(CD133+) (CECp) and activation markers (CD106+) are also measured. For CECs, 50 ul of blood is stained with the indicated MAbs; after RBC lysis, flow cytometry (FC) is performed for total CEC and CECp. For CTCs, 20 ml of blood is subjected to immunomagnetic capture using anti-EpCAM ferrofluid, followed by FC for EpCAM, CD45, and nucleic acid content. A Cox proportional hazards model was used to determine whether numbers of or changes in CEC and CTC at weeks 0, 3 and 12 could predict outcome. Markers of the ER, HER2 and VEGF pathways will be evaluated in archival tumor tissue, and plasma VEGF and bFGF will be measured.

Results: Twenty-eight pts have enrolled. Data is available on 24 pts: median age 49 yrs (32–77), median ECOG PS 0 (0–1). Preliminary toxicity and response data has been reported (Traina, BCRT 2005). The combination was generally well tolerated; one patient withdrew due to Gr 3 headaches. There were no other Gr 3–5 toxicities. 24 pts are evaluable for response: 1 pt had a partial remission, 12 pts have stable disease (SD) >6 mo; 4 pts have SD; 7 pts had progression. 22 patients were followed for up to 52 weeks (median 25 wks, range 5–52). Changes in CEC at 3 and 12 weeks were the best predictors of response (HR = 1.12 per unit change, p = 0.083, for 3-week; HR = 1.16 per unit change, p = 0.068, for 12-week change from baseline). When both 0–3 week and 3–12 week change were used as predictors in a model, hazard ratios were 1.20 (p = 0.040) and 1.13 (p = 0.184) respectively. If patients are divided into two equal sized groups based on combined hazard score, 6 of 7 progressions occurred in the high risk group (p = 0.088, log-rank test).

Conclusions: Combination L and B appears well tolerated. Additional safety and efficacy data is anticipated. This promising preliminary data indicate that CEC may serve as surrogate markers of response and progression. Updated data including CTC will be presented.

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Occult brain metastases in her-2-positive breast cancer patients

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Aim: The aim of the prospective study was to evaluate the frequency of occult brain metastases in breast cancer pts with HER-2 receptor overexpression, and to analyze overall survival and the cause of death of patients (pts) after whole brain radiotherapy (WBRT).

Material and Methods: MRI screening examination of the brain was performed in 60 HER-2 positive breast cancer pts currently treated in Breast Cancer Clinic with trastuzumab and chemotherapy because of visceral metastases and/or locoregional failure. In case of pts with occult brain metastases detected, the irradiation to the brain 30 Gy in 10 fraction was undertaken. Then, control MRI was planned to be performed 3, 6, 9, 12 months after radiotherapy in order to assess the extent of regression of metastases.

Results: In 20 (33%) pts occult brain metastases were detected: in 7 – solitary, in 13 – numerous. Pts with brain metastases were younger than those without them (median age at primary breast cancer 48 years vs 52 years), and more often with distant metastases to lungs and/or liver (18/20 pts). Median time from recurrence of the disease (visceral metastases/locoregional failure) to brain metastases was 9 months, mean 11 months. From among 10 patients with time of observation of at least 1 year after WBRT, 5 pts are still alive without symptoms of brain metastases, 5 patients died: 4- due to progression in viscera and only 1- because of progression in brain.

Conclusion: Our prospective study confirms high percentage of occult brain metastases in HER-2 positive breast cancer pts. Mean time of detection of occult brain metastases does not exceed 1 year from recurrence of the disease. Brain metastases after WBRT undertaken during asymptomatic period are not the main cause of death of breast cancer patients. In most cases those patients die of visceral metastases. It seems that it is reasonable to introduce MRI screening of the brain in HER-2 positive breast cancer pts with disseminated disease for early detection and irradiation of brain metastases before neurological symptoms appear. Longer follow-up period is necessary in order to assess the cause of death of pts.

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Breast cancer with HER2/neu over-expression – are we dealing with a heterogeneous disease?

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Background: HER2/neu over-expression (HER2+) occurs in approximately 25% of breast cancers and is often associated with a more aggressive disease. In this study we examined the effects of hormone receptor (HR) expression on clinical characteristics and natural history in HER2+ breast cancer.

Methods: A retrospective review of 137 patients (pts) with HER2+, metastatic, breast cancer was performed. HER2+ was defined as positive if immunohistochemical staining was +3 or if FISH was positive. HR was defined as positive if either estrogen or progesterone receptors staining were positive, regardless of intensity.

Results: Median age was 48 (range 24–80). At the time of diagnosis 60% were 50 years old or younger. The vast majority (92%) had invasive ductal carcinoma and 70% had grade III disease. Positive HR staining was found in 55 (40%) of the pts and negative HR staining in 82 (60%). No significant differences between the study groups were found in age, tumor histology, grade and number of involved metastatic sites at time of first recurrence.

At first recurrence, HR positive (HR+) pts had significantly lower rates of liver or brain metastasis compared to HR negative (HR-) pts (23% vs. 48%, respectively, p = 0.004) but significantly higher rates of soft tissue, bone or lung metastasis (93% vs. 74%, respectively, p = 0.006). Overall thru-ought the course of the disease, 96% of the HR+ pts developed soft tissue, bone or lung metastasis, compared with 85% in the HR- group (p = 0.043), and 50% developed liver or brain metastasis compared with 72% in the HR- group (p = 0.012).The mean disease free interval in the HR+ group was 24.5 months, compared to 15.4 months in the HR- group (p = 0.023). The mean overall survival was 101.4 months in the HR+ group, compared to 63.8 months in the HR- group (p = 0.015).

Conclusions: Compared to HER2+ HR+ breast cancer patients, patients with HER2+ HR- disease have a greater propensity for liver and CNS involvement and a markedly shorter disease free interval and reduced overall survival. These results suggest that metastatic breast cancer with HER2/neu over-expression is a heterogeneous disease, with HER2+, HR positive tumors, having a distinct and favorable biological nature compared with HER2+, HR negative tumors.

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Phase III trial of oral ibandronate and intravenous zoledronic acid in breast cancer patients with bone metastases: comparative bone turnover marker and safety data

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Bisphosphonates are a standard treatment for metastatic bone disease. Ibandronate is a single-nitrogen, non-cyclic bisphosphonate available in intravenous and oral formulations. In phase III trials, both formulations showed similar efficacies for reducing skeletal events, and tolerability profiles were comparable to placebo. Bone turnover markers are prognostic indicators of skeletal events. In this study, oral ibandronate and intravenous zoledronic acid were compared regarding their effects on bone turnover markers and safety profiles. The study was a 12-week, head-to-head, randomized, open-label phase III trial. Breast cancer patients with advanced disease and confirmed bone lesions received either oral ibandronate 50 mg daily (n = 128) or intravenous zoledronic acid 4 mg (n = 126) every 4 weeks. The primary endpoint was change in serum cross-linked C-terminal telopeptide of type I collagen (S-CTX) concentration at study end. Other assessments included levels of urinary CTX, and serum levels of bone specific alkaline phosphatase, amino-terminal procollagen propeptides of type I collagen, and osteocalcin. For the safety analysis, all AEs were recorded. Treatment with oral ibandronate was associated with comparable and statistically non-inferior reductions in bone marker levels to intravenous zoledronic acid. In addition, the number of patients with high S-CTX levels at baseline that were reduced to normal or low levels after treatment were 26/26 (100%) for ibandronate compared with 19/22 (86.4%) for zoledronic acid. The proportion of patients who experienced AEs was lower in the ibandronate group than the zoledronic acid group (65% vs 76%). In particular, there was a markedly lower incidence of AEs during the first 3 days of the study (8% vs 47%) explained by a lower incidence of acute-phase response AEs (e.g. pyrexia or flu-like illness). Overall, the