It is retospective analysis of efficacy and safety of taxanes or vinorelbine in first combination of trasuzumab in metastatic Her-2 overexpressed breast cancer pts.

Material and Methods: Forty pts with metastatic HER-2/neu overexpressed breast cancer were treated with weekly trastuzumab (4 mg/kg at initial dose and 2 mg/kg as maintenance dose) and: I – 17 pts with taxanes (docetaxel 100 mg/m^2 or paditaxel 175 mg/m^2) every three weeks or II – 23 pts weekly vinorelbine 25 mg/m^2. It was first combination of trastuzumab and chemotherapy in all pts, in group I – 8 pts were anthracydine pretreated because of mbc, in group II – 9 pts. Median age was I: 52 years (range: 32–64); II: 51 years (range:39–73). Median number of metastatic sites was 2 in both of these groups (r 1–4). All of the patients were evaluable for toxicities and tumor response.

Results: The objective response (OR) in taxanes and trastuzumab group was observed in 15 pts-88% (CR-5 pts, PR-10 pts), stable disease (SD) – in 2 pts 12%. Median TTP in

This group – 44 weeks. In vinorelbine and trastuzumab group: OR-14 pts (61%), SD-8 pts (35%), PD – 1 pt (4%); median TTP – 43 weeks.

There is no severe toxicites (including cardiac) in analyzed groups. Most frequent toxicites were in grade 1/2: fatigue, arthralgia, myalgia, nausea, peripheral neuropathy in group I and neutropenia, fatigue, neurotoxicity in group II.

Conclusion: This analysis showed that both taxanes and vinorelbine are effecive as first combination with trastuzumab in metastatic HER-2 overexpressed breast cancer in first line treatment or anthracycline pretreated patients. Objective response rate was better in group I, TTP are similar but there was no significant difference in these groups. Toxicities are rare and acceptable.

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Fulvestrant: a new opportunity in advanced breast cancer (ABC)

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Introduction: Fulvestrant (Ful) is a new oestrogen receptor (ER) antagonist. It downregulates ER without agonistic effects and has established efficacy after tamoxifen (TAM) failure in post-menopausal women with ABC. Preclinical data suggests treatment with Ful may be useful also following failure with an aromatase inibitor (AI), but few clinical data are available.

Methods: We retrospectively evaluated all postmenopausal patients (pts) in 9 Italian hospitals who received Ful 250 mg/monthly, under a compassionate-use programme, from March 2001 until August 2005. The main inclusion criteria were ER+ and/or PgR+; pretreatment with at least two endocrine agents (HT) and measurable disease.

Results: A total of 127 pts were treated. Median age was 67 years (range 39–92). 80 pts (63%) were ER+ PgR+; 27 pts (21.3%) were ER+ PgR-. 79 pts (62.2%) were treated with adjuvant therapy, 31 pts only chemotherapy (CTH), 27 pts with CTH + TAM and 20 pts with only TAM (1 pt unknown); 22 pts were treated with anthracyclines ± taxanes in adjuvant therapy. Prior to commencing Ful for metastatic disease, 125 pts had received ⩾2 lines of HT; 46 pts, 13 pts and 3 pts received 3, 4, and 5 endocrine agents respectively. All pts were treated with AIs and 78 pts (61.5%) with TAM. 83 patients (65.4%) were treated with at least one CTH; 55, 40, 12 and 3 pts respectively with 2, 3, 4 and 5 lines of CTH. 89/127 pts (70%) were exposed to anthracyclines + taxanes for metastatic disease. Our group of women was extremely heavily pretreated in relation to their ABC. The characteristics of metastases were: median site number 2 (range 1–5), 47 pts one site, 41 pts two sites, 29 pts three, 7 pts four and 3 pts five. 63 pts had prevalent visceral metastases, 51 bone metastases and 12 soft tissue metastases (1 pt biochemistry progression). The patients were treated for a median 6.5 months (range 1–34+) with very few side effects (1 pulmonary embolism, 1 deep venous thrombosis, 1 rash, 2 nausea, 1 vomiting, 1 hypertension, 1 muscular pain, 1 gastric pain, 1 asthenia, 1 mucositis, 1 headache and 1 vertigo). We obtained 2 CR, 5 PR (15+, 4+, 22, 15+, 14+ months), 45 SD and 65 PD, giving a clinical benefit (CR+PR+SD) rate of 41% in evaluable pts (median TTP 6.5 months; range 2–34+). 10 pts are not yet evaluable for response.

Conclusion: The clinical benefit reached in such a heavily-pretreated group of women stresses the ability of Ful as a new and additional hormonotherapy in ABC.

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Low incidence of cardiac events in an EORTC phase II study of CMF in combination with Trastuzumab in women with HER-2 positive metastatic breast cancer

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Objectives: Trastuzumab (T) combined with CT has significantly improved the time to progression, overall response rate and survival in metastatic breast cancer patients overexpressing HER-2 but with an increased risk of cardiac toxicity. This trial was designed to assess the incidence of the congestive heart failure and the therapeutic activity of T in combination with CMF.

Patients and Methods: Eligible patients with metastatic breast cancer, 1st or 2nd line, are enrolled in this single arm Phase II study of T IV weekly plus CMF, Bonadonna regimen, for a maximum of 8 cycles, followed by T alone. The cardiac monitoring includes a formal baseline measurement of LVEF before initiating T plus CMF therapy. Patients with abnormal cardiac function, high-doses of prior anthracycline (A) exposure, pre-existing heart disease and prior treatment with T were ineligible. Serial LVEF measurements are performed every 3 months during the study, and a patient experiencing a decline in LVEF of > 15% from baseline, or any decline in LVEF to > 5% below the lower limit of normal for the institution, regardless of symptoms, or who develops CHF was taken off protocol.

Results: The trial remains open but is expected to close to recruitment by March 2006. To date 66 patients have been treated with a median age of 55 (range, 31 to 75). 22 patients had prior exposure to A, 17 patients as adjuvant therapy and 5 for metastatic disease, combined with cyclophosphamide or taxanes. No NYHA grade 3 or 4 clinical CHF was observed. Only one grade 1 and one grade 2 CHF have been reported. The grade 1 occurred after 10 cycles (8 CMF+T, 2 T). The grade 2 occurred after 3 cycles of CMF in a patient who had had prior anthracyclines chemotherapy. The median baseline LVEF was 61% (range, 45% to 85%). In patients previously treated with A, nine have a drop of at least 6% during the combined treatment. The mean drop of LVEF observed was 2.65% (SD:6.22%) at 3 months and 3.15% (SD:6.19%) at 6 months.

Conclusion: There is a very low rate of cardiac events for patients treated with the combination of trastuzumab and CMF. Asymptomatic drops in LVEF occurred in patients irrespective of previous anthracycline exposure.

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Redox regulation of Prx II and Prx III in breast cancer metastasis to lung

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Peroxiredoxins are a novel class of antioxidants thought to be of particular importance in H_2O_2-mediated redox signalling and are known to be differentially expressed in various cancers. Previous studies in our group with the MDA-MB-435 parental cell line and various metastatic sublines demonstrated that Prx II and Prx III are specifically over-expressed only in the lung metastatic variants. Since the lung provides an entry for ROS, redox regulation is of particular importance in the lung microenvironment and a higher expression of antioxidant proteins in breast cancer may be a crucial factor in metastasis to lung.

We analyzed expression and redox regulation of Prx II and Prx III in 435 parental cells (435-P) and a lung metastatic variant (435-L3) by western blotting and flow cytometry. Exposing cells to H_2O_2-mediated oxidative stress led to a further induction of Prx II and Prx III in 435-L3, while the expression levels of Prx II and Prx III in 435-P remained almost unchanged. Confocal microscopy furthermore revealed that treatment with H_2O_2 induced the cytosolic Prx II to translocate almost completely to the nucleus while Prx III remained in the mitochondria. Whether Prx II interacts directly with nucleic DNA or simply serves as a scavenger for H_2O_2 has to be further elucidated.

Moreover, 435-L3 cells showed higher resistance and a minor level of cell death when stressed with H_2O_2 compared to 435-P. Depletion of Prx II or Prx III by siRNA methods rendered 435-L3 cells more sensitive to H_2O_2-induced stress. Simultaneous down-regulation of Prx II and Prx III however

had no further effect in increasing the sensitivity to oxidative stress. Taken together, these results suggest an important role for Prx II and Prx III in the protection of cells against oxidative stress in general and in the mechanism of lung metastasis in particular.

Future studies will explore the importance of the different cellular redox pathways in the metastatic process by further silencing (thioredoxin) or chemically blocking (catalase, glutathione system) various members of the redox system.

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An electronic data registry for the evaluation of fulvestrant in clinical practice

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Fulvestrant ('Faslodex') is currently licensed for the treatment of post-menopausal women with advanced breast cancer following relapse or progression on antioestrogen therapy. However, it is unclear how this agent is being used in clinical practice. An electronic data registry was developed to provide insight into current fulvestrant usage and to collect clinical outcomes data. The electronic registry was designed by MedNet Solutions, which enabled participating centres to enter data via a secure Internet site. Data from 213 patients from 34 physician practice sites were submitted, of these 196 patients (92%) have now discontinued fulvestrant treatment and 17 patients (8%) are ongoing. Almost all patients (200; 94%) had received prior endocrine therapy including tamoxifen, anastrozole, exemestane, letrozole, toremifene, or megestrol acetate. One-hundred-and-thirteen patients (53%) had prior exposure to tamoxifen, of these 51 (45%) had metastatic disease that had progressed on tamoxifen. A total of 1500 fulvestrant injections have been administered with patients receiving a mean of seven injections (range: 1–31). One-hundred-and-two patients (48%) gained clinical benefit (CB, complete response [CR, n = 3], partial response [PR, n = 52] or stable disease ⩾24 weeks [n = 47]) with fulvestrant treatment. In patients experiencing a CR or PR the median time to response was 2.0 months (range: 0.6–8.3 months) and the median duration of response was 4.7 months (range: 0.9–21.9 months). One hundred and fifty-eight patients (74%) have now progressed with a median time to progression of 4.6 months. Of the 196 patients who have completed fulvestrant treatment, 155 (79%) have received subsequent therapy, most commonly chemotherapy (55%). The electronic registry is a useful tool to monitor usage of fulvestrant and obtain outcomes data in clinical practice. These data support previous observations that fulvestrant lacks cross-resistance with other commonly used endocrine treatments and is a valuable new addition to the endocrine treatment sequence for patients with advanced breast cancer.

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Characterization of brain metastasis from human breast cancer in nude mice: longitudinal MR studies at 7 Tesla

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The current incidence of brain metastases seems to be the paradoxical result of the effectiveness of drugs that do not cross the blood-brain barrier (BBB). The aim of this study was characterize in vivo functional phenotypes that might be correlated with enhanced resistance to therapy in brain metastasis. For this, we optimized a model of brain metastasis by internal carotid injection of brain metastatic cells (435-Br1) from a well known breast cancer cell line MDA-MB-435, from which we had previously identified 19 differentially expressed proteins. We obtained morphologic and metabolic magnetic resonance (MR) analyses at high-field (Bruker PharmaScan, 7.0 Tesla). Tumour growth in female BALB/c nude mice was characterized by T2, CE-T1 (Gd-DTPA, i.v. 0.2 mmol/kg) and diffusion weighted imaging (b = 100, 400, 800 s/mm^2), and also by single voxel 1H MRS (TE 35 and 136 ms). Metastases were detected in vivo at different progression stages by T2 and CE-MRI in 5 of 7 mice inoculated. ADC maps showed higher values for metastasis than for non-afflicted tissue: 0.89±0.07 and 0.55±0.02 ($\times 10^{-3}$ mm^2/s), respectively, implying low tumour cellularity as confirmed by histology. MRS pattern changes indicate replacement of normal brain parenchyma by aggressive tumour cells (high Cho, low NAA). Tentative pattern recognition analysis of selected spectra, carried out in a Decision Support System (DSS) developed for human brain tumour spectra classification, INTERPRET SV (http://azizu.uab.es/INTERPRET), placed the spectral patterns in a clear progression towards malignancy, resembling human cases of healthy tissue being replaced by low grade glial and finally evolving towards an aggressive pattern (GBM/metastasis). IHC analyses of tissues led us to the assessment of the specific protein expression in metastasis induced by brain microenvironment. In conclusion, we have characterized by MRI and 1H MRS a model of brain metastasis developing a possible non-invasive tool for brain metastasis staging and grading in animal models to use in experimental treatments.

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Fulvestrant in postmenopausal women with metastatic breast cancer progressing on prior endocrine therapy – updated results from an expanded access programme

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Background: Fulvestrant ('Faslodex') is an oestrogen receptor (ER) antagonist with no agonist effects. Fulvestrant downregulates the ER, which leads to reduced cellular levels of progesterone receptor (PgR). This abstract reports the results of an expanded access programme in the Czech Republic (supported by AstraZeneca) in which postmenopausal women with metastatic breast cancer whose disease had progressed on prior endocrine therapy were treated with fulvestrant 250 mg.

Methods: Fulvestrant 250 mg was given as a single 5 mL intramuscular injection, once every 28 days until disease progression or other event necessitating withdrawal. Tumour response was assessed monthly using Union Internationale Contre le Cancer criteria. Time to progression (TTP) was defined from start of treatment until objective disease progression. Duration of response (DOR) was defined, for responding patients only, as the time from treatment initiation to disease progression.

Results: Between 8/2001 and 4/2005 a total of 64 patients (median age 66 years [range 39–92 years]) were treated in our centre. 87% of patients had ER-positive and/or PgR-positive disease. All had received prior endocrine treatment for advanced disease and 62% had received adjuvant endocrine treatment. Forty-one patients (64%) had also received prior chemotherapy. Thirty-two patients (50%) were receiving fulvestrant as their 3rd- or 4th-line endocrine treatment for advanced disease. Five patients (8%) had an objective response (1 CR and 4 PR(. All responses were greater than 90 weeks in duration. Thirty four patients (53%) had stable disease (SD) ⩾24 weeks giving an overall clinical benefit rate (CR +PR + SD ⩾ 24 weeks) of 61%. The median TTP was 26 weeks. Fulvestrant 250 mg was well tolerated and no WHO grade III/IV toxicities were observed.

Conclusion: Fulvestrant 250 mg is an endocrine agent with demonstrable efficacy and a very favourable tolerability profile in patients with advanced breast cancer. The monthly injection schedule supports both close patient monitoring and good compliance. Fulvestrant offers clinicians a new option for the treatment of postmenopausal women with advanced breast cancer progressing on prior endocrine therapy.

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Every two-weeks docetaxel in the treatment of elderly patients with advanced breast cancer

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Background: The study was conducted to investigate the efficacy and toxicity of bi-weekly docetaxel administration in elderly metastatic breast cancer patients.

Patients and Methods: Women aged ⩾65 years with histologically confirmed metastatic breast cancer were eligible for enrollement. Patients could have received prior systemic adijuvant chemotherapy. Docetaxel was given as first-line (after adjuvant chemoteraphy) in 10 patients and as second-line in 21 patients; 10 patients were pre-treated with antracyclines regimens. Docetaxel was administered at 50 mg/m^2 as 1-hour intravenous infusion every 2 weeks. Docetaxel dose was reduced by 25% for grade 2 neurologic toxicity, febrile neutropenia, grade 3 thrombocytopenia or of any grade 2 non-haematologic toxicity. Patients were premedicated with dexamethasone 4 mg i.m. taken the night before, mornig of, and evening after treatment. Patients continued to receive treatment until they developed either undue toxicity or until the time of disease progression.

Results: A total of 31 metastatic cancer women were entered into this study. The median age was 72 (range 65–78). ECOG performance status for all patients was 0–1. Most patients (21) had received prior chemotherapy, 10 patients had received first line anthracycline containing regimens. A total of 374 infusions were administered, 13.3 median, with a cumulative dose of 18,420 mg/m^2 (1083 mg/m^2 median). The projected