392 Poster

**Infusion therapy of pamidronate in combination with radiation therapy in cancer patients with advanced, painful, metastatic bone lesions**

I.A. Adamietz[1], P. Von Rottkay[2], M. Henke[3], F. Wenz[4], W. Haase[5], W. Wagner[6], F. Walter[7], W. Dornhoff[8], O. Schneider[9], K. Schmidt[10]. [1]*Ruhr-University – Marienhospital, Dept. of Radiotherapy, Herne, Germany;* [2]*Private Practice, Landshut, Germany;* [3]*University of Freiburg, Dept. of Radiotherapy, Freiburg, Germany;* [4]*University of Mannheim, Dept. of Radiotherapy, Mannheim, Germany;* [5]*Hospital of Vincentius, Dept. of Radiotherapy, Karslruhe, Germany;* [6]*Paracelsus Hospital, Radiology Department, Osnabrück, Germany;* [7]*Hospital of Duisburg, Dept. of Radiotherapy, Duisburg, Germany;* [8]*Mutterhaus der Boromäerinnen, Dept. of Radiotherapy, Trier,, Germany;* [9]*University of Bochum – Marienhospital, Dept. of Radiotherapy, Herne, Germany;* [10]*Novartis, Nuremberg, Germany*

**Introduction:** Palliative radiation therapy is successful in the treatment of painful bone metastases; however, complete pain relief can be achieved only in about half of the patients and almost every fourth patient is refractory to such therapy. Pamidronate (Aredia®), a bisphosphonate, has shown substantial analgesia in patients with preceding radiation therapy and therefore is a promising candidate for a combination with radiation therapy.

**Methods:** In a prospective, randomized, double-blind, placebo-controlled, multicenter parallel group design, cancer patients with solitary or multiple painful, metastatic osteolytic bone lesions in the region of femur, humerus, pelvis or spine were treated with palliative radiation therapy (2 Gy/day for 18 to 23 days depending on type of tumor) and one of the following: placebo, 90 mg pamidronate on day 1, 15 and 29 (2-weekly) or on day 1 and 29 (4-weekly interval). Patients were followed up until month 12 after start of therapy. Response to treatment was defined by an at least 50% decrease of intensity of bone pain over at least four weeks as measured on item 3 (worst pain during the past 24 hours) of the Brief Pain Inventory.

**Results:** N = 76 patients were treated (55% females, median age: 66 years) in nine radio-oncological centers in Germany. Half of the patients (48.0%) in the placebo group responded to radiation therapy alone; under combined pamidronate therapy, responder rate was higher after 2-weekly (73.1%) than after 4-weekly (56.0%) application. Sample size was too low to confirm a superior efficacy of the 2-weekly pamidronate therapy over placebo (p = 0.10, one-sided exact Fisher test). Pain relief by 50% of the baseline value was achieved after 28, 32 and 34 days under pamidronate therapy in 2-weekly and 4-weekly intervals or under placebo. In contrast to the placebo group, no clear advantage of the 2-weekly compared to the 4-weekly interval could be detected in further outcome measures (pain scores, Karnofsky-Index, quality of life, analgesics consumption).

**Conclusions:** The results of this study appear to support the claim that radiation therapy combined with pamidronate 90 mg infusion therapy is superior to radiation therapy alone in reducing the pain in progressive painful metastatic bone lesions. There is no advantage of the 2-week application schedule if the two modes of application are compared. There were no new findings regarding the toxicity of the test drug such as vomiting or anemia.

393 Poster

**Transcriptome analysis reveals an osteomimetic phenotype for human bone metastatic breast cancer cells**

A. Bellahcene[1], R. Bachelier[2], C. Detry[1], R. Lidereau[3], P. Clezardin[2], V. Castronovo[1]. [1]*University of Liege, Metastasis Research Laboratory, Liege, Belgium;* [2]*INSERM Unit Research 644, Lyon, France;* [3]*INSERM Unit Research 735, Centre René Huguenin, Saint Cloud, France*

Breast cancer metastatic cells exhibit the selective ability to seed and grow in the skeleton. In this study, gene microarraying was performed on a model of breast cancer bone metastasis consisting of the MDA-MB-231 cell line and its variant B02, which is characterized by a high affinity for bone in vivo. Analysis of B02 cells transcriptional profile revealed that 11 and 9 out of the 50 most up- and down-regulated genes, respectively, overlapped with genes expressed by cells of the osteoblastic lineage. For example, B02 cells surexpress osteoblast specific cadherin-11, which mediates the differentiation of mesenchymal cells into osteoblastic cells. In contrast, S100A4, recently described as a key negative regulator osteoblast differentiation, was the most down-regulated gene in B02 cells. We established a list of differentially expressed genes compatible with the acquisition of an osteomimetic phenotype by B02 breast cancer cells. RT-PCR and western blotting experiments allowed us to validate the modulation of several candidate genes. Finally, we verified the pathophysiological relevance of our data using immunohistochemistry on human breast primary tumors and matched liver and bone metastases. This is the first large-scale depiction of the osteomimetic phenotype adopted by bone metastatic breast cancer cells. Our results provide with well-built basis for functional studies aimed at the understanding of the molecular mechanisms that govern bone metastasis development.

394 Poster

**Extended survival in women receiving trastuzumab for brain metastases from HER2 positive metastatic breast cancer**

D.N. Church[1], R. Modgil[2], S. Guglani[2], A. Bahl[2], K. Hopkins[2], J.P. Braybrooke[1], C.G.A. Price[1]. [1]*Bristol Haematology and Oncology Centre, Medical Oncology, Bristol, United Kingdom;* [2]*Bristol Haematology and Oncology Centre, Clinical Oncology, Bristol, United Kingdom*

**Aim:** To assess survival of patients with brain metastases (BM) from HER2 positive metastatic breast cancer (MBC) treated with trastuzumab after diagnosis of BM.

Historical series indicate that symptomatic BM develop in 10–16% of patients with MBC, and are associated with a median survival of 3–6 months. The increased incidence of BM (28–43%) in patients receiving trastuzumab for HER2 positive disease is well recognised, but increasingly apparent is the favourable prognosis of such patients if trastuzumab is continued.

We have performed a retrospective review of 71 assessable patients treated at our institution who have received anti-neoplastic treatment for BM between May 2002 and April 2005. HER2 positivity was defined as 3+ on immunohistochemistry or positive on fluorescence in-situ hybridization (FISH).

The median survival after diagnosis of BM in patients in whom HER2 status was negative or unknown (n = 49) measured 3 months, with 8.1% (95% CI 3.2%-19.2%) of patients alive at 1 year; patients with HER2 positive disease who did not receive trastuzumab after diagnosis of BM (n = 8) had similar median (3 months) and 1 year (12.5%) survival. In contrast, the median survival of women with HER2 positive disease treated with trastuzumab after diagnosis of BM (n = 14) was significantly longer at 12 months (p = 0.002), with 57.1% (95% CI 32.6%-78.6%) alive at 1 year. Notable within this group are several patients with multiple BM who have displayed responses or prolonged stabilization of central nervous system (CNS) disease to systemic anti-neoplastic therapies added to trastuzumab.

Our experience confirms the favourable prognosis of patients with HER2 positive BM treated with trastuzumab after diagnosis of CNS metastases. While this improvement in survival may result from better control of systemic disease, another possibility is that trastuzumab may also have a beneficial effect on BM. Although trastuzumab does not cross the blood brain barrier (BBB) under physiological conditions and fails to accumulate in cerebrospinal fluid after intravenous administration, the disturbed BBB evident in BM may allow accumulation of sufficient concentrations within metastases to synergise with chemotherapy and radiotherapy, phenomena well demonstrated in preclinical work. Prospective confirmatory studies are required.

395 Poster

**A Phase II trial of letrozole in combination with bevacizumab in patients with hormone receptor-positive metastatic breast cancer: Correlation of response with circulating endothelial (CEC) and epithelial cells (CTC)**

H. Rugo[1], M. Dickler, Y. Traina, J. Scott, D. Moore, E. Brogi, J. Bruckner, S. Flores, C. Hudis, J. Park. [1]*University of California, San Francisco, San Francisco, CA, USA;* [2]*Memorial Sloan Kettering Cancer Center, New York, USA*

**Background:** Bevacizumab (B) added to chemotherapy prolongs PFS and OS in patients (pts) with metastatic breast cancer (MBC). In animal models of breast cancer, estrogen induces expression of VEGF that is suppressed by aromatase inhibition, suggesting that the combination of an aromatase inhibitor and B may be more effective than either agent alone. We performed a feasability study testing B with letrozole (L) for the treatment of hormone-receptor positive MBC. Identifying clinically relevant intermediate markers for angiogenesis that might predict response has been difficult, although CECs have been proposed as a marker of tumor progression and/or response to antiangiogenic therapy with B. We have previously shown that change in CEC predicts stable disease at first evaluation in a phase II study of erlotinib and B (Rugo, ASCO 2005). To explore markers of activity and response to B and L, we assayed CECs and CTCs at weeks 0 (baseline), 3, 12, and then Q 12 wks.

**Methods:** Eligible pts have MBC, are postmenopausal and are candidates for AI therapy. Prior non-steroidal AI use without progression is permitted. Therapy consists of L (2.5 mg daily) and B (15 mg/kg IV q3 weeks). A total of 42 pts will be enrolled in a two-step design; the primary endpoint is toxicity. CECs are defined as CD34/31+, CD45-. Progenitor

(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.

Supported in part by Genentech and Novartis.

**396** Poster

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

A. Niwinska[1], M. Tacikowska[2], T. Pienkowski[1], I. Lemanska[1], B. Bauer[1], H. Rudnicka[1]. [1]*Maria Sklodowska-Curie Memorial Cancer Center, Breast Cancer and Reconstructive Surgery Department, Warsaw, Poland;* [2]*Maria Sklodowska-Curie Memorial Cancer Center, Radiology Department, Warsaw, Poland*

**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.

**397** Poster

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

S. Paluch-Shimon[1], R. Catane[1], N. Ben-Baruch[2], L. Zach[1], J. Kopolovic[1], A. Kruglikova[2], T. Modiano[1], I. Wolf[1], A. Yosepovich[1], B. Kaufman[1]. [1]*Sheba Medical Centre, Tel Hashomer, Israel;* [2]*Kaplan Medical Centre, Rechovot, Israel*

**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.

**398** Poster

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

J.-J. Body[1], M. Lichinitser[2], S. Tjulandin[2], B. Bergström[3]. [1]*Institut Jules Bordet, Université Libre de Bruxell, Brussels, Belgium;* [2]*NN Blokhin Russian Cancer Research Centre, Moscow, Russia;* [3]*Hoffmann-La Roche Inc., Clinical Science, Nutley, New Jersey, USA*

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