data suggest that a convenient oral ibandronate dose of 50 mg/day has a similar efficacy to intravenous zoledronic acid for suppressing tumor-induced bone resorption, but it is associated with a lower incidence of AEs following treatment. Effects on bone markers may indicate the comparable efficacy of the two bisphosphonates for the prevention of skeletal-related events. Thus, oral ibandronate may provide similar benefits to intravenous zoledronic acid for metastatic breast cancer patients, but with a superior tolerability profile.

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Biological functions of brain metastasis from breast cancer

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Secondary to the increased survival of breast cancer patients following chemotherapy, cerebral metastases have recently become a significant clinical problem, with an incidence of 30–40%.

The aim of this study was to characterize functional phenotypes that might enhance brain metastasis in human breast cancers. We used a computer program (PIANA) to build a protein interaction network for a collection of 19 proteins identified by MALDI-TOF. We were able to associate this network of proteins into 8 functional groups.

The METABRE gene analyses of 4 brain metastases made with U133plus2 Affymetrix chips has been used to assess differentially expressed genes in brain metastases compared with a pool of breast tumors, after normalization using the RMA (Robust Multichip Averaging) algorithm. From this analysis we obtained 5.235 candidate genes, 2.467 overexpressed (> 2 fold) and 2.768 underexpressed (< 2 fold). We matched these genes with the PIANA brain network.

As a result we found 179 proteins, 122 overexpressed and 57 underexpressed, in the brain metastasis network belonging to the following functions: 23 protein folding and chaperones; 9 ubiquitination; 36 signal transduction and receptors; 13 kinases; 4 immunological; 5 protein transport; 4 peptidases; 12 structural; 9 cell adhesion; 22 DNA binding, repair and transcription; 8 REDOX; 4 carbohydrate and 7 lipid metabolism. Ten of these proteins belong to the METABRE specific brain metastasis signature: ARFGAP, RNF25, EHMT2, TOP1, RNPC2, eIF-3, MCM4, GRP 94, FN14, and INHA. Some of these are being validated in tissue samples with specific antibodies.

These results provide evidence that the characteristic phenotype of brain metastasis includes specific cell-cell and cell-matrix adhesion, a cohort of stress-inducible proteins, REDOX and detoxification pathways, and lipid and glucose metabolism.

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A multicenter phase II study of epirubicin with low-dose trastuzumab as a first line treatment in Her-2 overexpressing metastatic breast cancer: preliminary results

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Aims: To evaluate the activity and cardiac safety of the combination of epirubicin (E) with low-dose trastuzumab (LD-H) in patients with HER-2 overexpressing metatatic breast cancer.

Patients and Methods: This was a two step study: In the first step, H was given at a loading dose of 2 mg/kg on day 1, followed by 1 mg/kg weekly; in the second step (⩾12 objective responses/21 patients), the dose of H was mainatined to 1 mg/kg weekly. E was administered at 90 mg/m^2 on day 1 every 3 weeks. After 6–8 courses of this combination, H was administered as a single agent for a maximum of 52 weeks. To assess cardiotoxicity, pts were evaluated for the Left Ventricular Ejection Fraction (LVEF) at baseline, every two cycles during E and LD-H, and every three months during LD-H alone. Either ultrasonography or angioscintigraphy were used. Cardiotoxicity was defined as the appearance of signs or symptoms of congestive heart failure in ⩽10% of patients at an E dose of 720 mg/m^2 or in ⩽20% of patients at an E dose > 720 < 1000 mg/m^2.

Results: Twenty-one pts entered the first step: median age was 55 years (41–70 years), hormonal status was positive in 9 pts and negative in 10. Eight pts had received prior adjuvant anthracyclines, and 8 pts prior endocrine therapy. The majority of pts had > 2 organ sites of involvement with visceral lung metastases predominating. A median of 6 cycles (range 1–18) was administered with 134 cycles evaluable for toxicity. The regimen was well tolerated, with grade 3/4 neutropenia, alopecia, and thrombocytopenia occurring in 55%, 25% and 10% of the pts, respectively. Six episodes of cardiotoxicity were observed (an asymptomatic decrease in LVEF ⩾15% in 4 pts and an asymptomatic decline of LVEF at ⩽ 50% in 2 pts). At the time of analysis, 12 (57%) pts achieved a partial response, 6 (%) had stable disease, and 3 (%) had progressive disease. The median time to progression was 9.8 months (C.I.95%: 5. 5–14.1) and the median overall survival was not reached.

Conclusions: These preliminary results show that the combination of E plus LD-H possesses good antitumor activity, with limited cardiotoxicity. The Protocol Committee recommended to enter the second step of the study, maintaining the dose of H at 1 mg/kg weekly. Accrual is continuing; an update will be presented at the meeting.

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Subjective assessment of breast cancer related symptoms, activity levels and quality of life of patients with metastatic breast cancer under treatment with Anastrozole

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Introduction: Third generation aromatase inhibitors have earned their place in first-line therapy for advanced breast cancer with proven superiority over tamoxifen. Particularly relevant in this setting are quality of life and activity levels of the patients from a patient perspective, based on objective response-parameters.

Material and Methods: Over a period of 12 months, a total of 466 patients with metastatic breast cancer either to one (n = 272) or multiple sites (n = 167) were questioned in 3 monthly intervals, and the responses were analysed, for the following:

1. Subjective breast cancer related symptoms based on a score from 1 (no symptoms) to 4 (severe symptoms).
2. Personal activity levels based on a score from 1 (full activity, no symptoms) to 5 (bedridden, unable to provide for oneself).
3. Quality of life based on a score of 1 (excellent) to 7 (very poor).

Results: The median age was 61.7 years (35–94). At the start of the 12-month period 31% of the patients was asymptomatic. After 12 months this percentage had increased to 41% and the degree of reported moderate to severe symptoms reduced in this timeframe from 41% to 28% of syptomatic patients with an average score reduction from 2.8 to 2.2. A worsening of symptoms during the therapy was seen in 151/466 (32.4%) of patients. In 73/466 (15.7%) this reduction was first reported after 3 months of therapy had been completed. The percentage of patients with restricted activity was lower after 12 months 46.2% compared to 57.2% at the start of therapy. The group who classified their quality of life as excellent increased over this time-period from 3.6% to 12.8%, reflected in an increase in average score from 3.0 to 3.7.

Conclusion: The aromatase inhibitor anastrozole is a highly effective palliative treatment for metastatic breast cancer demonstrated by a reduction in symptomatic disease and a corresponding increase in activity levels and quality of life in the majority of patients over a period of 12 months.

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Brain metastases in HER-2 positive metastatic breast cancer (MBC) patients

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Background: Several recent reports suggested relatively high risk of brain relapse in HER2-positive breast cancer patients. This phenomenon has been attributed to either an aggressive behavior of this tumor type and/or an increased survival following trastuzumab therapy without brain protection owing to insufficient penetration of this drug to CNS. In this study we

assessed the risk of brain metastases in a large unselected series of HER2-positive MBC patients.

Material and Method: Study group included 173 consecutive HER2-positive (immunohistochemistry 3+ or FISH+) MBC patients from five Polish institutions. Patient age ranged from 30 to 81 years (median 49 years); 83 patients were premenopausal (47.9%), 88 – postmenopausal (50.9%) and in 2 patients menopausal status was unknown (1.2%). Dominant site of disease included viscera in 130 (75.1%), soft tissue in 21 (12.1%), bones in 19 (11.0%) and was unknown in 3 patients (1.7%). Data on ER/PR status were available for 151 patients (87.3%). ER+/PgR+, ER+/PgR-, ER-/PgR+, ER-/PgR- phenotypes were represented by 19.9%, 13.9%, 4.0% and 62.3% of this group, respectively. 66 patients (38.2%) had received prior (neo)adjuvant chemotherapy, 11 (6.4%) – adjuvant hormonotherapy, and 53 patients (30.6%) – a combination thereof. Disease-free interval to the development of MBC ranged between 0 and 124 months (median 14 months). A total of 126 patients (72.8%) received trastuzumab for MBC, usually in combination with chemo- and/or endocrine therapy. Statistical analysis included contingency tables, chi-square test, Kaplan-Meier survival analysis and Cox proportional hazard model.

Results: Median follow-up from the development of MBC was 3.8 years (range 0.5–12.3 years). 45 patients (26.0%) developed brain metastases including 26.2% and 25.5% who did and did not receive trastuzumab ($p = 0.93$). Median time to brain relapse from the diagnosis of MBC was 10 months (range, 0 to 65 months). Detailed analysis of factors related to the risk of CNS metastases will be presented during the conference.

Conclusion: HER2-positive MBC patients carry increased risk of brain relapse which does not seem to be reduced with trastuzumab treatment. This calls for more effective preventive measures.

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Oral bisphosphonates are associated with low persistence and compliance (adherence) in patients with breast cancer

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Introduction: It has been shown that skeletal complications can be reduced by bisphosphonates in patients with bone metastases. Because the optimum clinical benefit is only achieved in patients who remain on therapy, we studied the persistence and compliance (adherence) with oral bisphosphonates in patients with breast cancer in a naturalistic setting.

Material and Methods: Persistence and compliance with oral bisphosphonates for breast cancer patients was analysed using claims data from a large German sickness fund covering the time period from January 2000 to December 2003. Patients were included if they had an ICD-10 diagnosis for breast cancer AND were receiving oral bisphosphonates. The minimum time of continuous enrollment after the first observed oral bisphosphonate prescription was 7 months. Persistence was defined as the duration of continuous prescription refill without an interruption of longer than 30 days. Compliance (adherence) was measured in terms of the medication possession ratio (MPR: dispensed medication supply in a given period of time).

Results: There were n = 231 patients fulfilling the inclusion criteria with a mean age of 63.2 years (37–92 years). From these patients 102 (44.2%) received clodronate as the first prescription followed by 69 (29.9%) with alendronate, 31 (13.4%) with risedronate, and 29 (12.6%) with etidronate. A bone metastasis diagnoses was recorded for 58 patients (25.1%). At the end of 6 months, only 37.7% of the patients were found to be persistent with their oral bisphosphonate therapy. The median therapy duration was 103 days. A good compliance was assumed if an MPR of at least 80% was found. According to this definition, no more than 36.8% of the breast cancer patients showed a good compliance within 180 days following the first detected bisphosphonate prescription.

Conclusions: We found only 37.7% of breast cancer patients still remaining on bisphosphonate therapy after six months. It has been shown that an effect on skeletal morbidity outcomes cannot be expected before oral bisphosphonates have been administered for at least six months (Ross et al., Health Technol Assess 2004; 8(4):1–176). Therefore, further study needs to be evaluated to determine the impact of compliance and persistence on the outcome of skeletal morbidity such as severe bone pain, pathologic fracture, spinal cord compression, and hypercalcemia of malignancy.

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Intravenous and oral ibandronate have better safety and tolerability profiles than zoledronic acid: evidence from comparative phase III trials

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Recommendations state that all breast cancer patients with bone metastases should be treated with a bisphosphonate. Ibandronate is a single-nitrogen, non-cyclic bisphosphonate available in intravenous and oral formulations that had safety profiles comparable to placebo in phase III trials. Here, safety data from two comparative, open-label, phase III trials are reported. Patients were randomized to receive ibandronate or zoledronic acid for 12 weeks. In trial A, ibandronate-treated patients received intravenous ibandronate 6 mg on Day 1 (15-minute infusion) then daily oral ibandronate 50 mg from Day 2 onwards. In trial B, ibandronate-treated patients received daily oral ibandronate 50 mg only. The comparative treatment in both trials was intravenous zoledronic acid 4 mg (15-minute infusion) every 3–4 weeks. Trial A recruited 77 patients with either breast cancer or multiple myeloma and ⩾1 confirmed bone lesion; trial B recruited 274 metastatic breast cancer patients. All adverse events (AEs) were recorded. Results showed that fewer patients experienced AEs with intravenous or oral ibandronate than with zoledronic acid (trial A: 64% vs 74%; trial B: 65% vs 76%). In particular, the incidence of AEs on Days 1–3 was lower for ibandronate than zoledronic acid (trial A: 26% vs 47%; trial B: 8% vs 47%). This was mainly because of a zoledronic acid-associated acute-phase response (APR); pyrexia or flu-like symptoms occurred in 13% of the ibandronate group compared with 26% of the zoledronic acid group in trial A, and 1% compared with 27% in trial B. In both studies, fewer patients reported bone pain as an AE with ibandronate than zoledronic acid (trial A: 8% vs 16%; trial B: 12% vs 21%). The incidence of gastrointestinal (GI) AEs was slightly higher for ibandronate than zoledronic acid (trial A: 23% vs 21%; trial B: 23% vs 18%). Serious AEs and withdrawal rates were similar between treatment groups. In these comparative studies, fewer patients experienced AEs with ibandronate than zoledronic acid, regardless of ibandronate formulation or dosing schedule. In particular, there was a lower incidence of APR AEs for ibandronate than zoledronic acid, even with intravenous ibandronate treatment. Ibandronate is a well-tolerated treatment for metastatic bone disease with apparent AE advantages over intravenous zoledronic acid and no renal safety issues.

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Does Her2 status change in metastases of breast carcinomas?

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Introduction and Aim: There has been an ongoing debate as to whether metastatic breast carcinoma may change its Her2 status or it remains similar to that of the primary tumor. Our aim was to investigate various metastatic sites from the point of view of Her2 expression and to compare the Her2 status of the metastasis to that of the original primary tumor, where available.

Patients and Methods: Thirty six metastasis from primary breast carcinomas were investigated. Liver, pleura, bone marrow, skin, brain, urinary bladder metastases were collected. 11 cytological, 9 biopsy and 14 excision specimens, and, 2 metastases found at autopsy were available for this study. In 20 cases the Her2 status of the primary tumor was also known. The Her2 status of the primary tumor was known a) from the original histology report, b) was repeated during this study both by immunohistochemistry and FISH. The metastases were investigated both by immunohistochemistry and FISH. For immunohistochemistry, the ready to use CB11 (Novocastra) antibody was applied. FISH was performed using the the Ventana Benchmark system.

Results: Altogether, 22% (8/36) of the metastatic tumors proved to be Her2 positive by FISH. In the 20 cases where both the primary and the metastatic tumors were available for the study, 25% (5/20) of the primary tumors and 20% (4/20) of the metastatic tumors showed Her2 gene amplification by FISH. The liver metastasis of the fifth Her2 positive primary tumor was diagnosed by FNAB, and the Her2 status of this metastasis was established by immunocytochemistry with a result of score 3+. In case-by-case comparison, FISH positive cases had FISH positive metastases. However, slight changes in immunohistochemical results could be detected: from score 0 to 1+, 1+ to 2+, 2+ to 3+ occurred in single cases. There were three cases showing slight changes in the opposite direction: from 3+ to 2+