53 years (range 28−80 years). Four patients (13.3%) underwent resection of brain metastases, twenty-three patients (76.7%) received whole-brain radiation therapy, and six patients (20%) had gamma-knife surgery. The median overall survival time was 8 months (95% CI, 6–10 months). Patients with brain metastases had more breast tumors of larger size (p = 0.000), positive lymph node status (p = 0.049), higher histological grade (p = 0.001), higher rate of negative estrogen receptors (p = 0.023) and higher rate of HER2 over-expression (p = 0.000). By multivariate analysis, larger tumor size, negative estrogen receptor status and HER2 over-expression were found to be independent significant factors associated with brain metastases.

Conclusions: Primary breast cancers which metastasize to the brain in Chinese patients are usually estrogen receptor negative and HER2 over expressing. This finding is consistent with those observed in Western literatures. Targeted therapies towards HER2 over-expressed tumors which can cross the blood brain barrier are needed to treat breast cancer patients with brain metastases effectively.

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Skeletal-related event (SRE) history, bone metastasis location and number affect SRE risk and patient survival in metastatic breast cancer

P. Major[1], D. Habr[2], R. Cook[3]. *[1]McMaster University, Juravinski Cancer Centre, Hamilton Ontario, Canada; [2]Novartis Pharmaceuticals Corporation, Global Medical Affairs, East Hanover, USA; [3]University of Waterloo, Statistics and Actuarial Science, Waterloo Ontario, Canada*

Background: The majority of patients with advanced breast cancer develop bone metastases. Survival in these patients ranges from 2 to 3 years. The prognostic potential of certain skeletal health indices measured during bisphosphonate therapy have not been systematically investigated. We conducted a retrospective analysis of data from a pamidronate-controlled trial of zoledronic acid in patients with bone metastases from breast cancer (Rosen LS, et al. *Cancer* 2003;98:1735–1744) to determine the association between patient SRE history, and lesion number and location on SRE risk and survival.

Material and Methods: Only patients treated with zoledronic acid who had lesion site and number, SRE history, and bone pain data were included in this analysis. Univariate analyses were used to assess risk ratios (RR) for time to first SRE and death at baseline (n = 664), 6 (n = 553) and 12 months (n = 435). SREs included pathologic fracture, spinal cord compression, radiotherapy or surgery to bone.

Results: In patients who had a prior SRE at baseline, the risk of a subsequent SRE was increased 2.15-fold ($P < 0.0001$) compared with patients who had not experienced a prior SRE. Patients with prior SREs at 6 and 12 months also had a higher risk of subsequent SREs (RR = 2.305, $P < 0.0001$; RR = 1.88, $P = 0.016$, respectively). Similarly, patients with $\geqslant$4 bone lesions at each time point assessed had a significantly increased risk of experiencing another SRE ($P < 0.001$ for all). Lesions in weight-bearing bones did not significantly increase the risk of subsequent SREs. At baseline, patients with a prior SRE had a significantly increased risk of death compared with patients without prior SREs (RR = 1.361, $P = 0.0083$), and the risk was also higher at 6 months (RR = 1.543, $P = 0.0029$) and 12 months (RR = 1.455, $P = 0.0481$). Patients with $\geqslant$4 bone lesions at baseline, 6 and 12 months had a significantly higher risk of death (RR = 1.372, 1.666, 1.758, respectively; $P < 0.006$ for all). At 12 months, patients who had $\geqslant$1 lesion in a weight bearing bone had a 44% increased risk of death that was not statistically significant.

Conclusions: The disease parameters prior SRE and $\geqslant$4 bone lesions significantly increased the risk of subsequent SREs and death when assessed at baseline, 6 and 12 months. Patients with $\geqslant$1 lesion in weight-bearing bones only had an increased risk of death without affecting their risk of subsequent SREs. Multivariate analyses to place these parameters in context with other prognostic variable are under way.

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Retrospective analysis of chemotherapy choices and overall survival according to treatment in 96 patients >75 years old with metastatic breast cancer

M. Debled[1], N. Madranges[1], C. Mertens[1], A. Floquet[1], C. Donamaria[1], M. Durand[1], V. Brouste[1], L. Mauriac[1]. *[1]Institut Bergonié, Departement of Oncology, Bordeaux, France*

Background: The optimal treatment for patients (pts) >75 years of age with metastatic breast cancer (MBC) is unclear and shows wide variation between clinics and countries.

Methods: We analysed all pts treated from 1st January 2000 for MBC at the Institut Bergonié, Bordeaux, France. To be eligible, pts must have received their first line of chemotherapy at age >75 years.

Results: The analysis includes 96 pts (median age 78, range 75−91). Seven pts (7%) were $\geqslant$85 years and 34 (35%) were $\geqslant$80 years when they received their first chemotherapy for MBC. First-line chemotherapy consisted of capecitabine in 53 pts (55%), vinorelbine in 21 (22%, combined with gemcitabine in 2 pts [2%]), FEC_{50} in 12 (13%), docetaxel in 6 (6%), liposomal doxorubicin in 2 (2%), mitoxantrone in 1 (1%) and 'other' in 1 (1%). Choice of chemotherapy was not age dependent: median age was 78.4 years in the subgroup receiving capecitabine and 77.0 and 77.3 years in the subgroups receiving vinorelbine and FEC50, respectively. In our clinic, capecitabine was first used in January 2002 and was given in 53 of 67 patients (79%) treated thereafter. As of January 2008, median overall survival (OS) from the start of chemotherapy was 14.0 months (95% CI: 11.3−16.7). Survival rates at 3 months, 1 year and 2 years were 82.2% $\pm$4.1%, 56.1% $\pm$5.1%, and 25.0% $\pm$4.6%, respectively. Subanalysis according to age showed median OS of 15.2 months $\pm$3.4 (SE) in pts aged 75−76 (n = 33), 10.1 months $\pm$2.1 in pts aged 77−79 (n = 29) and 13.3 months $\pm$2.0 in pts aged $\geqslant$80 years (n = 34). Median OS was longest in pts receiving capecitabine (15.1 months $\pm$2.6, vs 10.0 months $\pm$3.2 in pts receiving other chemotherapy).

Conclusions: To our knowledge, there are no published data on efficacy outcomes with chemotherapy use in MBC pts >75 years. In the early part of this decade, various chemotherapy regimens were used, with vinorelbine and FEC among the most commonly administered. We now prefer capecitabine for a large majority of this pt population, based on high efficacy and good tolerability. Our observations support the use of capecitabine as first-line treatment in this setting, with many pts deriving substantial benefit from this therapy (median OS of 15.1 months).

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Randomized comparisons of weekly versus every-3-week nab-paclitaxelin patients with metastatic breast cancer

J. O'Shaughnessy[1], M. Lichinitser[2], S. Tjulandin[3], N. Davidson[4], H. Shaw[5], P. Bhar[6], W. Gradishar[7]. *[1]Baylor College of Medicine, Oncology, Houston Texas, USA; [2]Blokhin Cancer Research Center, Chemotherapy and Combination Treatment of Neoplasia, Moscow, Russian Federation; [3]Blokhin Cancer Research Center, Clinical Oncology, Moscow, Russian Federation; [4]Broomfield Hospital, Oncology, Chelmsford Essex, United Kingdom; [5]Duke, Medical Oncology, Durham, USA; [6]Abraxis BioScience Inc., Biostatistician, Los Angeles, USA; [7]Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, USA*

Background: Nanoparticle albumin-bound (nab)-paclitaxel is a novel taxane that has demonstrated nearly double the overall response rate (ORR) in patients with metastatic breast cancer (MBC) compared with solvent-based paclitaxel. The current analysis compares the safety and efficacy of 2 different dosing schedules of nab-paclitaxel from phase II and phase III trials in patients with MBC.

Materials and Methods: This is a subset analysis of the nab-paclitaxel arms of 2 large randomized phase II (CA-024) and III (CA-012; Gradishar et al. J Clin Oncol. 2005;23:7794–7803) trials that compared nab-paclitaxel with either solvent-based paclitaxel or docetaxel in patients with MBC. Patients received nab-paclitaxel 260 mg/m^2 intravenously (IV) every 3 weeks (q3w) in the phase III trial and 300 mg/m^2 IV q3w, 100 mg/m^2 IV weekly 3 out of 4 (qw 3/4), or 150 mg/m^2 IV qw 3/4 in the phase II trial. All doses were administered over 30 minutes without corticosteroid or antihistamine premedication or special tubing sets.

Results: See the table.

	Every 3 weeks		Weekly	
	300 mg/m^2 (n = 76)	260 mg/m^2 (n = 229)	150 mg/m^2 (n = 74)	100 mg/m^2 (n = 76)
Received as 1st-line therapy, %	100	43	100	100
ORR, %	46	33	74	63
mPFS, months	10.9	5.2	14.6	7.5
mOS, months	NA	14.9	NA	NA
Grade 4 neutropenia, %*	5	9	9	5
Grade 3 PN, %	17	10	14	8

Data from study CA-012 were previously reported (Gradishar et al. J Clin Oncol. 2005; 23:7794–7803).
ORR = Overall response rate; mPFS = Median progression-free survival; mOS = Median overall survival; NA = Not available because data is not yet mature for phase II study.
*Grade 4 neutropenia based on central laboratory data.

Conclusions: Nab-paclitaxel demonstrated efficacy and was well tolerated regardless of dose regimen. Grade 4 neutropenia and grade 3 sensory neuropathy were similar in the nab paclitaxel weekly groups compared with the nab-paclitaxel q3w groups. Because of the superior

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

B. Madej-Czerwonka[1], J. Szumilo[2], F. Burdan[3], A. Chroscicki[4], R. Maciejewski[3]. *[1]District Hospital of Lublin, Surgical Oncology Department, Lublin, Poland; [2]Medical University of Lublin, Clinical Pathomorphology Department, Lublin, Poland; [3]Medical University of Lublin, Anatomy Department, Lublin, Poland; [4]District Hospital of Lublin, General Surgery Department, Lublin, Poland*

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

G. Bernardo[1], R. Palumbo[1], A. Bernardo[1], C. Teragni[1], G. Poggi[1], A. Delmonte[1], A. Amatu[1], M. Frascaroli[2], I. Jedrychowska[2], M. Strada[2]. *[1]Fondazione Maugeri, Medical Oncology II, Pavia, Italy; [2]Fondazione Maugeri, Rehabilitative Oncology, Pavia, Italy*

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

B. Kaufman[1], R. Weitzen[1], A. Goldfarb[1], N. Ephrat[2], I. Kuchuk[1], T. Golan[1], I. Wolf[1], R. Elia[1]. *[1]The Chaim Sheba Medical Center, Oncology, Ramat Gan, Israel; [2]Kaplan Medical Center, Oncology, Rehovot, Israel*

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

A. Malmström[1], J. Hansen[2], L. Malmberg[3], L. Carlsson[4], J.H. Svensson[5], J. Ahlgren[6], C. Ahlin[7], T. Jansson[8], R. Westberg[9]. *[1]Dept of Oncology, Linkoping, Sweden; [2]Dept of Oncology, Karlstad, Sweden; [3]Dept of Oncology, Jönköping, Sweden; [4]Dept of Oncology, Sundsvall, Sweden; [5]Dept of Oncology, Göteborg, Sweden; [6]Dept of Oncology, Gävle, Sweden; [7]Dept of Oncology, Örebro, Sweden; [8]Dept of Oncology, Trondhein, Norway; [9]Dept of Oncology, Stockholm, Sweden*

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