progression-free survival of nab-paclitaxel 150 mg/m^2 weekly, a phase III trial comparing this dose to docetaxel 100 mg/m^2 every 3 weeks is planned.

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Bone metastases factors in an early breast cancer

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Formation of distant metastases that affect the skeletal system is the main cause of failure in the treatment of the early breast cancer. Presently applied prognostic factors do not sufficiently determine the risk of systemic dissemination.

The aim of the study was to evaluate selected neoplastic factors in reference to the formation of bone metastases in patients with early breast cancer.

Methods: 164 patients were operated and monitored post-operatively for five years. The tumour size and grade, lymph nodes involvement, expression of estrogen (ER), progesteron (PgR) and HER-2 receptors; level of cancer antigen 15−3 (CA15−3), Ki-67, Bcl-2, Bax, Bax/Bcl-2, Fas-L, TNF, ICAM-1, sICAM-1 were analyzed. Blood samples were collected pre-operatively. The expression of Ki-67, Bcl-2, Bax, Fas-L, TNF-α, ICAM-1, ER, PgR, HER-2 was determined immunohistochemically in primary tumour. The level of the serum marker was measured using ELISA. The prognostic value of the investigated factors was determined on the basis of clinical data.

Results: The overexpression of Ki-67, Bax, Fas-L, TNF, a low expression of Bcl-2 and ICAM-1, increased Bax/Bcl-2 ratio, increased level of sICAM-1 and CA 15-3, as well as higher number of involved axillary lymph nodes are characteristic for systemic dissemination. The analysis of 5-year survival time has revealed a higher number of deaths among patients with low expression of Bcl-2.

Conclusions: The overexpression of Bax and the increased level of sICAM-1 determines the formation of bone metastases in patients with an early breast cancer. On the basis of multifactorial analysis it may be concluded that the following positive factors in the prognosis for 5-year survival time are observed at the same time: low expression of Ki-67, overexpression of Bcl-2, low expression of Bax, as well as decreased Bax/Bcl-2 ratio.

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Trastuzumab plus intravenous or oral vinorelbine in chemonaive patients with HER-2 overexpressing metastatic breast cancer – final results of an extended phase II trial

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Background: The activity of trastuzumab (T) combined with chemotherapy in HER2-overespressing (HER2+) BC has been well documented in randomized trials, in both the adjuvant and metastatic setting. We report the updated results of our expanded experience on a combined regimen of T and Vinorelbine (VNR) given intravenously or orally as first-line treatment in HER2+ metastatic BC patients (pts).

Patients and methods: A total of 83 consecutive pts with histologically confirmed, measurable MBC, tumors scored as +3 positive for HER2 by immuno-histochemistry or FISH+, no prior chemotherapy for the metastatic disease were enrolled. Median age was 53 years (range 31–70); prior adjuvant chemotherapy in 63%; prior hormonal in 45%; visceral metastases in most cases (liver 56%, lung 34%). In the first 58 patients (Group A) treatment consisted of i.v. T (4 mg/Kg loading dose as a 90'infusion, then 2 mg/kg weekly in 60') followed by i.v. VNR (25 mg/m^2 weekly as 10' infusion) without a break, with one cycle consisting of 4 consecutive weeks. In the following 25 patients (Group B) VNR was given orally at the dose of 60 mg/m^2 weekly.

Results: All pts received at least 3 courses of therapy (median 5 and 4 per patient, respectively, range 3−12). The worst toxicity was haematological in both groups (grade 4 leukopenia in 11% and 10% of pts, respectively) with no significant cardiac or neurologic side effects. The overall response rate (RR) was 86% in Group A (95% CI 75%-92%), with 6 complete and 44 partial remissions, and 84% in group B (95% CI 63%-93%), with 4 complete and 17 partial remissions. Median TTP was 12 months (range 6−19); median overall survival was 34 and 31 months, respectively.

Conclusions: Our results confirm the high antitumoral activity of T/VNR combination as first-line treatment in HER2+ metastatic BC pts, with acceptable toxicity and no significant difference in patient compliance between the intravenous and oral VNR formulation, further improving the possibility of a "personalized" therapeutic strategy, based on the different clinical situations and patient preferences.

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A single-institution experience from the Lapatinib Expanded Access Program – effect of lapatinib and capecitabine combination therapy on CNS metastases in patients with ErbB2+ metastatic breast cancer

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Background: Brain metastases affect 25% to 30% of women with ErbB2+ metastatic breast cancer (MBC) and are associated with a high burden of disease and a poor prognosis. Cranial radiotherapy is effective as initial therapy for brain metastases; however, there is no standard treatment for patients whose CNS disease then progresses. Lapatinib is an oral, small molecule, tyrosine kinase inhibitor of ErbB1 (EGFR) and ErbB2 (HER2). When combined with capecitabine, lapatinib significantly improves time to disease progression in patients with ErbB2+ MBC previously treated with anthracyclines, taxanes, and trastuzumab (ATT). The Lapatinib Expanded Access Program (LEAP) was designed to provide access to lapatinib plus capecitabine before the commercial availability of lapatinib for the treatment of patients who have progressive disease (including CNS metastases) after ATT.

Material and Methods: Patients enrolled in LEAP were treated with lapatinib 1,250 mg/day and capecitabine 1,000 mg/m^2 PO BID. Among patients with CNS disease progression before study entry, response (RECIST) was assessed on-study via CT or MRI at baseline and every 6 weeks. Neurological symptoms were assessed via clinical assessment.

Results: Eleven of 48 (23%) patients (aged 37 to 62 years) enrolled at this single institution had a history of CNS disease; each of these 11 patients had received whole-brain radiotherapy (300 cGy $\times$ 10 fractions) before study entry, and 2 patients had also undergone surgical resection of brain lesions. Patients initially presented with various neurological symptoms including severe headache, loss of balance and gait disturbances, dizziness, difficulty in focusing visually, and vomiting. Among 7 patients evaluable for CNS response, 2 patients had a complete response, 2 patients had a partial response, and 3 patients had stable disease after treatment with lapatinib plus capecitabine. Marked neurological improvement was observed in 4 patients, and mild improvement in 2 patients. Lapatinib plus capecitabine was well tolerated; as expected, rash, diarrhea, and hand foot syndrome were the most common toxicities.

Conclusions: These preliminary results support previous hypothesis-generating data that lapatinib plus capecitabine is active in patients with ErbB2+ MBC and brain metastases previously treated with trastuzumab and cranial irradiation. Further investigation of lapatinib plus capecitabine in patients with ErbB2+ CNS metastases is warranted.

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A phase II study of gemcitabine plus capecitabine (GC) in heavily pre-treated metastatic breast cancer patients. The Swedish GC Breast Cancer Study Group

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Background: The gemcitabine, capecitabine (GC) combination is reported to be effective and tolerable in advanced pancreatic cancer. The aim of this study was to explore the value of GC in heavily pre-treated metastatic breast cancer pts.

Material and Methods: At inclusion, all pts had failed anthracyclines and taxanes and if applicable also endocrine treatment. At study entry 41% of pts presented with more than 2 metastatic sites with bone (68%) and liver (62%) beeing the most prominent. Gemcitabine (1250 mg/m^2, d1+8) and capecitabine (800 mg/m^2 twice daily, d1–14) were administered according to a 3-week schedule. GC was given as 3rd line (18 pts) or 4th line (14 pts) or 5th line (2 pts) chemotherapy. Lab tests were done on day 1+8 in cycles. Subjective toxicity was recorded according to the NCI-CTC v.2.0 criteria. Tumour evaluations were done every 3rd months according to the RECIST criteria. The primary objective was to investigate time to

progression. Secondary objectives were to record response rate, toxicity and survival time.

Results: A total of 34 pts were enrolled. Median age was 55 years (range 27−70). All subjects received study treatment and are eligible for toxicity, response and survival analyses. Treatment was given until PD or as long as pts wished to continue. Median number of cycles/pt was 5.5 (range 1−22) with a median cycle length of 22 days (range 20−29). Observed Gr 3/4 haematological toxicities were as follows (% of pts): anaemia 2.9/0.0, trombocytopenia 2.9/2.9, leucopenia 41.2/2.9 and granulocytopenia 44.1/14.7. No neutropenic infection was noted.

Pre-dominant subjective toxicities were Gr 3 fatigue (7 pts) and Gr 3 hand-foot syndrome (5 pts). Treatment was terminated in 5 pts before response evaluations were done. PR was obtained in 11 pts (32.4%, 95% CI = 18.0−50.6), SD in 10 pts (29.4%) and PD in a further 8 pts. The median time to progression is estimated to 4.3 months (range 0.3−14.8). The median survival time is estimated to 13.7 months (range 2.0−43.0).

Conclusion: In this heavily pre-treated late stage breast cancer patient cohort the gemcitabine/capecitabine treatment showed acceptable tolerance and a surprisingly high response rate and a longer than expected survival time.

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Quality of life and subjective improvement of breast cancer related symptoms in advanced breast cancer – results of the anastrozol-surveillance-trial

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Introduction: Third generation aromatase inhibitors have earned their place in first-line therapy for advanced BC with proven superiority over tamoxifen.

Particularly relevant in treatment of advanced BC are quality of life and subjective improvement of BC related symptoms. The anastrozol-surveillance-trial had the objective to evaluate these factors based on objective response parameters.

Material and Methods: The anastrozol surveillance trial was performed from 2000–2003. Under daily routine conditions and without any intervention, the participating physicians were ask to document data in a scoring system for patients, suffering from a advanced breast cancer, treat with anastrozole. Over a period of 6 months, a total of 730 evaluable patients with advanced breast cancer were questioned in 3 monthly intervals (3 visits) for subjective breast cancer related symptoms, general condition of the patient, acceptability of the anastrozol therapy, occurrence and severity of subjective BC related side effects and quality of life.

Results: The median age was 64 years (29−94). 80.3% of the patients was ER pos and 71.4% PgR pos; 99.2% had a previous therapy, in 44.4% a chemotherapy, in 56.4% a endocrine therapy. Within the group of patients were recorded 46.7% (n = 341) with bone-, 27.9% (n = 204) with visceral-, 18.9% (n = 138) with soft tissue metastases, 21.5% (n = 157) had a locally advanced carcinoma.

At the start of the 6-month period 33.4% of the patients were asymptomatic, 35.2% had mild, 22.7% moderate, 7.1% severe symptoms. A subjective improvement of BC related symptoms was seen for 56.7% (n = 414) at visit 2 and for 59.3% (n = 433) at visit 3. A complete remission at visit 3 was recorded for 16.7% (n = 122), a partial remission for 19.2% (n = 140), a disease stabilisation for 33.4% (n = 244) and a progression for 11.9% (n = 87).

After 6 months 30.3% of the patients were asymptomatic, 45.2% had mild symptoms. At both time points (visit 2 and 3), almost half of the subjects had a good quality of life according to the physicians judgement; in detail: 7.7% a excellent, 47.4% a good, 19.2% a rather good, 4.1% a neither good or bad, 3.8% a rather bad, 2.5% a bad and 2.1% a very bad quality of life.

Conclusion: The aromatase inhibitor anastrozole is a highly effective palliative treatment for advanced breast cancer demonstrated by a subjective improvement of BC related symptoms and remaining quality of life in the majority of patients over a period of 6 months.

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A phase II parallel group study with letrozole plus goserelin in premenopausal, and letrozole in postmenopausal metastatic breast cancer patients as first line hormone therapy

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Background: The use of goserelin in premenopausal patients is to produce castrated level of estradiol (E2), and the remaining peripheral E2 production is inhibited by letrozole, which would accomplish comparable clinical outcomes as in postmenopausal metastatic breast cancer patients by letrozole alone.

Material and Methods: Histologically diagnosed metastatic breast cancer (MBC) patients with positive hormone receptors were eligible. For premenopausal patients, goserelin 3.6 mg was injected subcutaneously every 4 weeks followed by letrozole 2.5 mg once a day beginning 1−2 weeks post 1st goserelin dose. Postmenopausal patients took letrozole 2.5 mg orally once a day. Serial serum E2, follicular stimulating hormone (FSH), luteinizing hormone (LH) were measured in premenopausal patients.

Results: Between 10/2005 and 12/2007, 73 patients were enrolled at the National Cancer Center Hospital. So far, 25 premenopausal and 33 postmenopausal patients were assessed for efficacy and adverse events (AE). The median age was 41 years (range, 32−52) for premenopausal patients and 53 years (range, 33−70) for postmenopausal patients. Clinical benefit (complete response (CR) + partial response (PR) + stable disease (SD) $\geqslant$24 weeks) rates were 44.0% for premenopausal and 60.6% for postmenopausal patients, the objective response rates (CR+PR) were 28.0% and 27.3%, respectively. With the median follow-up durations of 10 months and 15 months, respectively, the median time to disease progression was 7.6 months and 12.0 months. In premenopausal patients, the mean E2 level was dropped from 62.1$\pm$85.4 pg/mL at baseline to 10.7$\pm$7.5 pg/mL at week 4 on treatment and the median time of E2 decrease below 30 pg/mL was 12 days. 7 of 13 premenopausal patients with regular menstruation prior to entry still experienced vaginal bleeding within 1 month after 1st goserelin dose. Most of AEs were grade 1/2 fatigue, insomnia, hot flashes, bone pain, arthralgia, headache, anorexia, nausea and vaginal dryness. Premenopausal patients experienced significantly more hot flashes (68.0% versus 39.4%).

Conclusions: Clinical efficacies in premenopausal MBC patients by combined letrozole and goserelin therapy appear to be comparable to those in postmenopausal patients by letrozole alone. Letrozole is advised to begin after 1−2 weeks of 1st goserelin dose in premenopausal patients. Most AEs were mild in degree.

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Impact of brain metastases on health care costs associated with the management of patients with metastatic breast cancer in France and Germany

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Background: Brain metastases (BM) represent a morbidity that may impact greatly on cancer health care resources and costs. Rates of BM are thought to be particularly high among patients with ErbB2+ breast cancer and are usually associated with a short survival outcome. The objective of this study was to estimate resource utilisation and associated health care costs among metastatic breast cancer (MBC) patients who have developed BM compared to those who have not (controls).

Methods: Patient treatment histories, including medications, specialist visits, procedures, in-patient stays etc, were collected de novo from a panel of oncologists for women with MBC (French sample, N = 209; German sample, N = 164), last seen by the responding oncologist during Q3-Q4 2006. As an additional inclusion criterion, all patients had received/were receiving trastuzumab (TZ) in the metastatic setting. Quota sampling ensured at least 3 controls to each BM case (French sample, n = 58; German sample, n = 51). All costs within the observation period (initiation of TZ to date last seen) were calculated from a third-party payer perspective for patients who had developed BM and those who had not. Regression analyses took into account potential confounding of time related covariates.

Results: Following adjustment for significant time variables, the average cost for the management of MBC patients who had not developed BM was estimated as €40,780 (French sample) and €41,054 (German sample). The average incremental cost associated with patients who had developed BM was estimated as €12,993 [95% CI: €3,767, €21,019] (French sample) and €5,360 [95% CI: −€1,224, €11,946] (German sample).

Conclusions: Cost analyses based on retrospective patient data collections for France and Germany estimate higher costs for the treatment of MBC where patients have developed BM. In the case of the French sample, this cost difference was statistically significant.