increased investigator-assessed progression free survival (PFS) over letrozole alone (8.2 vs 3.0 mo, HR = 0.71 (0.53, 0.96) P = 0.019) for women with endocrine sensitive, HER2+ (ErbB2+), previously untreated MBC. Two sub-populations within the HER2+ pt cohort were examined in retrospective analyses: presence of baseline liver metastases and ⩾3 baseline metastatic organ sites.
Methods: 1286 pts were randomized to letrozole/lapatinib or letrozole/placebo. HER2+ was defined by a positive FISH ratio (>2.0) or by immunohistochemistry 3+. Investigator-assessed PFS in these subpopulations were analyzed using Kaplan-Meier with stratified log rank to compare treatment arms within each subgroup: pts with baseline liver metastasis (n = 71) and pts with ⩾3 baseline metastatic organ sites (n = 89).
Results: Pts with HER2 amplified breast cancer who had baseline liver metastasis derived a greater PFS benefit with combination lapatinib and letrozole: 2.7 to 4.4 mo, HR = 0.39 (0.23, 0.65), P ⩽ 0.001. Combination therapy for pts with ⩾3 baseline metastatic organ sites prolonged median PFS from 2.7 to 8.0 mo, HR = 0.59 (0.37, 0.94), P = 0.015.
Conclusions: These retrospective data provide further evidence of the effectiveness (prolonged PFS) of the oral lapatinib/letrozole combination in HER2 amplified, endocrine sensitive metastatic tumors in pts with visceral burden or higher number of metastases.

5078 POSTER

Treatment of leptomeningeal involvement of breast cancer with high-dose methotrexate and ifosfamide

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Background: Leptomeningeal spread in solid tumors has a poor prognosis. Intrathecal chemotherapy and radiation are symptomatic therapeutic approaches. Systemic chemotherapy with blood-brain-barrier crossing agents might be beneficial regarding its potential to treat concomitant brain metastases and systemic disease. In a pilot trial we treated patients with meningeal spread of breast cancer (BC) with high-dose methotrexate and ifosfamide (HDMTX/IFO).
Methods: From July 2007 all consecutive BC patients with leptomeningeal involvement and creatinine clearance >50 ml/min have been treated with 4 g/m^2 MTX as a 4 h infusion on day 1 (with dose adjustment for creatinine clearance and leucovorine rescue starting after 24 hours) and 1.5 g/m^2/day IFO as a 3 h infusion on days 3−5. Treatment was continued for a maximum of 8 cycles.
Results: Three female patients aged 59, 62 and 65 years have been treated thus far. All had concomitant systemic metastases (bone and liver), two patients had been pretreated with up to four systemic chemotherapy regimens. Presenting symptoms were hemi- and paraparesis, radicular pain and multiple cranial nerve palsies. In the first patient chemotherapy was stopped after two cycles due to renal toxicity CTC 2º. She remained neurologically stable for 1.5 months and then received intrathecal chemotherapy followed by six cycles of systemic chemotherapy with topotecan and ifosfamide. She was neurologically improved eleven months after start of HDMTX/IFO. Two patients received six and seven cycles chemotherapy and markedly improved neurologically with stable systemic disease. Time to neurological progression was 5.5 and 7.0 months and overall survival was 8.3 and 11.0 months, respectively.
Further grade 3 or 4 toxicities were thrombopenia 3º in one and leucopenia 3º in two patients.
Conclusion: Systemic chemotherapy with HDMTX/IFO is feasible and active in leptomeningeal involvement of BC. Further improvement may be achieved by additional intrathecal therapy. Liposomal cytarabine has demonstrated impressive activity in malignant leptomeningeal disease. Therefore we initiated a multicenter phase II trail combining systemic HDMTX/IFO and intrathecal liposomal cytarabine in BC patients with meningeal +/− brain relapse.

5079 POSTER

Role of paclitaxel in neoadjuvant chemotherapy in stage IIA-IIIA breast cancer

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Background: Neoadjuvant chemotherapy with doxorubicine and cyclophosphamide in **stage IIA-IIIA** breast cancer has a proven importance. In order to analyze the impact of adding paclitaxel to this regimen, a prospective study was designed in 2004.
Methods: The studied lot consisted in 124 patients admitted in the Oncology Clinic of Craiova, Romania between February 2004 and March 2009. The most important eligibility criteria were: stage IIA-IIIA breast carcinoma, her-2/neu negative, measurable disease and an ECOG performance status of 0 or 1. Patients were randomized 1:1 in order to receive the standard regimen (doxorubicine 60 mg/sqm, cyclophosphamide 600 mg/sqm;) – group A, or paclitaxel plus standard regimen (doxorubicine 60 mg/sqm, cyclophosphamide 600 mg/sqm and paclitaxel 200 mg/sqm;) – group B. Both regimens were administered in cycles repeated every 21 days. If partial response occurred after 2 cycles, patients undertook surgical treatment without further chemotherapy; if not, they were administered a total of 4 cycles, followed by surgery. Stratification criteria were: age, staging, involvement of axillary lymph nodes and hormonal receptors status. Primary endpoints of the study were the response rate for each arm of the study and the quality of life in each group; the latter was assessed using a specific questionnaire.
Results: 124 patients were randomized between February 2004 and March 2006: 62 in group A and 62 in group B. The groups were well balanced regarding the stratification criteria. A significant difference was found between response rates in the 2 groups: partial response rates were 64.51% in group B compared to only 51.62% in group A, while complete response occurred only in group B (1.61%). The remainder of the patients had stationary disease after the regimens: 33.87% of group A and 48.39% of group B. The odds ratio for developing a partial response after the triple association regimen compared to the double association one was 1.25:1. We observed significant toxicities for triple association regimen when compared with standard regime: 34% of grade 3 neutropenia versus 15% and 15% peripheral neuropathy versus 3%.
Conclusions: Despite the higher incidence of neutropenia in the triple association regimen, the higher response rate recommends it as neoadjuvant chemotherapy for stage IIA-IIIA breast cancer.

5080 POSTER

Safety and tolerability of fulvestrant high-dose (500 mg) in postmenopausal women with hormone receptor positive advanced breast cancer

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Background: Two open-label, multicenter Phase II trials, NEWEST (9238IL/0065) and FIRST (9238IL/0006), have shown improved biological and clinical efficacy with fulvestrant high-dose regimen (HD; 500 mg/month + 500 mg on day 14 of month 1) compared with fulvestrant approved-dose (AD, 250 mg/month) and anastrozole, respectively, in either the neoadjuvant and first-line setting in women with hormone receptor-positive advanced breast cancer. Here, safety and tolerability data are presented.
Material and Methods: NEWEST: 211 patients were randomised to fulvestrant HD (n = 109) or AD (n = 102) for 16 weeks prior to curative surgery. At 16 weeks, AEs, endometrial thickness, and serum bone markers were compared with baseline-data. FIRST: 205 patients were randomised to fulvestrant HD (n = 102) or anastrozole (n = 103) as first-line therapy until progression or withdrawal due to an AE.
Results: NEWEST: Incidence rates for any AE (irrespective of causality) were comparable in both groups (72.9% for fulvestrant HD vs. 69.3% for fulvestrant AD), with injection site pain being most common within the HD-group and hot flashes within the AD-group. SAEs other than death occurred in 13.1% in the HD-group and in 11.9% in the AD-group; 0.9% vs. 3% were judged as treatment-related. AEs leading to withdrawal of treatment were rare (0.9% for fulvestrant HD vs. 1% for fulvestrant AD). No adverse effects on endometrial thickness or serum bone markers were identified in either group. FIRST: Incidence rates for any AE were comparable in both groups (70.3% vs. 69.9%) as were incidence rates for drug-related AEs (29.7% for fulvestrant HD vs. 28.2% for anastrozole). Among drug-related AEs, hot flashes were most common in both groups (7.9% vs. 12.6%). SAEs were rare in both study groups (11.9% vs. 9.7%), including only one patient in the fulvestrant HD group with a drug-related SAE (hypertension). Three patients in each group (3.0% vs. 2.9%) experienced an AE leading to discontinuation of treatment.
Conclusions: The safety profile of fulvestrant HD is comparable with that of fulvestrant AD and anastrozole. Fulvestrant HD was well tolerated and

rates of drug-related withdrawal were very low in both the neoadjuvant and the first-line setting.
The ongoing phase III study CONFIRM will provide further clarification of the role of fulvestrant HD in postmenopausal patients with recurrent and metastatic breast cancer.
Sponsored by AstraZeneca. Fulvestrant HD and Fulvestrant for neo-adjuvant treatment are non-approved regimens.

5081 POSTER

Triple combination of 3-weekly trastuzumab (T) plus oral vinorelbine (VNR) and capecitabine (CAP) as first-line treatment in HER2-positive metastatic breast cancer (MBC): an active and well-tolerated regimen that allows patient compliance

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Background: Both VNR and CAP are known to be active agents combined with T in HER2+ MBC. The possibility of an *all-oral* formulation makes VNR/CAP an attractive new regimen to be combined with T. Based on our previous extended experience with weekly T and oral VNR in this patient population (*EJC Suppl. 2008, vol 6, nº7, abstr.418*), we designed a phase II trial to verify the activity and tolerability of a triple combination of T/VNR*os*/CAP, aiming to further improve clinical outcome and patient compliance.
Patients and Methods: Thirty-four consecutive chemo-naïve patients (pts) with measurable HER2+ (defined as IHC 3+ or FISH+) MBC were enrolled in a prospective phase II trial: median age 52 years (range 41−69); ECOG PS was 0 in 26 pts and 1 in 6; prior neo/adjuvant chemotherapy in 70%; visceral involvement in 82%, 12 pts had bone metastases combined with liver/lung lesions; >2 metastatic sites in 10 pts (29%). Patients received T on day 1 at loading dose of 8 mg/Kg as a 90-minute infusion, then 6 mg/Kg every 3 weeks, combined with VNR at a fixed dose of 60 mg/m^2 *per os* on days 1[amp;]8 and CAP at 1000 mg/m^2 bid days 1->14, every 3 weeks. Treatment was continued until progression or unacceptable toxicity.
Results: Median number of cycles per patient was 9 (range 4−12); median relative dose-intensity was 98% for T, 88% for VNR and 80% for CAP. Worst toxicity was haematological, with WHO 3−4 neutropenia in 36%-12% of pts; no patient developed febrile neutropenia; diarrhoea, mucositis and nausea/vomiting did not exceed gr.2; asymptomatic grade 2 LVEF decline was documented in 2 pts, at the 4th and 6th cycle; asthenia, hand&foot syndrome and constipation were transient and quickly reversible. The overall response rate (RR) was 88% (95% CI: 22−54) with 7 complete (20%, 4 in the liver, 3 in lymph nodes), and 22 partial (65%) responses; 3 pts had stable disease >6 months and 2 pts progressed, for an overall disease control of 94%. Median PFS was 12 months, median overall survival has not been reached.
Conclusions: The tested schedule appeared to be highly active and well tolerated as first-line treatment for HER2+ MBC, also improving patient compliance by allowing a more convenient once every three weeks hospital admission.

5082 POSTER

Lapatinib (L) plus capecitabine (C) in HER2+ metastatic breast cancer (MBC): exploratory analyses by prior therapy

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Background: EGF100151 demonstrated L+C improved time to progression (TTP) relative to C alone in women with HER2+, trastuzumab-exposed MBC (Geyer, NEJM;355(26):2006). Eligible patients (pts) had prior exposure to anthracyclines, taxane, and trastuzumab. These exploratory analyses evaluated TTP and overall survival (OS) in subgroups based on prior regimens.
Methods: TTP is based on independently reviewed data as of 03 April 2006, when enrollment was halted with 399 pts. OS was based on data as of 01 October 2008 and includes 9 pts who were in the screening process and permitted to enroll to L+C for a total of 408 pts. TTP and OS were evaluated using Kaplan Meier analyses. The three subgroups were defined as follows: (1) pts treated with <3 prior regimens; (2) pts treated with ⩾3 prior regimens, where a regimen was defined as any prior therapy in any setting (neo-adjuvant, adjuvant or metastatic); and (3) pts treated with only 1 prior metastatic trastuzumab regimen, regardless of other regimens received in neo-adjuvant or adjuvant settings. Cox regression with treatment (trt), prior regimens, and an interaction was performed.
Results: Table 1 presents results. Pts with <3 prior regimens on L+C had a 63% reduction in the risk of progression and a 49% reduction in the risk of death. Pts with ⩾3 prior regimens had a 41% reduction in risk of progression with L+C but no significant improvement in OS. TTP cox model indicated a significant trt effect and no effect due to prior regimens or the interaction. OS cox model indicated a significant interaction, however trt and number of regimens were not significant. Pts who received only 1 prior metastatic trastuzumab regimen had a 46% reduction in the risk of progression with L+C and a 37% reduction in the risk of death.

Table 1: Exploratory Analyses by Prior Regimens: TTP and OS

Subgroup	<3 regimens (any)		⩾3 regimens (any)		only 1 prior metastatic trastuzumab (2nd line trmt)	
(pts treated)	L+C	C	L+C	C	L+C	C
TTP						
N treated	29	37	169	164	44	44
Median wks	49.4	19.7	25.4	18.6	26.7	20.7
HR 95% CI, p	0.37 [0.18, 0.77] p = 0.006		0.59 [0.43, 0.82] p = 0.001		0.54 [0.28, 1.03], p = 0.046	
OS						
N treated	31	37	176	164	45	46
Median wks	87.3	55.1	71.4	66.6	94.3	62.6
HR 95% CI, p	0.51 [0.30, 0.86] p = 0.009		0.95 [0.76, 1.21] p = 0.698		0.63 [0.40, 1.00], p = 0.042	

Conclusion: Results from these exploratory analyses suggest there may be benefit in using L+C in pts treated with fewer prior regimens and with only one prior trastuzumab regimen.

5083 POSTER

Interaction between bisphosphonates and taxanes in patients with metastatic bone disease

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Background: A synergism between bisphosphonates (BP) and taxanes in breast cancer cell line MCF-7 was previously demonstrated *(Jagdev et al, BJC, 2001)*. Taxanes have important antitumor effect by interfering with microtubule structure and have showed to be very active in patients with prostate cancer and bone metastases. Since osteoclasts are rich in microtubules (needed for their polarity) it is possible that taxanes could act also directly on osteoclasts potentiating the action of BP.
The aim of the present study was to analyse the effect of adding taxanes in patients with solid tumors and bone metastases progression already treated with BP and chemotherapy.
Material and Methods: Twenty-six patients (median age 59.5) with bone metastases treated before with BP (zoledronate: 15; pamidronate: 5, pamidronate followed by zoledronate: 6) and previous chemotherapy regimens were included. Fourteen patients (53.8%) had breast cancer, 9 had prostate cancer, 2 had gastric cancer and 1 had lung cancer. The median time between the beginning of BP and the beginning of the taxane (paclitaxel – 9 patients or docetaxel – 17 patients) was 17 months. All patients continued on the same BP regimen at the moment of association of taxane and all patients had bone disease progression.
The bone resorption marker (NTx) was determined before adding taxanes and during the study.
Results: After received both drugs median time to progression in bone was 5.4 months; 34.6% (n = 9) of the patients didn't have any record of progression on bone until death. 13 patients (out of 14 with basal NTx record) had elevated levels of NTx before starting taxanes (median value: 8839 BCE; range: 38904−51.9 BCE (normal value ⩽64 BCE)). NTx determination at 3 or 6 month of therapy with taxanes decreased in all patients except one, but only 4 patients achieved NTx normalization.
Conclusions: Our results suggest a positive clinical impact of BP and taxanes combination therapy in metastatic bone disease.