in several tumor types. This study was designed to compare incidence of SREs and mortality between IV-bisphosphonate therapy and assess the benefit of long-term ZOL use in a real-life setting among women with BC.

Methods: A claims-based analysis using commercial and Medicare Advantage data from over 45 US managed care plans was used to evaluate SRE rates, and mortality in patients treated with ZOL or PAM. Patients included in this study were older than 18 years with a breast cancer and a bone metastasis diagnosis between 01/01/01 and 12/31/06, and had continuous enrollment in the health plan with no evidence of bone metastasis or IV-bisphosphonate for 6 months prior to an index date of first receipt of ZOL or PAM. Patients were followed until disenrollment (including mortality) or end of study (12/31/07). In this study, persistency was defined as the absence of a >45 day gap between ZOL treatments, and SREs were defined as evidence of pathologic fracture, spinal cord compression, and radiotherapy and/or surgery to bone.

Results: The study sample included 8,757 patients with a mean age of 58.1±12.4 years; approx. 30% were treated with ZOL, 15% with PAM, and 55% with no IV BP. Longer persistency with ZOL was associated with a lower risk of fracture and all SREs (trend test p-value=0.0026 and 0.0216, respectively) [TABLE 1]. Patients treated with ZOL were found to have moderately lower incidence of SRE (incidence risk 36.2 versus 40.0 per 100 person year; p = 0.0707) and significantly lower mortality (morality rate 6.2 versus 8.9 deaths per 100 person year; p = 0.0130) compared to ADP treated patients.

Conclusions: This study showed that in BC patients with BM, longer persistence with ZOL was found to be associated with lower risk of SRE and suggests that ZOL may be more effective in preventing and delaying SREs than PAM.

Table 1. Risk of ⩾1 event per 100 person-years by ZOL persistency

Persistency category (days)	SRE	Fracture
31–90	56.2	13.3
91–180	44.9	13.3
181–365	41.2	9.8
365–546	37.5	6.2
547+	27.9	4.9
P-value: Test for trend	0.0216	0.0026

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Impact of 4-weekly capecitabine plus paclitaxel (XP) combination therapy for metastatic breast cancer: a multicenter phase II trial (KBCSG-0609)

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Background: The combination of capecitabine and paclitaxel (XP) has demonstrated synergistic antitumor activity in preclinical models. We have previously reported a dose-finding study of the 4-weekly XP regimen in patients with inoperable or recurrent breast cancer (Masuda N, et al. Cancer Chemother Pharmacol 2008). The purpose of this phase II study was to evaluate the efficacy and safety of a 4-weekly XP regimen for MBC.

Materials and Methods: Eligible MBC pts had received ⩽1 prior chemotherapy regimen for MBC, and had received no prior P for metastatic disease and no prior X. Pts received X 825 mg/m^2 b.i.d., days 1−21, followed by a 1-week drug-free interval. P 80 mg/m^2 was administered IV weekly on days 1, 8, and 15 followed by 1-week rest period. Cycles were repeated every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR). Time to treatment failure (TTF), overall survival (OS), progression-free survival (PFS), and safety were secondary endpoints.

Results: In 44 eligible pts, median age was 57 years (range 35−73). Prior therapy included anthracycline in 34% and taxane in 16% of pts. 19% of pts had previously received chemotherapy for MBC. Lymph node and visceral metastases were present in 25% and 52% of pts, respectively. Among 41 evaluable pts, 17 achieved a partial response (PR), indicating a 41% ORR (95% CI: 27.8–56.6%). A further 6 pts had stable disease (SD) for ⩾6 months, giving a 56% clinical benefit rate. Disease control rate including any duration of SD was 85%. ORR in hormone receptor-positive MBC was 38%. ORR in hormone receptor-negative MBC was 50%. Median PFS was 8.3 months (95% CI: 5.2−9.9 months). OS is not mature. Median duration of combination therapy was 4 cycles. Six pts had switched to X mono therapy, and the median duration of X mono therapy was 5.5 cycles. Eleven pts remain on treatment. Grade 3/4 toxicities observed in ⩾5% pts were neutropenia (26%), leucopenia (10%), fatigue (7%), and hand-foot syndrome (7%). No pts discontinued treatment due to hand-foot syndrome and there was no G3/4 diarrhea. Follow-up is ongoing.

Conclusions: 4-weekly XP was an active 1st- or 2nd-line therapy at the recommended phase II dose of capecitabine (825 mg/m^2, b.i.d.) and paclitaxel (80 mg/m^2) with a manageable adverse event profile.

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Influence of disease free interval on the efficacy of capecitabine-bevacizumab for HER2-negative metastatic breast cancer (MBC) in the RIBBON-1 trial

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Background: In this randomised, placebo-controlled, phase-III study, bevacizumab (A) or placebo (p) was combined with (1) capecitabine (X) or (2) taxanes/anthracyclines in two independently powered cohorts. Progression-free survival (PFS), the primary endpoint, was significantly greater with A combined with chemotherapy in both cohorts. In this analysis of the X cohort only, we examined PFS by disease-free interval (DFI), to determine the potential benefit of XA in different patient populations.

Methods: In the X cohort, previously untreated patients with HER2-negative locally recurrent or MBC were randomised in a 2:1 ratio to X (1000 mg/m^2 b.i.d. on Days 1−14 per 3-week cycle) plus A (15 mg/kg q3w) or p. For data reported at a cut-off of 24-months, DFI was defined as the interval between diagnosis of primary cancer and diagnosis of metastatic disease. For the 12-month cut-off, the definition of interval between the last dose of adjuvant chemotherapy (or surgery, if no adjuvant chemotherapy) and recurrence was used.

Results: 615 patients were enrolled into the X cohort, with a median follow-up of 15.6 months. One third of patients (205) had DFI ⩽24 months; approximately 25% of patients had a DFI ⩽12 months (XA:27%; Xp: 22%). Overall, median PFS was significantly greater with the XA combination than the Xp control (stratified analysis hazard ratio [HR] 0.69 [0.56–0.84], p = 0.0002). In the subgroups, a consistent trend for greater PFS with XA was reported in patients with either DFI ⩽24 (HR 0.76 [0.54–1.06]; XA 8.2 mo; control 6.1 mo) or >24 months (HR 0.63 [0.50–0.80]; XA 8.9 mo, control 4.7 mo). Similarly, using a DFI cut-off of 12 months, XA provided an additional benefit to both patient subgroups.

Conclusions: The XA combination as first-line therapy for HER2-negative MBC provides a significantly greater PFS than control. Irrespective of the DFI tested, whether by 12 or 24-month cut-offs, clinical benefit was greater with the XA combination than with control.

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Intrathecal (IT) trastuzumab in leptomeningeal and central nervous system (CNS) metastases from HER2+ breast cancer (BC): What if we could bypass the blood–brain barrier (BBB)?

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Background: Leptomeningeal carcinomatosis (LC) is a rare but quickly fatal event in the natural history of BC. HER2+ BC has an increased risk of CNS metastases but there are few data on LC frequency in this context. Trastuzumab, a monoclonal antibody against the extracellular domain of the HER2 receptor, is highly effective in systemic control of HER2+ metastatic BC (MBC). However, it is not clear if it can penetrate the intact BBB, which can cause a dissociation between systemic and CNS response to therapy. We evaluated the feasibility, safety and clinical benefit of administering trastuzumab directly into the cerebrospinal fluid (CSF) of a patient with LC and CNS metastases from HER2+ MBC.

Methods: Weekly lumbar puncture (LP) with administration of trastuzumab 25 mg and prednisolone 25 mg was performed. We prospectively assessed functional outcome, leptomeningeal gadolinium enhancement in CNS-MRI and toxicity.

Results: Upon signed informed consent, weekly trastuzumab is being administered since November 2008 to a 44 year-old patient with LC and CNS metastases from HER2+/ER+/PgR− BC. She has MBC since 2006 (lymph node, lung and liver involvement) and had already received tamoxifen, letrozole, anthracyclines, taxanes, capecitabine, iv trastuzumab and lapatinib. She had previously undergone whole brain irradiation, IT

methotrexate and cytosine arabinoside for CNS metastases and LC and progressed. Before the starting of IT trastuzumab administration, the patient presented with headache, gait disturbance, disequilibrium, dysarthria, neck stiffness and reduced flexion of lower limbs. After the first three doses she recovered lower limb motion, resumed her daily physical activities and CSF cytology has been negative ever since. In January 2009 she started capecitabine and iv trastuzumab for worsening lung metastases, later changed in July 2009 to cisplatin/etoposide/trastuzumab for progressive brain metastases, which she is still on. She refused the placement of an Ommaya reservoir, and weekly LP are still being performed with excellent tolerance. So far the patient has received 50 administrations of IT trastuzumab without adverse events. There was an increase in gadolinium leptomeningeal enhancement over time, which was not associated with functional CNS deterioration; this has faded since cisplatin/etoposide was begun. The patient maintains excellent performance, exercises regularly, performs manual tasks and speaks fluently without dysarthria.

Conclusion: Administration of IT trastuzumab is feasible, safe and led to a dramatic functional improvement in a heavily pre-treated HER2+ MBC patient with LC. Further studies are warranted to confirm clinical activity and optimize trastuzumab delivery into the CNS, including dose, schedule and duration of treatment.

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Efficacy of first-line capecitabine plus bevacizumab in patients with ER/PgR-positive metastatic breast cancer (MBC) and those previously treated with hormone therapy

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Background: The RIBBON-1 phase-III study of bevacizumab (A) or placebo (p) was performed in two independently powered cohorts, with patients receiving capecitabine (X) or taxane/anthracycline. Progression-free survival (PFS), the primary endpoint, was significantly greater with A combined with chemotherapy in both cohorts. In this analysis, we assess the efficacy of first-line X-containing regimens only in women pretreated with hormone therapy.

Methods: Key inclusion criteria were: age $\geqslant$18 years; HER2-negative locally recurrent/MBC; ECOG score 0 or 1. Patients who had received prior chemotherapy for locally recurrent/MBC or with CNS metastases were excluded. Patients were randomised to X 1,000 mg/m^2 b.i.d. on Days 1−14 per 3-week cycle or p, plus A 15 mg/kg q3w, and stratified according to disease-free interval ($\leqslant$12 or >12 months), prior adjuvant chemotherapy (yes or no), and number of metastatic sites (<3 or $\geqslant$3). The primary endpoint of the study was investigator-assessed PFS. The cohort was independently powered to detect a statistically significant increase in PFS at the 0.05 level.

Results: In total, 615 patients were enrolled in the X cohort (XA: 409; Xp control: 206) and 74% of them had ER/PgR-positive status. Around 50% of patients had received prior hormone therapy for early breast cancer (XA 49.6%; control 52.9%) or locally recurrent/MBC (XA 46.0%; control 43.2%). Overall, PFS was significantly greater with the XA combination than Xp (hazard ratio [HR] 0.69, p = 0.0002; 8.6 vs 5.7 months). Subgroup analysis showed that in patients with ER/PgR-positive status, PFS was greater with XA than with control (HR 0.69 [0.55–0.87]; 9.2 vs 6.2 months for XA vs Xp, respectively). Similarly, PFS was greater with XA in the subgroup of patients receiving prior adjuvant hormone therapy (HR 0.71 [0.54–0.93]; 9.5 vs 6.1 months). Analysis of patients with ER/PgR-negative status also revealed an improvement in PFS with XA (HR 0.70 [0.48–1.01]; 6.1 vs 4.2 months), in-line with the significant overall benefit observed in the X cohort.

Conclusions: In the RIBBON-1 study overall, XA combination therapy achieved a significant improvement over Xp in PFS as first-line therapy for HER2-negative MBC. Here, we show that the XA combination provides clinical benefit in patients with hormone-positive or hormone-negative MBC, as well as in those previously treated with adjuvant hormone therapy.

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Characteristics of metastasis in the breast from extramammary malignancies

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Background: Breast metastasis from extramammary neoplasm is rare. We present the cases of metastasis to the breast after review of results in one institute and we want to show the difference of previous report.

Material and Methods: The surgical and pathology databases of Samsung Medical Center from November 1994 to March 2009 were investigated to identify all patients with a diagnosis of metastasis to the breast.

Results: Thirty three patients with breast metastases from extramammary neoplasm were studied. Gastric carcinoma was most common metastatic origin in this study. There were 4 cases with microcalcifications in their metastatic lesions. This is the first report of microcalcification of metastatic lesions to the breast from hepatocellular carcinoma and gastric cancer.

Conclusions: Pathologic examination and considering known clinical history may be helpful to differentiate the primary breast cancer and metastatic cancer. Metastasis to the breast from an extramammary neoplasm usually indicates disseminated metastatic disease and a poor prognosis. An accurate diagnosis of breast metastases, differentiating primary from metastatic breast carcinoma, is important for proper management.

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Bevacizumab (BV) in combination with chemotherapy in the treatment of HER2-negative metastatic breast cancer (mBC): PFS subgroup results from two phase III studies

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Background: Three multicentre, randomised phase III trials of taxane (T), capecitabine (Cap), or anthracycline (Anth) +/− BV established that combination with BV improves progression-free survival (PFS). Outcomes in clinically important subsets are important to demonstrate the consistency of treatment effect and may guide physicians when considering treatment options for patients. Here we compare the activity of BV in various clinically relevant patient subgroups across two phase III studies in mBC.

Methods: Kaplan-Meier methodology was used to estimate median PFS (mPFS) for patient subgroups from the AVADO and RIBBON-1 studies. Patients received BV in combination with docetaxel (D) or placebo (PL) in AVADO and C, T or Anth in RIBBON-1. PFS data based on investigator assessments were used for both trials. For the overall study results, stratified hazard ratios (HRs) are presented with the same stratification factors as the variables that were used for the randomisation, whereas unstratified HRs are presented for the subgroups. Updated data from the April 2009 cut-off (median follow-up 25 months) are shown for AVADO.

Results: In both studies, and in all subgroups shown, an improvement in PFS resulted from combination of BV with chemotherapy.

	AVADO		RIBBON-1			
PFS	PL+D (N = 241)	BV* +D (N = 247)	PL+Cap (N = 206)	BV*+Cap (N = 409)	PL+T/Anth (N = 207)	BV*+T/Anth (N = 415)
Triple-negative disease, n	111		137		142	
Median	6.1	8.1	4.2	6.1	6.2	6.5
HR	0.68		0.72		0.78	
95% CI	0.46–0.99		0.49–1.06		0.53–1.15	
Age $\geqslant$65 years, n	86		153		124	
Median	7.7	10.3	6.2	9.1	8.5	10.1
HR	0.68		0.69		0.83	
95% CI	0.43–1.08		0.47–1.02		0.52–1.34	
Prior adjuvant T, n	77		245		94	
Median	6.7	9.6	4.2	8.7	6.7	9.1
HR	0.51		0.62		0.65	
95% CI	0.32–0.82		0.45–0.84		0.39–1.07	

*15 mg/kg q3w; CI=confidence interval.

Conclusions: Although combination of BV with chemotherapy consistently improved mPFS across a number of clinically relevant subsets, regardless of the chemotherapy backbone used, absolute improvements in HRs and mPFS varied within subsets and across the trials.

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Long term survival and incidence of brain metastasis in HER2-positive (HER2+) metastatic breast cancer patients (MBC) treated with trastuzumab (T): an institutional based review

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Background: HER2+ status is associated with poor prognosis, high incidence of visceral and brain metastasis. However the addition of