%) and in 25/77 CLPBCs (32%). More specifically, HER2 was negative (0/1+) in PBC and positive (2+/3+) in metastases in 8 (10%) cases and it was positive (2+/3+) in PBC and negative (0/1+) in metastases in 4 (5%) patients (p=0.04). Concerning CLPBC, HER2 was negative in PBC and positive in CLPBC in 11 (14%) patients and it was positive in PBC and negative in CLPBC in 14 (18%) cases (p=0.9). HR positive PBC showed no significant difference in HER2 expression between PBC and metastases as compared to HR negative PBC (17% vs 13%, p=0.12). Conversely, HER2 discordance between PBC and CLPBC was significantly higher in HR negative than HR positive (57% vs 28% p= 0.02).

Conclusions: In patients with HER2 negative early breast cancer, HER2 status should be reassessed in the metastatic tissue at the time of disease progression, since changes in HER2 expression (from negative to positive) may occur in a significant percentage of patients. Detecting these modifications increases the chances of identifying patients who would benefit from anti-HER2 therapies. The high discordance between PBC and CLPBC is consistent with the fact that PBC and CLPBC often represent two phenotypically distinct diseases.

145P MULTICENTER PHASE III TRIAL TO EVALUATE PEGYLATED LIPOSOMAL DOXORUBICIN AS MAINTENANCE CHEMOTHERAPY (CT) VS OBSERVATION, AFTER FIRST-LINE CT WITH SEQUENTIAL DOXORUBICIN AND DOCETAXEL (A-T) IN METASTATIC BREAST CANCER (MBC). GEICAM 2001-01 STUDY

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Background: We have previously shown that A → T is a reference treatment as first-line CT for MBC patients (pts) (Alba et al, JCO 2004;22:2587-93).

Methods: Eligible pts had histologically-proven MBC, ECOG PS ≤ 2, adequate bone marrow, renal, hepatic and cardiac function (by left ventricular ejection fraction, LVEF). All pts received induction CT with 6 cycles of A-T (50/75 mg/m²/q21d). Pts with a complete or partial response (CR, PR), or stable disease (SD) were eligible. Pts were randomized to receive either pegylated liposomal doxorubicin (PLD, Caelyx™) 40 mg/m² q28d x 6 cycles or observation (O). Primary endpoint was time to progression (TTP); secondary endpoints included toxicity and overall survival (OS). We assumed an increase of median TTP of 66% (log-rank test) with maintenance PLD. With an alpha error of 0.01 (1-sided) and a power of 80%, 77 patients per arm were needed. Statistical analysis was performed on intent to treat population.

Results: Of 288 pts registered, 155 were randomized (78 PLD, 77 O). Median age was 57 years (range 30-74). Disease status of pts following induction therapy and at randomization to PLD vs O: CR 4% vs 9%, PR 49% vs 61%, SD 47% vs 30%. Median number of PLD cycles was 6 (range 0-6). Median TTP from randomization was 8.32 mo with PLD vs 4.93 mo with O (p=.0008). Median TTP from initial induction treatment was 13.18 mo with PLD vs 10.06 mo with O (p=.0005). At 12 mo. 81% of PLD pts and 66% of O pts were alive (p=.04). LVEF dropped below 50% in 2 pts in PLD group vs none in O group; 5 pts in PLD group vs 1 pt in O group had a LVEF decline of 10 or more percentage points. There were no cases of congestive heart failure in either group. Grade 3 hand-foot syndrome occurred in 4% of pts in the PLD group. Other grade 3/4 toxicities between treatment arms were unremarkable.

Conclusion: Maintenance CT with PLD in MBC pts after induction CT significantly prolongs TTP, with no late cardiotoxicity. Overall survival data will be presented.

146P CLINICAL AND BIOLOGICAL ACTIVITY OF METRONOMIC CAPECITABINE AND CYCLOPHOSPHAMIDE IN COMBINATION WITH BEVACIZUMAB IN METASTATIC BREAST CANCER

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Background: Metronomic low-dose chemotherapy has shown efficacy in metastatic breast cancer (MBC). Preclinical and clinical studies support its combination with targeted anti-angiogenic agents like bevacizumab.

Patients and methods: The clinical and biological activity of metronomic cyclophosphamide (Endoxan®, Baxter; 50 mg daily) and capecitabine (Xeloda®, Roche; 500 mg thrice daily) in combination with bevacizumab (Avastin®, Roche; 10 mg/kg i.v. every two weeks) was investigated in patients with MBC.

Results: 47 patients were enrolled (35 pretreated for MBC), and 46 are evaluable for response. We observed 1 CR (2%), 21 PR (46%), 19 SD (41%), and 5 PD (11%), for an overall response rate of 48% (95% CI 33-63%). On 40 patients in whom the period of observation and treatment was longer than 24 weeks, we observed 8 additional long-

term disease stabilization (SD \geq 24 weeks), for an overall clinical benefit of 68% (95% CI 51-81%). Median time to progression was 42 weeks (95% CI 26-72). Treatment was well tolerated. Grade 3/4 side effects included: hypertension (8 patients), leucopenia (2), neutropenia (2), transaminitis (2), prot ϵ inuria (1), nausea (1), vomiting (1). All side effects were manageable and reversible. Baseline total circulating endothelial cells (CEC) count and viable CEC count were both significantly increased in patients who achieved a clinical response (p=0.02 and p=0.02, respectively) and a clinical benefit (p=0.01 and p=0.03, respectively). Viable CEC count was related to total CEC count (correlation index 0.97); a similar correlation was found between apoptotic and total CEC count. Patients who had \geq 0.27 baseline apoptotic CECs/ μ L (25th percentile distribution value) had a significantly better progression-free survival (p=0.04).

Conclusions: Metronomic capecitabine and cyclophosphamide combined with bevacizumab provide long-term disease control in MBC, with no significant toxicity. Baseline CEC count was related to response, and might represent an indirect measure of the angiogenic turnover, supporting further studies on this surrogate marker for the selection of patients candidates to anti-angiogenic treatments.

147P QUALITY OF LIFE (QOL) AMONG PATIENTS (PTS) WITH LOCALLY RECURRENT (LR) OR METASTATIC BREAST CANCER (MBC): RESULTS FROM THE PHASE III AVADO STUDY OF FIRST-LINE BEVACIZUMAB (BV) PLUS DOCETAXEL (D) VERSUS D PLUS PLACEBO (PL)

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Background: The anti-VEGF therapy BV (Avastin[®]) has significantly improved overall and/or progression-free survival (PFS) in several tumour types. In the randomised, double-blind, placebo-controlled phase III AVADO study, two doses of first-line BV combined with D significantly improved PFS and response rates compared with D alone in pts with LR or mBC. BV had only limited impact on the known safety profile of 100mg/m² docetaxel. Here we present QoL data.

Methods: Pts with HER2-negative LR or mBC, ECOG PS 0-1, adequate LVEF and no CNS metastases were randomised to D (100mg/m²) + PL (n=241), D + BV 7.5mg/kg (n=248) or D + BV 15mg/kg (n=247). Pts completed self-assessed Functional Assessment of Cancer Therapy-General (FACT-G) and FACT-Breast (FACT-B) questionnaires pre-treatment and during therapy cycles 3 (with 1st disease assessment), 5 and 11. If disease progressed before cycle 11, a final assessment was made within 14-28 days of disease progression; otherwise, upon disease progression.

Results: QoL assessments were completed by 656 pts at baseline, 570 at cycle 3, 510 at cycle 5, 289 at cycle 11. Baseline scores were well balanced between arms. The D + BV arms showed slight improvements in mean FACT-B scores from baseline at most assessments, driven mainly by an increase in the emotional well-being score, while the D + PL arm showed small mean decreases. Mean changes from baseline in FACT-G total and subscale scores were similar for all study arms; mean physical, social and functional well-being scores decreased slightly, mean emotional well-being scores increased slightly. Differences between trial arms were not statistically significant at most time points assessed.

Conclusions: The addition of BV to D resulted in superior efficacy in women with LR or mBC, without adversely affecting patient QoL, compared with D alone. Mean change from baseline (95% CI); p-value vs D + PL.

Assessment	D + PL	D + BV 7.5mg/kg	D + BV 15mg/kg
Cycle 3			
FACT-G	-0.26(-2.33,1.81)	0.09(-1.69,1.88);0.796	-1.95(-3.81,-0.09);0.217
FACT-B	-0.61(-1.50,0.28)	0.75(0.08,1.41);0.012	0.03(-0.37,0.98);0.088
FACT-G & FACT-B	-1.51(-4.03,1.01)	0.81(-1.34,2.96);0.161	-1.87(-4.06,0.31);0.823
Cycle 5			
FACT-G	-3.56(-5.75,-1.37)	-2.05(-3.88,-0.22);0.303	-3.51(-5.51,-1.52);0.976
FACT-B	-0.73(-1.63,0.16)	-0.16(-0.99,0.67);0.334	-0.02(-0.75,0.70);0.225
FACT-G & FACT-B	-4.85(-7.44,-2.26)	-2.34(-4.63,-0.05);0.158	-3.66(-6.08,-1.24);0.500
Cycle 11			
FACT-G	0.45(-2.45,3.35)	1.81(-1.34,4.96);0.527	-0.85(-3.44,1.73);0.528
FACT-B	-0.38(-1.70,0.93)	0.50(-0.72,1.72);0.338	0.18(-1.00,1.37);0.524
FACT-G & FACT-B	-0.51(-4.10,3.08)	2.44(-1.59,6.47);0.282	-0.91(-4.27,2.45);0.879

148P THE EFFICACY AND SAFETY OF NON-PEGYLATED LIPOSOMAL DOXORUBICIN MYOCET AND DOCETAXEL AS FRONT LINE TREATMENT IN HER2-NEU NEGATIVE METASTATIC BREAST CANCER PATIENTS: RESULTS OF A PHASE II TRIAL

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Background: First line docetaxel (D) and doxorubicin yield up to 55% response rates in previous studies, in relapse situation for patients (pts) having received anthracyclin in adjuvant setting with the risk to run on cardiotoxicity regarding anthracyclin cumulative dose. The objective of the study is to evaluate efficacy and safety of MyocetTM (M) and D as frontline chemotherapy in her2-neu negative metastatic breast cancer (MBC) who have been pre-treated with anthracyclin in adjuvant setting.

Methods: Eligible pts were > 18 years, with MBC relapsing at least 12 months after previous anthracyclin and/or taxan, WHO performance status 0-1-2, left ventricular ejection fraction(LVEF) > 50%, measurable target lesions, cumulative dose of doxorubicin or epirubicin or mitoxantron are respectively under 360, 600, 75 mg/m². Treatment: M=60mg/m² (90 min infusion) was followed by D: 75 mg/m² (60 min infusion), q3weeks for a minimum of 6 cycles. Clinical adverse events review, haematology assessment were performed each cycle, LVEF each 2 cycles, tumor assessment was performed after 2 and 4 cycles.

Results: 36 pts with median age 56 (40-71) entered the study. All with metastatic lesions (liver 19, bone 15, lung 12, soft tissues 6, skin 3, pleural 2, multiple 18). Premenopausal 6 pts, negative hormonal receptors 5pts. A total of 212 M and D cycles were administered, G-CSF was used in 11 pts, Erythropoietin in 2 pts. No treatment related death has been reported. Grade 3-4 toxicity: febrile neutropenia 4 pts, neutropenia 6 pts, thrombocytopenia 2 pts, peripheral edema 1 pt. Cardiotoxicity: Mean baseline LVEF=62.8%, 59.5% after cycle 4, 58.3% after cycle 6. No PPE were noted. Efficacy: Overall Objective Response Rate (ITT)=58%, IC 95%(34-74) at median follow up 34 months (13-47): median PFS=11 months (4-36), median response duration: 10 months (2-33), median overall survival=24 months (3-45).

Conclusion: M and D combination shows a high overall response rate and prolonged survival time compare to previously published anthracyclines and taxanes combinations, with manageable hematologic toxicity and non significant changes in LVEF.

149P COMPARATIVE EFFICACY OF FIRST-LINE DOCETAXEL + CAPECITABINE (XT) VERSUS DOCETAXEL + EPIRUBICIN (ET): POOLED ANALYSIS OF TWO RANDOMISED TRIALS

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Purpose: Taxane-based combination therapies are the most active first-line regimens for metastatic breast cancer (MBC), but selection of the most appropriate treatment can be difficult. XT significantly improves response rate (RR), time to progression and overall survival (OS) compared with docetaxel alone, and in a recent phase III trial, capecitabine plus paclitaxel showed similar efficacy to epirubicin plus paclitaxel. Two French trials, ERASME-4 and CAPEDOC-EPIDOC,

aimed to compare the efficacy of first-line XT vs ET in MBC. Both were terminated prematurely due to poor accrual, but because the study designs were so similar, we pooled available data to gain information on the relative efficacy of these regimens.

Methods: In both trials, patients (pts) who had received no chemotherapy for MBC received 3-weekly cycles of either XT (docetaxel 75 mg/m², d1 + capecitabine 1,000 mg/m² twice daily, d1-14) or ET (docetaxel 75 mg/m², epirubicin 75 mg/m², both d1; primary prevention of febrile neutropenia [FN] with growth factor support was recommended with ET). The primary endpoint was progression-free survival (PFS) rate in both trials. In ERASME, it was planned to recruit 106 pts, giving 95% power to test a 6-month PFS rate of 75% (XT) vs 60% (ET). Secondary endpoints included duration of PFS and OS.

Results: Between March 2003 and January 2007, 92 pts were enrolled in the two trials. Pt characteristics were well balanced between treatment arms; most had received adjuvant anthracycline therapy. Efficacy after median follow-up of 15 months is shown below.

	XT (n=45)	ET (n=47)	P value
6-month PFS rate (95% CI)	78% (63-89)	74% (60-86)	0.81
Median PFS, months	12	9	0.08
Median OS, months	28	28	0.92

Toxicity was generally mild or moderate with only one episode of FN. Grade 3 hand-foot syndrome occurred in 17% of XT pts vs 0% of ET pts. Conclusion: These data confirm that XT is an active first-line regimen and suggest that XT may extend PFS compared with ET. We consider XT to be a valid, non-anthracycline-containing alternative to ET in this setting.

150P AN INTERNATIONAL PHASE II STUDY OF AN ALL-ORAL COMBINATION OF ORAL VINOURELBINE (NVBO) AND CAPECITABINE (X) IN HER2-NEGATIVE METASTATIC BREAST CANCER (MBC): LATEST RESULTS WITH A MEDIAN FOLLOW-UP OF 33.5 MONTHS

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Background: Oral chemotherapy (CT) is attractive for patients (pts) with MBC. The all-oral regimen of NVBo and X is active with good tolerability in MBC. We report an updated analysis of efficacy and safety from an international phase II study of NVBo plus X.

Methods: Main eligibility criteria included: measurable HER2-negative, CT-naive MBC, relapse ≥ 6 months after completing (neo)adjuvant CT, Karnofsky PS ≥ 70%, age ≥ 18 years. Study treatment: 3-weekly cycles of NVBo 80 mg/m² (after a first cycle at 60) d1 and d8, plus X 1000 (750 if ≥ 65 years) mg/m² twice-daily d1-14. Treatment was continued until progression or unacceptable toxicity.

Results: 55 pts were enrolled and 54 were treated: median age: 58.5 years (41% ≥ 65); prior (neo)adjuvant CT in 63%; type of CT: anthracycline 67%, anthracycline + taxane 18%, CMF 15%; visceral involvement in 78%; > 2 metastatic sites in 46%. Median 7 cycles (range 1-58); median relative dose intensity: NVBo 87%, X 87%; NVBo escalated to the recommended dose of 80 mg/m² in 91% of pts. G3/4 NCI CTC v2 adverse events: (n=53) neutropenia 49% of pts, (n=54) vomiting 9%, stomatitis 7%, asthenia 7%, febrile neutropenia 6%, infection with G3/4 neutropenia 6%, nausea 4%, diarrhea 4%, hand-foot syndrome 4%, thrombosis/embolism 4%. Efficacy (n=46 evaluable pts): objective response rate (RECIST) 52% (95% CI [37-67]), CR 2%, PR 50%, SD 28%, PD 20%, disease control (CR+PR+SD ≥ 6 months) 63% (95% CI [48-77]). Median duration of response was 7 months (95% CI [6-12]), median progression-free survival was 8.4 months (95% CI [6-10]). After a median follow-up of 33.5 months, overall survival results are not mature yet. 26 of the 54 pts treated in the study are still alive.

Conclusion: The all-oral combination of NVBo and X is an effective and well-tolerated first-line therapy for MBC. Based on these results and the high convenience of oral CT, evaluation of this regimen vs i.v. combinations in a randomized trial is ongoing.

151P HIGH EFFICACY OF THE COMBINATION CHEMOTHERAPY (CT) OF ORAL VINOURELBINE (NVBO) AND CAPECITABINE (X) WITH TRASTUZUMAB (H) IN HER2-POSITIVE METASTATIC BREAST CANCER (MBC): UPDATED ANALYSIS OF THE RESULTS OF AN INTERNATIONAL PHASE II TRIAL

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Background: CT plus H is the standard treatment of HER2-positive MBC. Combination therapy of H plus vinorelbine is an active and safe regimen in this setting. All-oral combination of NVBo and X has been reported as an active and safe regimen in MBC. We report efficacy and safety information from an updated analysis of all 50 patients included in this trial with a median follow-up of 28.5 months.

Materials and methods: In this multicentre trial, main eligibility criteria included: HER2-positive disease (defined as IHC 3+ or FISH+), documented measurable metastatic disease previously untreated by CT, relapse ≥ 6 months after the end of neoadjuvant or adjuvant CT, Karnofsky PS ≥ 70. NVBo was given as a 60 mg/m² (cycle 1) or 80 mg/m² (from cycle 2) dose D1 & D8 every 3 weeks, X at 1000 (750 if ≥ 65 y) mg/m² bid D1-D14 every 3 weeks, H at 4 mg/kg on D1 as a loading dose then 2 mg/kg i.v. weekly starting on D8. Treatment was continued until progression.

Results: Median age: 53.5y (18% ≥ 65y); prior (neo)adjuvant CT 27 pts (54%); visceral involvement 41 pts (82%), > 2 metastatic sites 17 pts (34%); Median number of cycles: 10 (range 1-56); Median relative dose intensity: NVBo 75%, X 77%, H 96%; NVBo escalated to the recommended dose of 80 mg/m²: 84%; G3/4 NCI CTC v2 adverse events per pt: (n=49) neutropenia 69%, (n=50) febrile neutropenia 8%, infection without neutropenia 4%, stomatitis 4%, nausea 4%, vomiting 12%, diarrhoea 16%, hand-foot syndrome 20%, asthenia 8%, LVEF decline 6%, alopecia (grade 2) 14%; Efficacy (n=44 evaluable patients): objective response rate (RECIST) 77% (95% CI [62-89]), CR 18%, PR 59%, SD 18%, PD 5%, disease control (CR+PR+SD ≥ 6 months) 93% (95% CI [81-99]), Median duration of response was 14.3 months (95% CI [10-17]), median progression-free survival was 12.8 months (95% CI [11-17]), overall survival results are not mature yet. Treatment is ongoing in 5 pts.

Conclusion: This trial results show, in patients with HER-2 positive MBC, a high efficacy of the combination of NVBo and X plus H. This regimen can be safely administered for this patient population.

152P INTERIM RESULTS OF A PHASE II STUDY OF NAB-PACLITAXEL, BEVACIZUMAB, AND GEMCITABINE AS FIRST-LINE THERAPY FOR PATIENTS WITH HER2-NEGATIVE METASTATIC BREAST CANCER (MBC)

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In a phase III study in patients with MBC, nab-paclitaxel (Abraxane®) demonstrated nearly double the overall response rate (P = 0.001) and significantly longer time to tumor progression (P = 0.006) versus solvent-based paclitaxel (JCO.

2005;23:7794-7803). Improvement in time to progression and response rates have also been demonstrated when solvent-based paclitaxel was combined with gemcitabine (Gemzar®) or bevacizumab (Avastin®). The current study is the first to examine the efficacy and safety of combination therapy with nab-paclitaxel, bevacizumab, and gemcitabine for first-line treatment of patients with MBC. Patients (≥ 18 years with untreated HER2-negative MBC or metastases diagnosed ≥ 6 months after primary systemic treatment) received gemcitabine 1,500 mg/m², nab-paclitaxel 150 mg/m², and bevacizumab 10 mg/kg (each administered intravenously over 30 minutes) on days 1 and 15 of 28-day cycles. Cycles were repeated for the duration of therapy. Progression-free survival was the primary endpoint; secondary endpoints included rates of complete or partial response, overall survival, safety, and toxicity. To date, 22 patients (95% female, 34 to 69 years) have been enrolled. All patients were evaluated for safety, estrogen receptor (ER) status, and progesterone receptor (PR) status; 16 patients received ≥ 2 cycles and were evaluated for efficacy. All patients were HER2-negative;

64% and 36% were ER+ and PR+, respectively. The most common sites of metastases were bone (45%), liver (36%), and lung (27%). Twelve (75%) patients achieved partial response, 1 (6%) had stable disease, and 3 (19%) had progressive disease. There were no grade 3/4 adverse events, and the most commonly reported side effects were alopecia (36%) and joint aches (27%). Three patients were hospitalized because of port site infection or hematotoxicity. In this interim analysis, first-line combination therapy with nab-paclitaxel, bevacizumab, and gemcitabine demonstrated a 75% overall response rate in patients with MBC. These data suggest that this triplet regimen may represent an important new first-line option for the treatment of patients with MBC.

153P SYNERGY OF NAB®-PACLITAXEL AND BEVACIZUMAB ERADICATES LARGE ORTHOTOPIC BREAST TUMORS AND LYMPHATIC AND PULMONARY METASTASIS

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Background: Nab-paclitaxel (Abraxane[®], nab-pac) is an albumin-bound 130-nm particle form of paclitaxel that demonstrated greater efficacy and was well tolerated compared to solvent-based paclitaxel (Taxol[®]) and docetaxel (Taxotere[®]). We have previously shown that reactionary angiogenesis induced by chemotherapy correlated with increased VEGF production in tumors, and the combination of nab-pac and anti-VEGF-A antibody (bevacizumab, bev) has superior efficacy against both primary tumors and metastasis than monotherapies in medium-sized MDA-MB-231 tumors (~230 mm³) (Ran et al., AACR 2007, #2201). Herein, we studied the combination of nab-pac and bev on the growth and metastasis of large-sized (450-600 mm³) breast tumors.

Material and methods: Luciferase-tagged MDA-MB-231-Luc⁺ human breast carcinoma cells were implanted into mammary fat pads of nu/nu mice and allowed to reach an size of 450-600 mm³, before treatment with nab-pac at 10 or 30 mg/kg on the qdx5 schedule for 2 cycles separated by one week. Bev (4 mg/kg) was administered concurrently with nab-pac, and continued for the duration of the experiment. Metastases to lymph nodes and lungs analyzed by monitoring luciferase activity.

Results: Complete regressions and total elimination of metastasis were achieved in 100% of mice bearing large orthotopic MDA-MB-231-Luc⁺ tumors after treatment with 2 cycles of concurrent 30 mg/kg nab-pac and 4 mg/kg bev. Three cycles of combined therapy with 10 mg/kg nab-pac resulted in 80% regressions and 98% reduction in metastatic burden. Bev effect was optimal when administered concurrently with nab-pac and continued for the duration of the experiment. Bev administered sequentially after nab-pac delivered no benefits of the combined therapy.

Conclusions: Repetitive cycles of nab-paclitaxel given concurrently with bevacizumab at 4 mg/kg can eradicate both large primary tumors (450-600 mm³) and lymphatic and pulmonary metastases in an aggressive breast cancer xenograft model. The suppression of paclitaxel-induced reactionary angiogenesis by bevacizumab can significantly enhance the antitumor and antimetastatic efficacy of Abraxane (nab-paclitaxel).

154P MULTICENTER, PHASE II STUDY OF LAROTAXEL IN PATIENTS (PTS) WITH METASTATIC BREAST CANCER (MBC) PROGRESSING AFTER ANTHRACYCLINES, TAXANES AND CAPECITABINE

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Background: Larotaxel (XRP9881), a new taxoid, has shown activity in a broad spectrum of tumor models resistant/refractory to taxanes and has demonstrated clinical activity in taxanes-exposed, resistant MBC pts. **Methods:** Eligible pts pre-treated with anthracyclines, taxanes and capecitabine who progressed or relapsed within 6 months from taxanes/capecitabine, received larotaxel 90mg/m², 1-hour IV infusion, every 3 weeks (q3w). Pts with ECOG PS 2 or history of febrile neutropenia (FN) started with 75mg/m². The primary endpoint was objective response rate (RR)

assessed per RECIST by an Independent Review Committee in the Intent-to-treat population.

Results: Between Aug 2004 and Oct 2006, 168 pts were treated (34 started at 75mg/m²). Median age was 53 years (26-74), 66.7% of the patients received at least 2 metastatic regimens, 17% and 14% of pts were respectively triple negative and HER2+. Median number of cycles was 4 (1-27). The RR was 7.7% (95% CI: 4.2-12.9); 8.9% among 134 pts started at 90mg/m², 43% of patients had stable disease for at least 12 weeks. Median duration of response was 13.1 weeks (95% CI: 6.1-25.1); median PFS was 13 weeks (95% CI: 11.1-16.1) and median OS was 43.3 weeks (95% CI: 36.3-53.1). Main adverse events (AEs) per pt were (all grades (Gr), Gr 3-4) fatigue (70.8%, 14.9%), musculoskeletal pain (66.7%, 11.3%) and diarrhea (57.1%, 9.5%). Other Gr 3-4 AEs were: peripheral sensory neuropathy (4.2%), nausea/vomiting (3%) and stomatitis (0.6%). No Gr 3-4 AEs were observed for peripheral edema (all Gr, 4.8%), nails disorders (all Gr, 6%) and allergic reactions (all Gr, 6.5%). Gr 3-4 neutropenia and thrombocytopenia per pt were respectively 78% and 7.1%. Gr 3-4 FN, neutropenic infection and infection were respectively 6.5%, 1.8% and 1.2%. Seven deaths (4.2%) within 30 days of last dose related to larotaxel were reported (6 septic and 1 sudden death).

Conclusion: Larotaxel (at 75-90mg/m² q3w) demonstrated limited activity in these heavily pre-treated pts progressing after anthracyclines, taxanes and capecitabine. Neutropenia, fatigue, musculoskeletal pain and diarrhea were the most frequent toxicities.

155P A MULTICENTRE PHASE I DOSE FINDING STUDY TO INVESTIGATE THE COMBINATION OF BENDAMUSTINE WITH WEEKLY PACLITAXEL AS FIRST OR SECOND LINE THERAPY IN PATIENTS WITH ANTHRACYCLINE PRETREATED METASTATIC BREAST CANCER – THE RITA TRIAL

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Background: The aim of the RiTa trial is to establish a feasible combination of bendamustine and paclitaxel in a weekly schedule in anthracycline pretreated metastatic breast cancer patients.

Methods: The RiTa trial is a prospective multicentre phase I dose finding study. The starting dose of bendamustine was 50 mg/m² and was stepwise increased by 10 mg/m² up to 70 mg/m². The starting dose of paclitaxel was 60 mg/m² and was increased up to 90 mg/m². There are five predefined dose levels with 3 patients per dose level (maximum 6 patients) and 6 patients in the last dose-level according to the Goodman design. Dose limiting toxicities were severe neutropenia and thrombocytopenia as well as non-haematological toxicities ³ NCI-CTC grade 3 (except emesis and alopecia) in the 1st cycle.

Results: Between September 2005 and February 2007, 18 patients (pts) had been enrolled with a median age of 62 years (range 38-72). 83.3% of all pts had liver metastases, 55.6% bone metastases, 22.2% lung metastases. No dose limiting toxicity up to 70 mg/m² bendamustine and 90 mg/m² paclitaxel occurred during the 1st cycle. Over all cycles the following severe haematological toxicities (grade 3 and 4) were documented: neutropenia 5 pts (1 pt dose-level 1, 2 pts dose-level 3, 1 pt dose-level 4, 1 pt dose-level 5), anaemia 1 pt in dose-level 2. Relevant grade 3 and 4 non-haematological toxicities over all cycles were fatigue 2 pts (1 pt in dose-level 1 and 2), dyspnoea 1 pt in dose-level 5, infection 4 pts (1pt in dose-level 3 and 3 pts in dose-level 5) and bone pain 1 pt in dose-level 2. Five serious adverse events (2 fatigue, 1 anaemia, 1 allergic reaction, 1 dehydration), but no therapy related death occurred. Five of the 18 pts showed a complete or partial remission, 6 pts stable disease and 5 progressed during treatment. The median progression free survival was 8.5 months.

Conclusion: The treatment with weekly bendamustine and paclitaxel is a feasible and effective regimen in patients with metastatic breast cancer. The determined dose for the phase II study will be 70 mg/m² bendamustine and 90 mg/m² paclitaxel.

156P ERIBULIN MESYLATE (E7389) IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC BREAST CANCER PREVIOUSLY TREATED WITH AN ANTHRACYCLINE AND A TAXANE: PHASE II NEUROPATHY DATA

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Purpose: To summarise neuropathy data for eribulin mesylate (E7389), a non-taxane microtubule dynamics inhibitor with a novel mechanism of action, from two Phase II studies in patients (pts) with extensively pretreated locally advanced or metastatic breast cancer.

Methods: Two single-arm, open-label studies recruited pts with measurable disease, ECOG performance status 0–2, neuropathy Grade ≤2, prior anthracycline and taxane treatment, and progression on or within 6 months of their last chemotherapy (CT). Eribulin mesylate (1.4 mg/m²) was administered as a ≤5 min intravenous infusion on Days 1 and 8 of a 21-day cycle or on Days 1, 8 and 15 of a 28-day cycle. The primary efficacy endpoint was objective response rate (ORR; RECIST) assessed by independent review. Adverse event (AE) rates were graded according to NCI CTC v3.0. Neuropathy AE rates were evaluated using two approaches: investigator classification of relatedness (both studies), and pre-trial classification of neuropathy severity and evaluation of worsening (one study).

Results: Patients in the two studies had received a median of four prior CT regimens. Eribulin was administered to 394 pts (safety population) for a median of four cycles. In the study for which pre-trial neuropathy severity was classified, 235 of 291 eribulin-treated pts (81%) had no pre-existing neuropathy and 56 pts (19%) had pre-existing neuropathy. In these two groups, only 23% developed neuropathy and 21% noted worsening neuropathy during eribulin therapy, respectively. Nine pts had pre-existing Grade 2 chemotherapy-related neuropathy. Of these, three achieved a partial response, two had stable disease and none discontinued eribulin therapy due to neuropathy. Based upon investigator classification of treatment-related AEs reported in the two studies, the rates of neuropathy were: 26% overall, 21% Grade 1/2, 5.3% Grade 3, and no Grade 4. The combined ORR was 9.8% in the eligible population (N=356).

Conclusions: Eribulin was associated with a manageable level of neuropathy, and pre-existing neuropathy usually did not worsen with eribulin treatment.

157P A PHASE I STUDY OF S-1, A NOVEL ORAL FLUOROPYRIMIDINE, COMBINED WITH DOCETAXEL FOR ADVANCED OR RECURRENT BREAST CANCER

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Background: S-1 is a novel oral fluoropyrimidine consisting of tegafur, gimeracil, and oteracil. S-1 monotherapy demonstrated 20% overall response rate for refractory metastatic breast cancer (MBC) patients after anthracycline and taxane therapy. Docetaxel (DOC) is one of the most active chemotherapies for (MBC), combination of DOC plus S-1 is possible promising treatment option for MBC. We conducted a Phase I study to establish the dose limiting toxicity (DLT) and maximal tolerated dose (MTD) of S-1 plus DOC.

Patients and methods: Eligible patients (pts) had advanced or recurrent breast cancer, age 20 to 70 years old, with ECOG PS 0-1. DOC was administered on Day 1 and S-1 was administered Day 1 to 14 followed by a 7 day rest. Cycles were repeated every 3 weeks until disease progression, unacceptable toxicity, or withdraw of consent. Planned dose escalation was Level 1: DOC 60mg/m², S-1 32.5mg/m² BID per day; Level 2: DOC 60mg/m², S-1 40mg/m² BID; Level 3: DOC 70mg/m², S-1 40mg/m² BID, respectively. DLT was defined as any of the following events occurring during cycle1; grade 4 neutropenia for 4 days or more, grade ≥3 febrile neutropenia (ANC<1,000, 38â"F), grade ≥3 non-hematologic toxicities other than nausea, vomiting, anorexia, or fatigue.

Results: Twelve pts (median age 59, range: 37-66) were enrolled. The only DLT observed was grade 4 neutropenia for 4 days or more, occurring in 1 of 6 pts at Level 2 and 2 of 3 at Level 3. Efficacy data will be present at the meeting.

Conclusions: Based on our findings we recommend dose of S-1 40mg/m² BID Day1-14 and DOC 60 mg/m², Day1 every 3 weeks for phase II studies in advanced or recurrent breast cancer.

158P ELIXIR: A LARGE, PROSPECTIVE COHORT STUDY EVALUATING ROUTINE CLINICAL USE OF CAPECITABINE (CAP) IN ADVANCED BREAST CANCER (ABC) IN FRANCE

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Purpose: This French pharmaco-epidemiological study aims to assess use, efficacy, tolerability (reported by patients [pts] and physicians) and compliance with Cap in routine oncology practice, to analyse characteristics of pts treated with Cap and to identify the principal prognostic factors for disease progression.

Methods: Physicians were recruited using a step-by-step method to ensure proportional representation from all types of medical practice (comprehensive cancer centres, university hospitals, general hospitals, private clinics) and avoid selection bias. Data on pts' baseline characteristics, Cap treatment dose/schedule, efficacy, tolerability and compliance were collected by physicians. Tolerability and compliance data were also collected from pts.

Results: From Dec 05 to Nov 07, 83 participating physicians enrolled 616 analysable pts into ELIXIR (range 1–30 pts per physician). Physicians were representative of those treating BC in France. Baseline data for 616 pts are below.

	Overall (n=616)	1 st -line Cap (n=256 [42%])	2 nd -line Cap (n=217 [35%])	3 rd -line or later Cap (n=143 [23%])
Median age, yrs (range)	63 (32–96)	69 (34–96)	60 (32–92)	60 (35–83)
M1 at first diagnosis	14%	12%	14%	18%
ER and/or PR positive	77%	74%	79%	82%
HER2 status (n=415)	22%	17%	23%	29%
Positive				
Median disease-free interval (DFI), yrs (range)	3.1 (0–33)	3.4 (0–31)	2.9 (0–33)	3.2 (0–29)
DFI <12 months	21%	18%	23%	25%
DFI ≥24 months	66%	67%	64%	69%
Metastatic sites <3	72%	79%	68%	67%
Liver	37%	26%	40%	54%
Bone only	23%	31%	19%	15%
Neoadjuvant chemotherapy	13%	12%	15%	12%
Anthracycline-based without taxane	7%	6%	9%	6%
Taxane-based	6%	7%	5%	6%
Adjuvant chemotherapy	47%	43%	53%	45%
Anthracycline-based without taxane	34%	28%	39%	38%
Taxane-based	9%	11%	10%	2%
Endocrine therapy for ABC	63%	54%	64%	77%

Cap prescription: most pts received Cap as monotherapy (72%) and in the first-line setting (42%). The most common chemotherapy partner was vinorelbine (n=60). 56 pts received Cap + trastuzumab. The mean daily dose of Cap was 1920 mg/m² (range 317–2791). Self-administered questionnaires were received from 81% of pts.

Conclusions: In this large, prospective cohort study, Cap was given most commonly as first-line therapy for ABC (42% of pts). Pts receiving Cap in this setting appeared to have less aggressive disease (more bone-only metastasis, fewer metastatic sites). Efficacy, tolerability and compliance data will be available early in 2009.

159P **FULVESTRANT AS FIRST-LINE TREATMENT FOR ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN AFTER PROGRESSION ON PRIOR ADJUVANT THERAPY WITH THIRD-GENERATION AROMATASE INHIBITORS: A PHASE II TRIAL**

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The aim of this phase II study was to evaluate the activity and safety of fulvestrant in postmenopausal hormone-sensitive women with advanced breast cancer (ABC) progressing after adjuvant treatment with AI. The primary end point was time to progression (TTP) and the secondary end point was the clinical benefit (CB) rate. Fifty-two consecutive patients were enrolled: median age of 67 years (range 35-78); ECOG performance status of 0-1 in 90%. Anthracycline-based adjuvant chemotherapy had been given in 45% of patients, with sequential hormonal therapy, and 92% of patients had received radiotherapy. The prior endocrine therapy consisted of anastrozole in 51% of patients, letrozole in 34%, and exemestane switching from tamoxifen in 15% of patients (adjuvant setting only). Disease-free-interval was 5 years in 45%. Dominant metastatic sites were viscera (liver/lung in 72% of cases) and bone (20% of cases). Fulvestrant was administered at registered dose of 250 mg via intramuscular injection every 28 days, until disease progression or other reason for discontinuation. Treatment allowed good patient compliance, with mild-moderate side effects (hot flashes 30%, fatigue 25%, headache 10%, injection site reactions 8%, nausea 5%). The median number of given cycles was 6 (range 4-12+). Nine out of 52 patients (17%, 95% CI 9.3% to 29.7%) achieved an objective response, with one complete and 8 partial remissions (3 in the lung, 4 in the liver and 2 in soft tissue sites); median response duration was 14.5 months (range 4-22 months). In addition, 16 patients had stable disease lasting 6-18 months, for an overall CB rate of 48% (95% CI 35.1% to 61.3%). Median TTP was 6 months (6-22). Our results confirm that fulvestrant is a well-tolerated and effective strategy as first-line treatment in hormone-sensitive postmenopausal women who had progressed after prior adjuvant treatment with third-generation IA. The good treatment compliance and the possibility to delay the less-tolerated chemotherapy option could positively affect patient's quality of life

160P **ORAL VINORELBINE IN METASTATIC BREAST CANCER – THE VIENNA EXPERIENCE**

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Background: Metastatic breast carcinoma is an incurable disease. Treatment aim remains palliative – to control symptoms and, where possible, prolong survival, while maintaining quality of life. Therefore, there is an important role for oral chemotherapy, as it was found to receive higher patient acceptance. Here, we report the experience with oral vinorelbine (OV) in anthracyclin-resistant metastatic breast cancer.

Patients and methods: A total of 100 consecutive patients were included as eligible for OV and followed prospectively. Her2-positive subjects received a combination of OV and trastuzumab. As earlier described, OV was administered at a dose of 60 mg/m² on day 1 and 8, q=21, without dose escalation. Trastuzumab was given every three weeks at a dose of 6 mg/kg following a loading dose of 8 mg/kg. Time to progression (TTP) was defined as primary endpoint. Secondary endpoints were clinical benefit rate (CBR; CR + PR + SD ≥ 6 months), overall survival (OS), and toxicity. Response was evaluated every three cycles using WHO criteria. TTP and OS were estimated using the Kaplan-Meier product limit method. A multivariate analysis (Cox regression model) was performed to evaluate factors significantly associated with TTP. Results: Median age was 62 years. TTP was median 7 months, range 2 – 14. 4% experienced CR, 21% PR, and 26% SD ≥ 6 months, resulting in a CBR of 51%. OS was median 17 months. In the Cox regression model, TTP was significantly associated with treatment line. Other factors, including age > 65 years, had no influence. Neutropenia (14%), and nausea (9%) were the only treatment-related adverse events that occurred with grade 3 or 4 intensity. In patients on OV and trastuzumab, consistently superior TTP and response rate were observed.

Conclusions: OV appears to be feasible and safe at the dose and schedule chosen. Of note is the activity and good tolerability in elderly patients. As earlier reported, the combination of OV and trastuzumab offers a highly active regimen in Her2-positive disease. Similar to other treatment options, OV is most effective when used in the first-line setting. Updated results will be presented.

161P **AN ANALYSIS OF THE PHARMACOKINETIC (PK) PROFILE OF FULVESTRANT 500 MG VS 250 MG: DATA FROM THE NEWEST STUDY**

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Background: NEWEST (Neoadjuvant Endocrine therapy for Women with Estrogen-Sensitive Tumours) is a randomized, Phase II study comparing fulvestrant approved dose (AD; 250 mg/month) with a high-dose regimen (HD; 500 mg/month plus 500 mg on Day 14 of Month 1) as neoadjuvant therapy for postmenopausal women with newly diagnosed, oestrogen receptor (ER)-positive, locally advanced breast cancer. In the primary analysis, fulvestrant HD resulted in a statistically significant greater reduction in Ki67 labelling index (LI) and greater ER and progesterone receptor (PgR) downregulation compared with AD. Here we report PK data from NEWEST.

Methods: Core biopsies were taken at baseline, Wk 4 and at surgery (Wk 16), and assessed for changes in Ki67 LI, ER and PgR expression (ER and PgR Intensity Score analysed using ChromaVision™ Automated Cellular Imaging System). Blood samples for PK analysis were taken on Days 0, 28, 56, 84, and 112. An additional sample was taken between Days 6-10 (both groups) and Days 20-24 (HD only). HPLC-MS and liquid-liquid extraction were used to determine fulvestrant plasma levels. Plasma samples were analysed using NONMEM and Bayesian PK parameter estimates were used to determine C_{max} and AUC_{0-28 days} at Wks 4 and 16. Correlations between fulvestrant plasma levels, magnitude of biomarker (Ki67 LI, ER, and PgR) downregulation and clinical activity were assessed.

Results: A total of 208 women were included in the PK analyses. Fulvestrant plasma levels and exposure were greater for fulvestrant HD than AD at Wks 4 and 16 (Wk 4: C_{max} HD 24.5 ± 6.9 vs AD 8.8 ± 1.7 ng/mL; AUC_{0-28 days} HD 12804 ± 3550 vs AD 4005 ± 840 ng.h/mL). Increased monthly fulvestrant exposure correlated with increased Ki67 LI, ER and PgR downregulation. Detailed modelling of the endpoints suggested a non-linear decrease in both Ki67 and PgR to a plateau of approximately 20-30% of baseline values. ER levels were downregulated to approximately 50% of pre-treatment values. Conclusions: Increased fulvestrant exposure correlates with increased downregulation of Ki67 LI, ER and PgR. The relationship between drug levels and clinical response will also be presented. Fulvestrant HD is currently being investigated in the metastatic disease setting.

162P **THE IMPACT OF LEPTIN AND ESTRADIOL LEVELS ON CLINICAL OUTCOMES IN METASTATIC BREAST CANCER (MBC) PATIENTS TREATED WITH AROMATASE INHIBITORS (AIS)**

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Background: Aromatase plays a critical role in estrogen biosynthesis and affects body fat distribution and regulation. Leptin, a cytokine synthesized in adipose tissue, has been implicated as a link between obesity and breast cancer. Total body aromatization in postmenopausal breast cancer patients is strongly correlated to plasma leptin levels. Therefore, we aimed to identify whether serum leptin and estradiol levels could affect the outcome in MBC patients treated with AIs or not.

Patients and Methods: A total of 42 metastatic breast cancer patients treated with first line hormonal therapy were enrolled in this study. Pretreatment body weight, height and BMI were measured. Serum leptin and estradiol levels were measured. Estrogen, progesterone and c-erb-B2 receptors status were evaluated in analyses. Univariate and multivariate Cox regression analyses, and Kaplan Meier survival curves subjected to log rank testing were utilized for the survival analyses. Forward likelihood ratio was used for the multivariate selection process. A P value < 0.05 was considered to be significant.

Results: Median age was 51 years (range 28 – 75). Median body weight, height and BMI were found to be 70.5 kg (range 46-115), 156 cm (range 137-167), 29.2 (range 18-45), respectively. Median leptin level was 19700 pg/ml (3900-91900) and estradiol level 31.9 pg/ml (25.2 – 181.9). 32 patients were treated with letrozole and 10 patients with anastrozole. Factors associated with overall survival in the univariate analysis were age and c-erb-B2 expression intensity (+++ versus others by immunohistochemistry), whereas no factors retained significance in the multivariate analysis. Likewise, predictors of progression free survival were c-erb-B2 expression intensity, estradiol and leptin levels. However, leptin and estradiol levels were significant in the multivariate analysis. Median progression free survival figures for patients with leptin levels of <19700 pg/ml and ≥19700 pg/ml were 957 versus 376 days (Log rank statistic = 6.95, P = 0.008).

Conclusions: This study suggests that serum leptin levels may serve as a potential predictive marker in metastatic breast cancer patients treated with AIs.

163P POLYMORPHISM C3435T OF THE MDR-1 GENE PREDICT RESPONSE TO PREOPERATIVE CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER WITH EXPRESSION HER2/NEU

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Background: P-glycoprotein (mdr-1), encoded by the MDR-1 gene, confers multi-drug resistance against antineoplastic agents and is important for the transmembrane transition of various other common therapeutic drugs. Recently, the T/T genotype at position 3435 in exon 26 was found to correlate with clinical response to chemotherapy in cancer patients. Anthracycline therapy has better survival, if it is related to Her-2 expression in breast cancer patients, but the mechanism of cell cancer sensitivity which expressed Her-2 to anthracycline if it is related to P-glycoprotein expression is still unclear.

Purpose: The purpose of this study was to reveal those mechanisms, which in the future could be used as the basis of anthracycline application in breast cancer patients.

Patient and methods: The analytical observational research in nineteen patients diagnosed between January until December 2005 with locally advanced breast cancer treated by preoperative anthracycline chemotherapy to evaluate its predictive outcome was performed. All samples were analysed by immunohistochemistry, PCR, and sequencing methodology of the MDR1 target gene.

Results: The results of this study showed that the difference in clinical response of breast cancer patients caused by variation of MDR-1 gene exon 26 on 3435 position, which can make difference in clinical response without affecting the positive or negative Her-2 expression. Patient with mutation type pattern (genotype T/T) have clinical response, while patients who do not show clinical response have wild type pattern.

Conclusion: Our result showed that breast cancer patients with positive Her-2 expression are not always responsive to anthracycline application, meaning that only patients with mutation type pattern (genotype T/T) of MDR-1 gene exon 26 on 3435 position have clinical response, while patients who do not show clinical response have wild type pattern.

164P BREAST CANCER PATIENTS WHO DEVELOPED CENTRAL NERVOUS SYSTEM (CNS) METASTASIS. P53 IMMUNOSTAINING POSITIVITY IN THE PRIMARY TUMOR CORRELATES WITH INCREASED ANGIOGENESIS AND EARLIER DEVELOPMENT OF CNS METASTASES

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Background: Better characterization of clinical parameters and primary tumor characteristics of women with breast cancer who developed CNS metastasis may offer insights into the metastatic process and allow new forms of prevention and treatment of this complication.

Methods: We reviewed the medical records of 950 patients with breast cancer treated at our institutions during 1997 to 2003 and found that 38 (4%) developed CNS metastases. In these 38 patients, we analyzed the clinical course, pathology and the primary tumor immunohistochemistry profile of hormone receptors, HER-2, p53, and microvessel density by the Chalkey count technique using the anti-CD105 antibody E-9.

Results: Median age was 54 years (30-75), 11% < 40 years and median tumor size was 3.5 cm (1.2-17). Median number of positive axillary nodes was 6 (0-27) with negative axillary lymph nodes 29%. Only two patients (5%) had grade 1 tumors. Treatment was brain radiotherapy in 79% of the patients, with 8% living longer than one year. The median survival after the development of CNS metastases was of 4.5 months. In these patients, hormone negative receptor status was found in 63% HER-2 was overexpressed in 68%, p53 was positive in 46% and mean microvessel density was > 7 in 59%. After the diagnosis of breast cancer, the median time to the development of CNS metastases was 22 months Factors related to a faster development of CNS metastasis were p53 positivity and primary tumor size greater than 5 cm (19,3 vs 31,6 months, P = .0330 and 18,5 vs 31,5 months, P =.008, respectively). Primary p53 positive tumors had higher microvessel density counts (P = 0,015), greater mean tumor size (6,1 vs. 3,8 cm, P = 0,057) and were more frequently hormone receptor negative (P = 0,043).

Conclusions: We found that p53 positivity in the primary tumor of breast cancer patients who developed CNS metastases correlates with earlier development of this complication. This finding may be related to an intrinsic more aggressive phenotype as shown by increased angiogenesis, greater primary tumor size and more frequent negative hormone receptor status found in p53 positive patients.

165P INFLAMMATORY BREAST CANCER (IBC) AND BLOOD GROUP ASSOCIATIONS

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Background: Associations between breast cancer and the ABO blood groups have been previously reported implicating rapidly advanced locally breast cancer with blood type A. The association and the prognostic value of ABO blood grouping in inflammatory breast cancer (IBC) has not been determined yet.

Purpose: To assess the relation between blood groups with distribution, clinical and pathological parameters, and prognosis of IBC.

Methods: We conducted a prospective study to evaluate the distribution of ABO in newly diagnosed IBC patients. All clinical diagnosed and histological diagnoses were confirmed. Fifty patients with newly diagnosed IBC evaluated at the IBC Clinic in MDACC between Aug 2006 to Sept 2007 and 50 control subjects (healthy blood donors from our institution) were enrolled. Blood samples were obtained into vacuum tubes containing EDTA from each donor's venous circulation. All blood typing of patients and controls were performed by the blood bank, department of laboratory medicine, MDACC.

Results: The blood type distributions of the patient group were 24 (48%), 8 (16%), 18 (36%) and 0 (0%) for A, B, O and AB respectively, whereas for controls were 12 (24%), 6 (12%), 27 (54%) and 5 (10%). Type A was more frequent in IBC group (p=0.012). The median age of patients group was 53.3 and control group 32.8. Among IBC patients with blood type A 38% were Her2/neu-/HR+, 17% Her2/neu+/HR-, 8% Her2+/HR+ and 38% triple negative. Grade III reported for 67% of this group and 21% had metastatic disease at presentation. Prognosis data will be available Aug 2008.

Conclusion: We observed an excess of blood type A individuals in our IBC patient series. The results suggest that clinicopathological patterns of IBC in association with ABO warrant further evaluation with genomic technology and immune studies. Department of Breast Medical Oncology, IBC Group, The UT. M.D Anderson Cancer Center.

166 DOCETAXEL IN COMBINATION WITH NON PEGYLATED LIPOSOME-ENCAPSULATED DOXORUBICIN (MYOCET®) FOR THE TREATMENT OF METASTATIC BREAST CANCER (MBC) PATIENTS: A PHASE II CLINICAL STUDY

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Background: the current status of treatment of the MBC patients (pts) is based on anthracycline and taxane therapies. However, mostly pts receive anthracycline-based therapy in adjuvant setting and dose-cumulative cardiotoxicity represents a limit for the re-treatment in metastatic setting. Liposome-encapsulated doxorubicin could be a valid choice in this subset of pts.

Methods: we have designed a phase II clinical study to define the activity and cardiac tolerability of non-pegylated liposome-encapsulated doxorubicin 60 mg/sqm iv day 1 in combination with docetaxel 37.5 mg/sqm iv days 1 and 8, every three weeks for six courses in MBC pts pretreated with an anthracycline-based chemotherapy. Cardiac ultrasound exam was performed baseline and every two cycles.

Results: 20 pts have been enrolled in the study with a median age of 58 years (range 41-74) and a median number of 2 metastatic sites of disease (range 1-3). The median cumulative drug dose of epirubicin before entered the study was of 420 mg/sqm (range 360-540). As planned, all pts had a baseline left-ventricle ejection fraction (LVEF) above 50%. So far a total of 92 courses of chemotherapy have been administered with a median number of 5 cycles for pts (range 1-6). Treatment was generally well tolerated. Main toxicities (NCI criteria) were: G 3 diarrhoea 1% of cy, G 3 mucositis 1%, G 3 nausea/vomiting 1% and G 4 leucopenia 6% (2 episodes of FN). No significant reduction of LVEF has been registered by ultrasound monitoring. 17/20 pts were evaluable for activity: 8 pts (47%) (95% CI: 23% to 71%) obtained a partial response, 8 pts (47%) had stable disease and 1 pt (6%) progressed during treatment. Median time to PFS observed was 10.6 months (95% CI: 9.4 to 11.7).

Conclusions: the study is ongoing because of the promising activity and the good profile of tolerability of this combination. Supported by ARCO foundation.

167 PHASE II TRIAL OF PACLITAXEL AND URACIL-TEGAFUR IN METASTATIC BREAST CANCER. TEGATAX TRIAL

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Introduction: This Phase II trial investigated the combination paclitaxel (P) and uracil-tegafur (UFT) in patients (pts) with metastatic breast cancer (MBC).

Methods: Eligibility criteria included HER-2 negative MBC, an ECOG performance status of 0-2, exposure to >1 prior chemotherapy regimen at the metastatic setting, and a previous exposure to an anthracycline containing regimen. Additional criteria included measurable disease, neuropathy <Grade 1, no uncontrolled brain metastases and adequate organ function. Each 35-day cycle consisted of P at 80 mg/m² IV on days 1, 8, 15, 21 and 28, UFT at 300 mg/m² and folinic acid at 30 mg PO TID from days 1 to 28. Treatment was continued until disease progression, unacceptable toxicity, intolerance or withdrawal of consent. Responses were evaluated by RECIST criteria every 2 cycles. The primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DR) and safety.

Results: Between 2003 and 2007, 31 patients were enrolled. Median age was 66 yrs (range 44-78), 7% of pts was triple negative and 81% of pts had visceral disease. A total of 18 pts had received adjuvant chemotherapy; 97% and 3% had 1 and 2 lines of chemotherapy for metastatic diseases, respectively. and 74% had a previous docetaxel containing treatment. One patient did not receive treatment and was subsequently excluded from analysis. Median of 4 and 3 cycles of P and UFT were administered with a relative dose intensity of 85.3% and 94.3 %, respectively. Among 30 treated pts, 12 (40%) (IC95% 22,5-57,5) had confirmed ORR. Stable and progressive disease were reported in 43% and 17%, respectively. Median DR was 8.4 month (IC95% 4.9-11.7), median PFS was 14.6 months and median OS was 23 months. Thirteen pts (43%) experience grade 3/4 adverse event : neuropathy (4), diarrhea (2), neutropenia (5), febrile neutropenia (3), thrombocytopenia (1), anemia (1) and abnormal liver function test (1). One death occurred related to the study drugs (febrile neutropenia). Chemotherapy was discontinued due to toxicity in 9 of pts, P was stopped in 41% pts and UFT in 51%.

Conclusion: ORR is encouraging and warranted further studies with other doses and schedules.

168 BEVACIZUMAB, CARBOPLATIN AND VINORELBINE FOR METASTATIC BREAST CANCER

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Introduction: Monoclonal anti-VEGF antibody bevacizumab in combination with paclitaxel has recently been approved as first-line treatment for metastatic breast cancer. However, there are many breast cancer patients who are not candidates for the combination, either due to intolerance of paclitaxel or due to paclitaxel-resistant disease. Moreover, there have been reports of bevacizumab activity beyond the first line of treatment. We use a combination of bevacizumab, carboplatin and vinorelbine (ACV) in metastatic breast cancer patients that are resistant to taxanes (DFS less than 6 months after taxanes for adjuvant or metastatic disease) or cannot tolerate taxane treatment.

Patients and methods: We analyzed the outcome of 15 patients (age 33-66 years, mean: 49.2) with metastatic breast cancer, that were treated with the combination of bevacizumab (10 mg/m², day 1, 21), carboplatin (AUC 5, day 1, 21) and vinorelbine (30 mg/m² iv, day 1,21 and 30 mg/m² iv or 50 mg/m² pos on day 8). After four cycles of treatment patients were evaluated for objective outcomes and if they had a clinical benefit (CR, PR or SD), four additional cycles were given. At the completion of treatment patients that still had a clinical benefit continued to receive bevacizumab monotherapy (every 3 weeks at the same dose level), with hormonal treatment, where applicable, until disease progression. Three patients received the combination as first-line chemotherapy.

Results: Until now a total of 105 cycles have been given (mean number of cycles 7). Two patients had disease progression after 4 cycles of treatment and were discontinued. There were 11 patients with objective responses (73.3%), with three complete responders (20%). Median progression-free survival (Kaplan-Meier) is 278 days. Treatment was well tolerated; however, in three patients a dose-adjustment was required, mainly due to hematological toxicity. There were six patients with grade 4 neutropenia, but only one episode of febrile neutropenia that needed iv. antibiotics. G-CSF was administered in ten patients and erythropoietin in six. One patient, receiving ACV as third line treatment had an impressive partial response in lung and complete response in liver metastases; however she developed an asymptomatic thrombosis of the inferior vena cava. Treatment was discontinued and she received LMWH, hormonal treatment and

ibandronate. She is still progression-free and asymptomatic. There were no treatment-related deaths.

Conclusions: Bevacizumab, carboplatin and vinorelbine is an effective combination for the treatment of metastatic breast cancer, even beyond the first line. The main toxicity is hematological; it is, however, easily managed.

169 FRENCH EXPERIENCE OF PATIENTS' MANAGEMENT WHEN RECEIVING VINORELBINE ORAL CHEMOTHERAPY (NVBO) FOR A METASTATIC BREAST CANCER: FIRST RESULTS OF A PROSPECTIVE OBSERVATIONAL SURVEY ON PRACTICES

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Background: An observatory on practices has been implemented in France with the aim of investigating the correlation between patient (pt) profile and the use of an oral chemotherapy (OCT), NVBO.

Methods and Materials: Three questionnaires were used: a "Physician" questionnaire (medical practice conditions, physician profile, prescription habits, role of OCT), a "Patient" questionnaire (completed by the physician describing the pt disease history and characteristics, general condition, prescription selection factors, monitoring and compliance), and a Patient Preference self-questionnaire (partly based on the EORTC QLQ-BR23). 350 pts were planned, 5-15 patients per physician.

Results : An interim analysis was performed on the first 200 pts enrolled since 02/2006 in 37 centres: private centers (45%), public hospitals (44%) and cancer institutes (11%). Pts had previously received CT [82.5% - intravenous(iv) CT in 77% (including iv + OCT in 8 %)] and hormonal therapy (72.5%). 31 % of patients had already received OCT (41.9% with a slowly progressing tumour). The breast tumours were mainly considered as having limited aggressiveness (82.7%) with no visceral metastasis (37.8%) or with slowly progressing visceral metastasis (DFI > 24-36 months) for 44.9% of them. Physician's major parameters of OCT choice were: patient-related factors (QOL 97.3% and pt preference 83.7%); treatment-related factors (efficacy 94.6%, maintenance or consolidation 37.8%); venous administration concerns (54%) and economic reasons (58.3%). NVBO was prescribed as monotherapy in 56% and combined with others agents in 44% (iv in 50.6% and oral in 64.4%). According to physicians, pts preference for OCT was related to: reduced hospital stays (78.4%), improved QOL (freedom 63.9% and convenience 70.6%). Treatment compliance, according to patient declarations, was 91.5%.

Conclusions: NVBO brings added value in terms of pt acceptance, allowing optimal compliance to treatment schedule. Final data will be presented at the congress.

170 BENEFIT OF NEOADJUVANT DOCETAXEL IN TREATMENT OF BREAST CANCER

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Aim: To prospectively compare neoadjuvant docetaxel with anthracycline-based chemotherapy as regards efficacy and toxicity in patients with locally advanced breast cancer who initially failed to respond on other anthracycline based combination.

Patients and methods: Patients with locally advanced breast cancer were randomized to receive either 3 cycles of FAC (arm A) or 3 cycles of TAC (arm B). Clinical and radiological tumor responses were assessed after 3 cycles. Responders continued on the same regimen for another 3 cycles before surgery. Non-responders in arm A received 3 cycles of docetaxel single agent at a dose of 100mg/m². Non-responders in arm B were treated by surgery or radiotherapy followed by second line chemotherapy.

Results: Thirty female patients were enrolled in each arm. None of the patients achieved CR in both arms. PR was documented in a 100% of the patients in arm A, whereas only 17 patients (56.7%) achieved PR in arm B. The rest of the patients in arm B had stable disease in 9 patients (30%) and progressive disease in 3 patients (10%). After 6 cycles of chemotherapy CR was achieved in 3 patients (10%) and 8 patients (26.7%) respectively in arm A and B. In arm A 22 patients (73.3%) had PR, 4 patients (13.4%) had SD and one patient (3.3%) had PD. The remaining 22 patients (73.3%) in arm B continued to have PR. Assessment of the conservation rate showed that

conservative surgery was done in 12 patients (40%) in arm A versus 20 patients (66.7%) in arm B. There was no statistically significant difference between both arms regarding disease-free survival, but grade III-IV toxicities were more evident in arm B.

Conclusion: Neoadjuvant docetaxel improved response rate and breast conservation rate in patients with locally advanced breast cancer, but with more side effects.

171 RESPONSE EVALUATION TO INDUCTION CHEMOTHERAPY IN PATIENTS WITH INFLAMMATORY BREAST CARCINOMA

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Background: Response evaluation in patients with inflammatory breast carcinoma (IBC) still represents challenge, because standard criteria especially for partial remission and disease stabilization definition, usually cannot be applied. The aim of this retrospective analysis is to evaluate responses to induction chemotherapy in IBC pts.

Patients and methods: Among 2154 breast carcinoma (BC) pts. registered during one year at the Institute for Oncology and Radiology of Serbia (IORS), 178 patients (8, 2%) had clinical diagnose of IBC.

Results: Data were available for 82 IBC pts. Median age was 59 range (42-81); stage III 76%, stage IV (24%); Lymphangiiosis confirmed in 56% pts.; underlying BC confirmed in 95% pts. and 4,8% pts. had only skin lymphangiiosis, without underlying BC Steroid receptor status is assessed in 93%pts. At least one receptor + 61% (47 pts.); both receptor - 39% (30 pts/) HER2 status (IHH, Dako) assessed in 52 patients (83%): HER2 3+ 33%; triple negative 11% Induction chemotherapy: FAC in 65 pts. (79%) CMF in 18 pts.(20%) 6 pts treated with tamoxifen only, due to poor PS Trastuzumab was not given. Responses were evaluated after 4-6 chemotherapy cycles. Clinical and mammography CR was defined as complete disappearance of previously palpable breast tumor; no clinical and mammography signs of cancer mastitis; no enlarged regional lymph nodes, and disappearance of all metastatic sites, if any. CR is achieved in 4 pts (4,8%) all treated with FAC, for stage III One CR achieved in HER 2 3+ IBC.PD as best response is recorded in 24,3 % of pts. Responses that could be only defined as disease control, defined as no CR, no PD, without certain characteristics for either PR or SD, is achieved in 75, 9% of pts. and 17% could not be interpreted.

Conclusion: Incidence of IBC seems to be higher than reported in the literature (8,2% vs 1-4%), Clinically and by mammography, CR was achieved in 4,8% patients. However, responses other than CR and PD could not be accurately defined because inconsistency of response description. Therefore, there is a clear need for determination of specific response criteria for IBC.

172 PROGNOSTIC FACTORS IN PATIENTS WITH BREAST CANCER AND MALIGNANT PLEURAL EFFUSION

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Background: malignant pleural effusion (MPE) is frequently seen in patients with breast cancer and has been associated with poor prognosis in studies performed more than 2 decades ago. As recent advances in breast cancer treatment have improved survival, we investigated current survival and prognostic factors in these patients.

Patients and methods: we analyzed data from all patients (n= 49) registered during 2000-2006 with breast cancer and cytological confirmed MPE at Medical Centre Alkmaar Hospital. Results: Median age at the time of diagnosis of MPE was 65 years (range 32-89years). Most effusions were uni- and ipsilateral to the affected breast (66%). When MPE presented as the only site of breast cancer recurrence, survival was significantly longer (49 vs. 16 months, p=0,005). However, metastatic disease at other sites was common: 38% at diagnosis of MPE, 89% during follow up. An interval < 5 years from breast cancer diagnosis to detection of MPE was associated with worse prognosis (11 vs. 27 months, p=0.029). A majority of 45 patients (90%) had hormone receptor positive disease, with a trend for improved survival (20 vs. 7 months, p=0.12). Worse outcome was observed in her2 overexpression (6 vs. 30 months, p=0,01). Treatment consisted of pleurodesis in 24 patients (67%) and systemic therapy in 48 patients (98%), chemotherapy n=25, hormone therapy n=35, both n=19). Hormone therapy was associated with survival benefit (21 vs. 5 months, p=0.01). Median survival from the onset of MPE was 9.3 months (range 0.1-81 months). One and two years after MPE diagnosis, 23 (47%) and 15 (31%) patients were alive, respectively.

Conclusions: Prognosis of MPE in breast cancer is highly variable. Favorable prognostic factors are a long interval from initial diagnosis to MPE, MPE being the only site of recurrence, hormone receptor positive disease and lack of her2 overexpression. Compared to historic literature our results suggest that prognosis of breast cancer patients with MPE has improved over time.

173 CLINICAL EXPERIENCE WITH METRONOMIC CHEMOTHERAPY IN HEAVILY PRETREATED METASTATIC BREAST CANCER PATIENTS

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Background: Anticancer chemotherapy is thought to be effective by direct cytotoxicity on tumor cells. Alternative mechanisms of efficacy have been ascribed to several common anticancer agents, when given on continuous low doses, postulating an antiangiogenic effect. Oral Cyclophosphamide (CTX) and oral Methotrexate (MTX) are among the most studied drugs in this context.

Objectives: We report our experience in the treatment of heavily pretreated metastatic breast cancer patients, using a metronomic chemotherapy schedule based on low-doses oral MTX and CTX. Data on clinical efficacy and toxicity are presented.

Patients and methods: Patients included in the study had histologically confirmed metastatic breast carcinoma and have received more than two lines of chemotherapy for metastatic disease. Oral MTX was administered 2.5 mg twice a day on days 1 and 2 each week and oral CTX 50 mg per day taken daily. Results: Between December 2006 and February 2008 thirty-five patients were enrolled: median age 59.2 years (range 34 - 88); ECOG 0-1 74%; ER 77.1%; Her2 positive 37.1%; >2 sites of metastatic disease 85.7%; visceral metastatic disease in 83%; 80% of patients have been previously treated with antracyclines, taxanes and capecitabine for metastatic disease. Among the 27 evaluable patients, 6 patients (22.2%) achieved a partial response (PR), and there was an overall clinical benefit (PR + stable disease (SD) after 12 weeks) in 55.5%. Progression free survival was 5.8 months, and overall survival was 5.9 months. The toxicity profile was excellent, the most remarkable events were grade ≥ 2 leucopenia in 7 patients, grade ≥ 2 hepatic toxicity in 5 patients and grade 1-2 nausea/vomiting in 7 patients.

Conclusions: Metronomic chemotherapy with CTX and MTX shows activity in metastatic breast cancer. The favourable toxicity profile of this oral treatment makes of it a suitable option for heavily pretreated patients.

174 N/T QUOTIENT: A CLINICAL PROGNOSTICAL FACTOR RELATED WITH EXPRESSION OF BIOLOGICAL PREDICTIVE FACTORS

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Introduction: The N/T quotient is the relationship between the number of positive axillary lymph nodes (N) and the size of the primary tumour (T). There are studies that related this quotient to time to progression in patients with metastatic breast cancer. Furthermore, breast cancer can be classify according to the immunochemical study in different biological profiles, each with a different prognosis.

Objectives: Analyze the quotient N/T in the different biological profiles according to immunohistochemical study.

Method: We analyzed a series of 230 women with breast cancer and a known N/T quotient between ≤ 2 and >2 . The patients were classified retrospectively, according to age of diagnosis, histological type, differentiation grade, stage, hormonal receptors (ER and PR) and erb2. The data were analyzed using contingency tables and Chi-square distribution, according to the statistical program SPSS.12.0. RESULTS: The mean age at diagnosis was 56.7 years (26-85). The most common stage was Ib (42,7%). The most frequent histological type was infiltrating ductal carcinoma with moderate grade of differentiation (35,6%). We also analyze the grade the differentiation, estrogen expression, progesterone, Ki67, and Her-2 in patients with N/T quotient ≤ 2 or >2 . In the analysis the triple negative fenotype is more frequent in that women with N/ T > 2 quotient (19%), p= 0,0018.

Conclusion: Those patients with high N/T quotient (> 2) have more aggressive fenotype.

175 CARDIAC TOXICITY WITH TRASTUZUMAB IN METASTATIC BREAST CANCER-USE BEYOND ONE YEAR

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Introduction: In patients with breast cancer the duration of treatment with adjuvant trastuzumab (Herceptin) is one year. In patients with metastatic breast cancer who continue to benefit from trastuzumab, the time frame to stop trastuzumab is not defined. The most common limiting factor is cardiac dysfunction. With this background the data sheet for metastatic breast cancer receiving trastuzumab for one year and beyond were studied at our centre.

Methods: All the patients receiving trastuzumab in metastatic breast cancer for more than one year were reviewed for the incidence of cardiac toxicity. As a practice MUGA

scans were done at baseline for all the patients and followed every 3 months. Left ventricular ejection fraction (LVEF) decrease of >15% points or to <50% was used as a surrogate for clinical cardiac events.

Results: Forty six patients were identified receiving trastuzumab ranging from 12 months to 33 months. Baseline MUGA scan was showing essentially normal LVEF (mean 59%). Three patients (6.5%) stopped trastuzumab after a non symptomatic significant fall of LVEF. Of which one patient was restarted with trastuzumab after 3 months when she recovered her LVEF. Total duration of trastuzumab received was from 12 months to 33 months (mean 15.5 months).

Conclusion: The risk of cardiac toxicity observed was matching with international experience. In one of the patients the decline in LVEF was reversible and we could restart trastuzumab treatment safely. With regular follow up by MUGA scans trastuzumab can be given safely for longer periods.

176 CLINICAL EXPERIENCE WITH FULVESTRANT, PURE OESTROGEN RECEPTOR (RE) ANTAGONIST WITH NO AGONIST EFFECTS, IN PRE-TREATED ADVANCED BREAST CANCER PATIENTS

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Objective: To determine Fulvestrant (F) Clinical Benefit (CB) in pre-treated patients (pts) with hormone-receptor positive advanced breast cancer (ABC).

Methods: Eighty four ABC patients treated with F 250 mg i.m. monthly were evaluated. Histology: 76% ductal, 17% lobular, 7% others. Median age: 64 (42 - 79). Hormone Receptor status: RE y RP+: 58 pts (69%), RE+ y RP-: 19 pts (22%), RE- y RP+: 4 pts (5%) and unknown: 3 pts (4%). Non visceral metastases 61 pts (73%) and visceral metastases: 23 pts (27%). Fifty percent of pts received 2 or more prior therapies for advanced disease (chemo and/or endocrine therapies).

Results: The mean of F doses was 8 (2-21). 60 pts (71%) experienced CB with F: 5 pts CR (6%), 19 pts PR (22%) y 36 pts (43%) SD \geq 24 weeks. There was a non significant statistical trend to greater CB in first and second line treatments versus more than 2 (75% vs 67%), and in RE+ y RP+ tumors vs RE+ y RP- vs RE- y RP+ ones (74% vs 68% vs 50%). The median time to progression (TTP) was 16.8 months in pts with CB vs 4.2 months in pts without CB (p<.0001). There were no serious adverse events only hot flushes in 8 pts (9%), gastrointestinal disturbances in 11pts (13%), injection site pain in 3 pts (3%), arthralgia and weight gain in 1 pt.

Conclusion: Fulvestrant showed an important clinical activity even in heavily pre-treated ABC patients with a good toxicity profile. The right selection of patients in terms of hormonosensitivity criteria was key for achieving this endpoint.

177 FULVESTRANT FOR METASTATIC BREAST CANCER: EXPERIENCE WITH 74 PATIENTS

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Introduction: Fulvestrant is a estrogen receptor (ER) antagonist without known agonist effect. Phase III trials have demonstrated similar efficacy with aromatase inhibitors (AI) in post-menopausal women for metastatic breast cancer in second and third line of treatment.

Methods: Retrospective analysis of 74 patients with metastatic breast cancer treated with fulvestrant at our institution from 2003 to 2006. Primary end-point was to evaluate time to progression. Clinical variables were compared to survival, and safety data were analysed.

Results: Median age was 55 years. Majority (67.5%) were both ER and progesterone receptor positive and 18.9% were Her2 positive. 67.5% of patients presented bone metastasis, 36% lung metastasis, 17% lymph nodes, 13% liver, 9.5% skin. Overall, 59% of patients presented visceral metastasis and 40.5% non-visceral metastasis. 54% had received previous chemotherapy, with median lines of therapy of 1. Median time to progression (TTP) was 11 months, 13 months if fulvestrant was used for first line hormone therapy, 6 months for second line and 12 months for third line (P=0.89). TTP for patients with both positive ER and PR was 14.4 months, ER positive and PR negative was 6 months, ER negative and PR positive was 3 months (P=0.001). TTP for patients with visceral metastasis was 7 months and 14 months for non-visceral metastasis (P=0.09). Sixteen patients were on fulvestrant therapy by February 2008. No grade 3 or 4 adverse events were observed.

Conclusion: Fulvestrant is effective for the treatment of patients with metastatic breast cancer. TTP was influenced by hormone receptors status in our study. In accordance with the literature, this study showed that fulvestrant was an option for patients with visceral metastasis.

178 QUALITY OF LIFE RESPONSE IN WOMEN WITH ADVANCED BREAST CANCER RECEIVING FASLODEX (FULVESTRANT) AFTER PROGRESSION ON PRIOR ANTIESTROGEN THERAPY

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The major goals of treatment of advanced breast cancer patients are maintenance of quality of life (QoL) and palliation of cancer-related symptoms. We aimed to study QoL treatment response and symptom dynamics in advanced breast cancer patients receiving once-monthly i.m. injection of Faslodex (fulvestrant) 250 mg. 114 postmenopausal women with disease progression after prior antiestrogen therapy were enrolled in phase IV multicenter longitudinal study (the data collection will be finalized by September 2008). QoL was assessed using SF-36; symptoms – M.D. Anderson Symptom Inventory at base-line and at different time points within the year of treatment. The distribution of patients according to the grades of QoL impairment using normative data was provided. To evaluate QoL response the Integral QoL Index was calculated at base-line and in 5 months. Data on 62 women (mean age – 56.5; SD 9.5) were included in the preliminary analysis. Half of the patients experienced critical (22.5%) or severe (27.5%) QoL impairment. Moderate and mild QoL impairment was observed in 12.5% and 7.5% of patients, respectively. 30% of patients had no QoL impairment. All patients with critical and severe QoL impairment experienced fatigue; 90 % - pain, sleep disturbance, distress, and dyspnea. More than half of the patients reported significant (5 and higher on 0-10 scale) level of these symptoms. After 5 months of treatment QoL stabilization was shown in 58% of patients, QoL improvement – in 29% of patients, and QoL worsening – in 13% of patients. The majority of patients with fatigue, pain, and distress before treatment had either symptom reduction (42-49%) or symptom stabilization (29 - 37%). Sleep disturbance and dyspnea reduced in 38% and 37% of patients and stabilized in 35% and 37% of patients, respectively. The preliminary data show that the use of the fulvestrant in the adjuvant settings for advanced breast cancer patients resulted in high QoL response rates, namely the majority of the patients experienced QoL improvement or QoL stabilization after 5 months of treatment. Symptom relief was observed in almost half of the patients. Evaluation of QoL response rate is a key issue for management of advanced cancer patients.

179 ADVANCED BREAST CANCER PATIENT POPULATION IS HETEROGENOUS IN TERMS OF QUALITY OF LIFE (QOL) IMPAIRMENT

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Taking into account that in advanced breast cancer (ABC) QoL is the major outcome, treatment strategy might be dependant on the degree of QoL impairment. We have analyzed the following grades of QoL impairment as compared to a population norm (PN): mild (25% decrease from a PN), moderate (25-50% decrease), severe (50-75% decrease) and critical (>75% decrease). We aimed to study distribution of ABC patients according to the grades of QoL impairment. 250 women (mean age 56.1) were enrolled in the study. To compare with controls a gender- and age-adjusted sample from the population norm was used. SF-36 and M.D. Anderson Symptom Inventory (consists of 0-10 scale for thirteen symptoms) were used for patient-reported outcomes assessment. To distribute patients according to the grades of QoL impairment the Integral QoL Index was calculated for each patient on the basis of SF-36 scales. The majority of patients experienced critical (25.6%) or severe (16.8%) QoL impairment. Moderate and mild QoL impairment was observed in 13.6 % and 11.2% of patients, respectively. 32.8% of patients had no QoL impairment. The value of QoL indices differed significantly depending on the grade of QoL impairment (P<0.01, Mann-Whitney test). The number of symptoms experienced by a patient simultaneously differed significantly across the groups (P<0.01, Fisher's exact test). In the group with critical QoL impairment the largest number of patients (28%) reported all 13 symptoms. On average, patients in the groups with critical and severe QoL impairment had 10 symptoms simultaneously while patients with moderate and mild QoL impairment experienced on average 7 symptoms at the same time. Patients with no QoL impairment reported in average of 4 symptoms. The results show that population of ABC patients is heterogeneous in terms of quality of life impairment. The majority of patients exhibit critical or severe QoL impairment compared with a population norm. The number of symptoms experienced by the patients differed significantly depending on the group of QoL impairment. Grading of QoL impairment with the special emphasis to the groups with critical and severe QoL impairment is worthwhile to provide adequate management of advanced breast cancer.

180 **COMBINATION OF PALONOSETRON AND BROMAZEPAM AS PRECAUTION AGAINST VOMITING CAUSED BY CHEMOTHERAPY IN PATIENTS WITH BREAST CANCER**

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Palonosetron (P), a selective competitor of the 5-HT₃ receptor, is a highly effective drug against nausea and vomiting caused by chemotherapeutic cytotoxic factors that have highly emetic side effects. Its effectiveness though is decreased in patients who are treated with factors that only moderately cause vomiting. In this study, a combination of palonosetron (P) and bromazepam (B) was used as a precaution

for patients with breast cancer (BC), treated with chemotherapy with moderate vomiting side effects. The scheme administered as follows: palonosetron 250 µg iv bolus 30 min before chemotherapy; bromazepam - tab 3 mg p.os. 60 cases out of the 64 patients originally included in this study were studied. Results: The total degree of response was 93.4%. Complete or significant response was observed at 53.2% of the patients. As far as the safety and tolerance are concerned the present study showed that all patients tolerated the treatment well and side effects; (8 patients displayed fatigue, 6 headache, 4 tachycardia, 2 constipation, and 2 fever) were mild and temporary.

Conclusion: The combination of P and B is highly effective at controlling vomiting caused from moderately vomit-producing cytotoxic chemotherapeutic factors that are given to patients with breast cancer.