three phase III trials in mBC. Recent preclinical data suggest that some anti-angiogenic agents (VEGFR tyrosine kinase inhibitors [TKIs] or VEGFR antibodies) increase the malignant potential of tumours (Pàez-Ribes; Ebos: Cancer Cell 2009:15). Although BV has a distinctly different mechanism of action, exploratory analyses to investigate these findings were performed on data from AVADO, a placebo (PL)-controlled study in first-line mBC.

Materials and Methods: Patients (pts) were treated with D (100 mg/m^2) q3w for up to 9 cycles, in combination with PL or BV (7.5 or 15 mg/kg) q3w until disease progression (PD) or unacceptable toxicity. Mortality rates were calculated at 30-day intervals up to day 210 after discontinuation of PL or BV for any reason. For pts discontinuing PL or BV for toxicity, PFS was analysed using Kaplan-Meier methods. In the overall population, the proportion of pts with new metastatic lesions was analysed at PD.

Results: As of 30 April 2009, 91 pts had discontinued PL or BV for toxicity; median PFS from discontinuation was longer in the BV arms than the PL arm. Mortality rates in pts stopping BV or PL for any reason (n = 463) were similar or lower in the BV arms than the PL arm at all 30-day intervals for the first 210 days after discontinuation, the timeframe over which the analyses were performed. At PD, fewer BV than PL pts had developed new lesions.

	PL + D	BV 7.5 mg + D	BV 15 mg + D
ITT population, n	241	248	247
Pts with PD, n (%)	208 (86)	212 (85)	210 (85)
Pts with PD & new lesion, n (%)	160 (77)*	154 (73)*	138 (66)*
All pts discontinuing BV or PL, n	139	153	171
Mortality, n (%)			
day 90	28 (21)	25 (17)	14 (9)
day 150	35 (26)	34 (23)	27 (17)
day 210	43 (33)	45 (32)	37 (24)
Pts discontinuing BV or PL due to toxicity, n	29	27	35
PFS from discontinuation of BV or PL			
median, months	3.3	6.4	6.8
HR vs PL		0.71	0.73
[95% CI]		[0.40–1.27]	[0.42–1.24]

*% of pts with PD.

Conclusions: Although preclinical data suggest that anti-angiogenic therapy may increase tumour malignant potential, exploratory data from a large clinical trial of BV do not support this theory. PFS in AVADO was longer after discontinuation of BV than after discontinuation of PL. Mortality rates up to day 210 after PL/BV discontinuation were similar. The proportion of BV pts with new metastatic lesions at PD was lower than that of PL pts, suggesting that metastatic spread was not increased.

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An indirect comparison of aromatase inhibitors (AIs) in the first line treatment of post menopausal women with hormone receptor positive (HR+) metastatic breast cancer (MBC)

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Background: Tamoxifen has in the past been the most widely used 1st line hormonal therapy for post-menopausal patients with HR+ MBC. Third-generation AIs, which have shown superior efficacy in early and advanced disease compared with tamoxifen, have been insufficiently explored in head-to-head trials in the 1st line setting. Hence, an indirect comparison was made of the relative effects of 2 non-steroidal (letrozole, anastrozole) and 1 steroidal (exemestane) AI.

Methods: Seven databases, from database inception to Jan. 2009, were searched for randomized controlled trials of AIs. Letrozole, anastrozole, and exemestane were compared, using tamoxifen as the common comparator, via the Bucher et al method (J Clin Epidemiol 1997; 50:683–691).

Outcomes were overall survival (OS), progression free survival (PFS), time to progression (TTP), objective response rate (ORR), adverse events (AEs) and quality of life (QOL).

Table: Hazard and Odds Ratios (HR) with 95% CIs

	Treatment 1 vs Treatment 2*		
	Anastrozole vs Letrozole	Exemestane vs Letrozole	Exemestane vs Anastrozole
OS	HR = 1.08 (0.87, 1.32)	1.18 (0.86, 1.61)	1.10 (0.79, 1.52)
PFS/TTP	HR = 1.22 (0.96, 1.54)	1.24 (0.95, 1.62)	1.02 (0.79, 1.35)
ORR	OR = 1.68 (1.12, 2.52)	0.96 (0.57, 1.62)	0.57 (0.35, 0.95)

*Hazard or odds ratio <1 indicates greater likelihood of better response on treatment 1.

Results: Four trials were included: 2 comparing tamoxifen with anastrozole (Bonneterre & Nabholtz 2001), 1 with letrozole (PO25) and 1 with exemestane (EORTC 10951). No significant differences were observed among the 3 AIs in OS, PFS/TTP or AEs; only ORR showed some advantage for letrozole and exemestane over anastrozole. QOL could not be compared as it was only reported for PO25.

Conclusions: Paucity of data in head-to head comparisons between AIs in this population make it difficult to conclusively differentiate between the drugs. Hence these AIs appear to be used interchangeably in clinical practice. Though results of this study need to be interpreted with caution because they are based on indirect comparisons, they suggest a class effect for all AIs.

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Analysis of risk factors associated with early development of brain metastases in breast cancer

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Background: Different groups reported an increased incidence of brain metastases (BM) from Her2-positive breast cancer in recent years; similar results were observed in triple-negative disease. Longer survival as well as the inability of most anti-cancer drugs to pass through an intact blood–brain barrier may add to this phenomenon. Furthermore, based on preclinical data, it was suggested that the Her2-positive subtype itself featured higher propensity to brain tissue.

We tried to correlated clinical and histopathological risk factors with early development of brain metastases, as such high-risk patients may derive the largest benefit from strategies of screening or prophylaxis.

Material and Methods: 230 patients with BM were identified at two Austrian centres. Patients received whole brain radiotherapy (WBRT) with or without boost irradiation or surgical resection. Data concerning case history and histology were available. Time to development of BM was defined as primary study endpoint. Multivariate analyses (Cox regression model; binary logistic regression model) were used in order to identify risk factors associated with early development of BM and BM as first site of disease progression (age; hormone receptor [HR] status; Her2-status; histological subtype; grading; stage 4 at primary diagnosis; adjuvant treatment; time to recurrence <12 months; visceral metastases; palliative chemotherapy; trastuzumab).

Results: Median age was 50 years; median time to development of BM was 36 months (mo), 95% CI 32.33–39.67. Overall survival following WBRT was 8 mo, 95% CI 6.06–9.94. HR-negative disease ($p = 0.043$; OR 1.68) and time to recurrence <12 mo ($p < 0.0001$; OR 3.57) predicted for early development of brain metastases, while palliative chemotherapy had a preventive effect ($p < 0.0001$; OR 0.31). Lobular histology correlated with BM as first site of disease progression ($p = 0.033$; OR 1.22).

Conclusions: Risk factors for development of BM were already published. We tried to identify a population at risk for early development of BM.

While Her2-positive disease shows increased risk for BM, our data suggest that Her2-status is not correlated with early development of BM or BM as first site of tumour progression. HR-negative disease and early disease recurrence predicted for shorter time BM. As those are typical features indicating a more aggressive tumour phenotype, we were not able to define reliably risk factors predicting for early development of brain metastases.

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Retrospective database analysis of the effect of zoledronic acid on skeletal-related events and mortality in women with breast cancer and bone metastasis in a managed care plan

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Background: Breast cancer (BC) patients with malignant bone lesions (BM) often experience skeletal-related events (SRE) including pathologic fracture, spinal cord compression, hypercalcemia of malignancy, which require radiotherapy and/or surgery to bone and are associated with significant morbidity and mortality and reduced quality of life. Zoledronic acid (ZOL) and pamidronate disodium (PAM), from the drug class bisphosphanates (BP), have proven to reduce and delay incidence of SREs

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

484 Poster

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