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