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