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+

in one case and from 2+ to 0 in two cases. Nevertheless, the Her2 status of the metastatic tumors, as defined by FISH, did not change.

Conclusion: Our results suggest that Her2 status does not change in metastatic breast carcinoma. However, at present it is necessary to investigate the Her2 status of late metastases of breast carcinomas, because in many cases the Her2 status of the primary tumor is unknown.

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Correlation between hormonal receptor levels and efficacy of hormonal therapy and chemotherapy in metastatic breast cancer

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Endocrine responsiveness defined by HR predicts the response to HT. It seems that the level of expression of HR correlates with the response to HT or even ChT. The aim of our analysis was to evaluate the response to first line HT and/or ChT for metastatic disease according to the HR levels in primary tumour.

Data of 260 patients (pts) treated for early breast cancer (BC) at Institute of Oncology Ljubljana from 1994 to 2001, that developed distant metastases in the median follow up time of 8.23 (4–11) years were reviewed. Response to HT was revived in 201 pts (aromatase inhibitors: 62%), and response to ChT in 187 postmenopausal pts (antracycline or taxane based: 57%). Response to HT was defined as clinical benefit (CB), including CR, PR and S for at least 3 months, response to ChT was defined as response rate (RR), including CR and PR. Progression free survival (PFS) was defined as time interval from the beginning of treatment till the date of confirmed disease progression or death due to BC. Response and PFS were analysed in subgroups of pts according to the imunohistochemical expression of ER, PR or both (rich ⩾90%, intermediate 10–90%, poor <10%). Kaplan Meier curves, log rank tests and STEPP curves were used for statistical analyses.

Response to HT was significantly different in subgroups of ER rich, ER intermediate and ER poor pts (65%, 57% and 27%, respectively; $p = 0.001$), however no difference between ER rich and ER intermediate groups was found ($p = 0.355$). Even higher differences in response were seen in subgroups of PR rich, PR intermediate and PR poor (75%, 59% and 40%, respectively; $p < 0.001$), with a trend for significant difference also between PR rich and PR intermediate groups ($p = 0.063$). When both receptors were taken into account, response in HT was higher in ER rich/PR rich compared to ER rich/PR poor subgroup of pts (81% vs. 54%; $p = 0.065$). In STEPP analysis all ER positive (⩾10%) pts responded equally well to HT, while the response continuously rose from PR 0% to PR 100%. Similar results for PFS were obtained in all subgroups. In our set of pts no significant differences in efficacy of ChT according to HR levels were confirmed.

We confirmed that the level of ER and PR predict the response to HT. In addition, we assume that ER positivity as such predicts a good response to HT, while in PR the level of receptor expression matters.

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Exemestane after non-steroidal aromatase inhibitors for post-menopausal women with advanced breast cancer

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Aims: To assess the efficacy of the type 1, steroidal aromatase inactivator, Exemestane in post-menopausal women with locally advanced and/or metastatic breast cancer, who have previously received Tamoxifen and a non-steroidal third generation aromatase inhibitor (AI).

Methods and Materials: A retrospective analysis was performed on thirty one consecutive patients who commenced Exemestane 25 mg/day orally, from January 2000 to June 2005. Patients were required to have positive oestrogen receptor (ER) and/or progesterone receptor (PR) status or if unknown, had to have a clear response to previous hormonal treatment (n = 2). Previous hormonal treatment included Tamoxifen and a non-steroidal third generation AI (Anastrozole or Letrozole). Patients were followed up every 3 months until they developed clinical or radiological disease progression.

Results: Median patient age was 64 years (range 34–90 years). 12 patients had locally advanced disease alone, 19 had metastatic disease and 8 had both locally advanced and metastatic disease. Sites of metastatic disease include soft tissue (n = 4), lung (n = 4), liver (n = 8) and bone (n = 13). The average number of recurrences prior to starting Exemestane was three (range 1–6). 15 patients (48.4%) also had previous chemotherapy. There were 2 complete responses (CR), 4 partial responses (PR), 12 with stable disease (SD) and 12 with progressive disease (PD). The objective response rate (CR + PR) was 19.4% and the overall clinical benefit (CR + PR + SD ⩾24 weeks) was 41.9%. The median durations of objective response and overall clinical benefit were 18.3 months and 16.2 months respectively. One patient required discontinuation of Exemestane due to vertigo.

Conclusions: This data supports the anti-tumour activity of Exemestane 25 mg daily in patients with locally advanced and/or metastatic breast cancer who have been previously exposed to non-steroidal third generation AIs and Tamoxifen.

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Phase II study with dose finding of Oral Vinorelbine in combination with Capecitabine as first-line chemotherapy of Metastatic Breast Cancer (MBC): Preliminary results of the phase II part of the study

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Several drugs are active in MBC. However, only few are available orally. The combination of Oral vinorelbine (VRL) and Capecitabine (Cape) has the advantage of its ease of use with no overlapping toxicity. Results of the phase I part of the study showed no interaction when both drugs are given concomitantly and established the following regimen: Oral VRL 60 mg/m^2 weekly with Cape 2000 mg/m^2/d from D1 to D14 every 3 weeks as one of the recommended dose for the phase II (F. Nolè; ASCO 2005, abstr 666). The present study investigated this weekly schedule to evaluate efficacy and tolerance of this combination in patients (pts) who had received no prior line of chemotherapy (CT) for MBC disease. Prior adjuvant chemotherapy with anthracycline and/or taxanes was allowed. Patients had at least one measurable lesion (WHO criteria) and KPS ⩾ 70%. The characteristics of the first 23 patients treated, were median age of 59 years, prior adjuvant chemotherapy in 78.3%, prior adjuvant hormonotherapy in 69.6%, disease free interval <2 years in 21.7%, visceral involvement in 82.6% (liver 60.9%, lung 47.8%). A total of 169 cycles were given with a median of 7 cycles. Median relative dose intensity (RDI) for Oral VRL and Cape were 72.6% and 85.3%, respectively. Neutropenia was the main side effects with grade 3–4 in 52.2% of pts and 12.5% of cycles, without any episode of complicated neutropenia. Grade 1 stomatitis were reported in 26.2% of pts and 10.7% of cycles, hand foot syndrome was observed in 39.1% of pts and 26.1% of cycles, with no grade 3. This combination demonstrated to be effective with RR of 47.8% [95% CI: 26.8–69.4] in the ITT population of 23 pts and 55% [95% CI: 31.5–76.9] in the 20 evaluable patients.

Conclusion: the combination of oral VRL 60 mg/m^2 weekly with Cape 2000 mg/m^2/d D1-D14 every 3 weeks demonstrated to be effective and safe in patients with MBC as first line chemotherapy. A total of 45 evaluable patients is planned in the study.

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Continued use of goserelin to achieve ovarian function suppression in combination with a further aromatase inhibitor (exemestane) following prior treatment with anastrozole and/or tamoxifen in premenopausal women with oestrogen receptor positive advanced breast cancer

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Introduction: The use of goserelin to achieve ovarian function suppression is a well-established therapeutic strategy in premenopausal women with oestrogen receptor positive (ER+) breast cancer. We have previously reported clinical/endocrine data of combined use of goserelin plus tamoxifen or anastrozole (a non-steroidal aromatase inhibitor) in premenopausal women with ER+ advanced breast cancer. We now report the clinical experience of continued use of goserelin given alongside exemestane (a steroidal aromatase inhibitor) in the same setting following prior treatment with anastrozole and/or tamoxifen.

Methods: Thirteen patients [median age: 45 (33–54) years] (advanced primary = 1, bone only = 6, bone + pleura = 4, bone + liver = 2) seen over a 32-month period were treated with goserelin 3.6 mg 4-weekly plus exemestane 25 mg daily as second to fourth line endocrine therapy. All patients had disease assessable by UICC criteria and received therapy for ⩾6 months (except for those who progressed prior).