toxicities were: neutropenic infection that was 16.8% vs 9.2% respectively for TH and TCH, thrombocytopenia (2% vs 15%), asthenia (5% vs 12%), anemia (5% vs 11%), and diarrhea (2% vs 10%). Two pts died (1.5%) due to sepsis in TCH. Absolute LVEF decline >15% were seen in 5.5% vs 6.7% of pts. One pt (0.8%) had a symptomatic CHF in TH arm. The serum HER2 ECD analysis is underway and will be presented.
**Conclusion:** Both TH (T 100) and TCH (T 75) were highly effective treatment regimens in women having HER2-positive MBC, demonstrating high response rates, median TTP >10 months, and median overall survival >36 months in both TH and TCH. Cardiac toxicity was no significant problem with either treatment.

**2099** ORAL

**Multiple lines of trastuzumab provide a survival benefit for women with metastatic breast cancer: results from the Hermine cohort study**

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**Background:** The efficacy and safety of trastuzumab (Herceptin®; H) in combination with taxanes have been demonstrated in clinical trials of patients (pts) with HER2-positive metastatic breast cancer (MBC). There is considerable interest in the efficacy of continuing H after disease progression. Data from the Hermine cohort study of H for MBC in routine clinical practice were analysed to determine whether continuation of H is beneficial.
**Material and Methods:** Hermine was an observational French cohort study of pts with HER2-positive MBC who began their initial H treatment between January and December 2002. Study end points included duration of treatment, progression-free survival (PFS) and overall survival (OS). Minimum follow-up was 2 years. We present data from exploratory analyses of pts treated with H in the first- or second-line setting who continued to receive H-based treatment at disease progression or who discontinued.
**Results:** A total of 623 pts were enrolled, of whom 221 and 117 received their first H regimen as first- or second-line treatment, respectively. Among pts receiving first-line H, median OS from first H treatment was longer in pts who continued to receive H compared with those who discontinued (not yet reached after 27.8 months' follow-up vs 16.8 months [95% CI: 12.5−19.5]; $p < 0.0001$). Similarly, in the first-line setting, OS at 2 years was 73.7% in pts who continued H compared with 24.7% in pts who discontinued. Median OS from the date of first progression for pts who received first-line H was 21.3 vs 4.6 months for pts who continued H compared with those who discontinued, respectively ($p < 0.0001$). Among pts receiving second-line H, median OS from the first H treatment was again longer in those who continued treatment with H after progression compared with those who discontinued (27.2 vs 15.6 months, respectively; $p = 0.076$). In addition, median OS from the date of first progression for pts who received second-line H was 15.5 vs 11 months for pts who continued H compared with those who discontinued H, respectively ($p = 0.023$).
**Conclusion:** Continuing H after disease progression in women with HER2-positive MBC who received H in the first- or second-line setting appears to be associated with a survival advantage.

**2100** ORAL

**Prediction of brain relapse (BR) in HER-2 positive metastatic breast cancer (MBC) patients (pts)**

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**Background:** We have earlier demonstrated a high risk of BR in HER2 positive MBC pts (J Clin Oncol, 2006; 24, 18S). The present study, based on longer follow-up and increased number of events, includes extensive analysis of clinical and pathological factors determining the risk of BR in this group.
**Material and Methods:** Study group included 264 consecutive HER2-MBC pts aged from 24 to 77 years (median 49 years). A total of 131 pts (50%) were premenopausal, 130 (49%) – postmenopausal and 3 (2%) – with unknown menopausal status. Dominant site of disease included soft tissue (28 pts, 11%), bones (26 pts, 10%) and viscera (210 pts, 80%). A total of 210 pts (80%) were administered trastuzumab for metastatic disease, usually in combination with other systemic therapies. Statistical analysis included contingency tables, chi-square test, Kaplan-Meier survival analysis and Cox proportional hazard model.
**Results:** After a median follow-up of 2.8 years the clinical BR occurred in 75 pts (28%). Median time from treatment dissemination to BR was 10 months (range, 0−81 months), and the cumulative one- and two-year risk of BR was 17% and 31%, respectively. The cumulative one-year risk of BR in post- and premenopausal pts was 8% and 24%, and the two-year risk – 29% and 33%, respectively ($p = 0.019$). The cumulative one- and two-year risk of BR in pts administered trastuzumab was 11% and 25%, respectively, compared to 14% and 33%, respectively in pts who did not receive trastuzumab ($p = 0.54$). In the multivariate analysis premenopausal status (HR = 1.96; $p = 0.008$), and time to distant relapse shorter than two years (HR = 1.72; $p = 0.031$) were significantly related to the risk of BR, whereas lobular carcinoma was at borderline level (HR = 2.12, $p = 0.061$). Based on the multivariate analysis a prognostic index of the risk of BR in HER-2 positive MBC pts was developed. In the low-risk group (0−1 unfavorable variables; 68% of all pts) the cumulative one- and two-year risk of BR was 11% and 23%, respectively, compared to 28% an 46%, respectively in the high-risk group (2−3 unfavorable variables; 32% of all pts). The hazard risk of BR in the high- vs. low-risk group was 2.42 ($p < 0.001$). The median survival in pts with BR was 9 months, with 39% and 13% one- and two-year survival probability, respectively.
**Conclusions:** Clinical and pathological factors may select MBC patient categories with particularly high risk of BR in whom preventive strategies should be considered.

**2101** ORAL

**Phase III study of ixabepilone plus capecitabine in patients with metastatic breast cancer (MBC) progressing after anthracyclines and taxanes: subgroup analysis of patients receiving ixabepilone in the first-line setting**

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**Background:** Anthracyclines and taxanes are increasingly used as adjuvant therapy in breast cancer. Patients who progress within 1 year of adjuvant taxane and anthracycline therapy have limited therapeutic options for first-line treatment in the metastatic setting. Ixabepilone, a semi-synthetic analog of epothilone B, was developed to overcome tumor resistance mechanisms. This phase-III trial evaluated ixabepilone plus capecitabine vs capecitabine alone.
**Methods:** 752 MBC patients resistant to anthracyclines and taxanes were randomized to ixabepilone (40 mg/m$^2$ iv over 3h on day 1 every 3 weeks) in combination with capecitabine (2000 mg/m$^2$ po in 2 divided doses, on days 1−14 of a 21-day cycle), or capecitabine alone (2500 mg/m$^2$ on the same schedule). Resistance was defined as disease progression within 3−4 months following anthracycline/taxane in the metastatic setting and 6−12 months following adjuvant anthracycline/taxane therapy. A prospectively-defined subset analysis was performed in patients who received ixabepilone plus capecitabine as first-line treatment after adjuvant anthracycline/taxane.

| | Total population | | First-line after adjuvant A/T[a] | |
|---|---|---|---|---|
| | Ixabepilone + capecitabine (N = 375) | Capecitabine (N = 377) | Ixabepilone + capecitabine (N = 25) | Capecitabine (N = 30) |
| PFS (mo), median (95% CI) | 5.8 (5.5–7.0) | 4.2 (3.8–4.5) | 7.0 (4.5–8.8) | 2.1 (1.4–4.2) |
| Hazard ratio (95.17% CI) | 0.75 (0.64–0.88) | | 0.46 (0.25–0.85) | |
| Objective response rate (%) | 35 | 14 | 44 | 10 |

A/T, anthracycline/taxane.

**Results:** Ixabepilone plus capecitabine was superior to capecitabine with a 40% prolongation of median progression-free survival (PFS) ($p < 0.001$). Fifty-five patients received ixabepilone plus capecitabine or capecitabine as first-line therapy. PFS was again prolonged for patients receiving

combination therapy (with a 54% reduction in the estimated risk of disease progression).
Grade 3−4 treatment-related sensory neuropathy (21% vs 0%), fatigue (9% vs 3%), and neutropenia (68% vs 11%) were more frequent with combination therapy in the total population.
**Conclusion:** Ixabepilone plus capecitabine is superior to capecitabine alone in MBC patients rapidly progressing after anthracycline/taxane treatment. This benefit is also confirmed in first-line patients who progress after adjuvant anthracycline/taxane therapy.

**2102** ORAL

**New insights in epirubicin (E) cardiac toxicity. An analysis of 1097 patients (pts) treated for metastatic breast cancer (MBC)**

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**Background:** The object of the study was to conduct an analysis and assess a recommended cumulative dose of E corresponding to a 5% risk for cardiotoxicity taking into account: dose administrations, concurrent risk of dying of MBC and possible predictors of cardiotoxicity. Methods. Data from 1097 consecutive anthracycline naive pts was retrieved retrospectively. Pts developing cardiac heart failure according to New York Heart Association (NYHA) Class $\geqslant$ II were recorded as having E cardiotoxicity. Statistics: two extended Cox multivariate analysis (events: cardiotoxicity and mortality of MBC) followed by competing risk analysis.
**Results:** 125 pts (11.4%) developed cardiotoxicity. Predictors for increasing the cardiotoxicity hazard ratio (HR) were: 1. cumulative dose of E: as the rate increased with 37% per every 100 mg/m$^2$ E, when given as first line treatment for advanced disease, 2. increasing age as the rate increased with 28.7% per additional 10 year, 3. x-ray including the heart (HR = 2.08), 4. tamoxifen for relapse (HR = 1.87), 5. predisposition to cardiac disease (HR = 3.01). Mortality rate for MBC: the survival was significant lower in pts with increasing tumour burden, poorer performance status, previous adjuvant CMF, and with increasing age. The HR for mortality was significantly increased by increased duration of treatment with E and was highest in the first three months than later on. The risk of cardiotoxicity increased mostly during the first 8 months after cessation of E nearly becoming constant later on. The cumulative dose of E corresponding to a 5% cardiotoxicity risk was found to be both significantly lower than previously assumed (900 mg/m$^2$) and depend on predictors for mortality and cardiotoxicity. Thus, for pts with no predictors at age 40 the level of 5% risk was 806 mg/m$^2$, at age 50: 739 mg/m$^2$, at age 60: 673 mg/m$^2$, and at age 70: 609 mg/m$^2$.
**Conclusion:** The risk of cardiotoxicity of E was more pronounced than expected and occurred on a much lower cumulative dose of E. Increasing age, x-ray, tamoxifen and pre-disposition to cardiac disease contributed significantly to this.

**2103** ORAL

**A randomized, double-blind phase 2 study of the oral tyrosine kinase inhibitor (TKI) axitinib (AG-013736; AG) in combination with docetaxel (DOC) vs DOC plus placebo (PL) in first-line metastatic breast cancer (MBC)**

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**Background:** Single-agent DOC is commonly used to treat MBC. AG is a potent TKI of VEGFR 1, 2 & 3. A phase 1 lead-in study identified 80 mg/m$^2$ q3wks of DOC in combination with 5 mg BID of AG as the recommended phase 2 dose. The primary objective was to determine whether the time to progression (TTP) of the AG+DOC arm is superior to that of the DOC+PL arm.
**Methods:** Pts with no prior chemotherapy for MBC and $\geqslant$12 mos from adjuvant chemotherapy (aCT), measurable disease, ECOG performance status (PS) of 0–2, and no uncontrolled brain metastases were randomly assigned (2:1) to receive treatment with either DOC+AG or DOC+PL, without prophylactic growth factor in cycle 1. Tumor measurements were performed q9wks. Pts were stratified according to estrogen receptor (ER) status, prior aCT and PS (0/1 or 2).
**Results:** A total of 168 pts were randomized. 92 pts had received prior aCT, 27 of whom received a prior taxane. Treatment arms were well balanced for prior adjuvant and taxane therapy. A median of 7 cycles of AG+DOC (range: 1–18) and 7 cycles of DOC+PL (range: 1–23) were administered. The most common non-hematologic all-grade adverse events observed in the AG+DOC arm included diarrhea (60%), nausea (53%), alopecia (51%), fatigue (49%), stomatitis (44%), and vomiting (40%). Grade 3/4 adverse events that were increased with AG+DOC vs DOC+PL included febrile neutropenia (16 vs 7%), fatigue (13 vs 5%), stomatitis (13 vs 2%), diarrhea (11 vs 0%), and hypertension (5 vs 2%). Other grade 3/4 hematologic toxicities were similar in both arms. The median TTP (by RECIST) was 8.2 mo with AG+DOC and 7.0 mo with DOC+PL, with a hazard ratio (AG:PL) of 0.73 (prespecified, one-sided p = 0.052). The overall response rate (ORR) was 40% in the AG+DOC arm and 23% in the DOC+PL arm (p = 0.038), with a duration of response of 6.9 and 5.3 mo respectively. In a hypothesis-generating subgroup analysis, the median TTP in patients receiving prior aCT was 9.0 mo with AG+DOC and 6.3 mo with DOC+PL, with a hazard ratio of 0.54 (p = 0.012). Within this stratum, ORR was 45% in the AG+DOC arm and 13% in the DOC+PL arm (p = 0.003).
**Conclusions:** The anti-angiogenic TKI AG combined with DOC (80 mg/m$^2$ q3wks) as first-line therapy for MBC has an acceptable safety profile and promising anti-tumor activity.

## *Poster presentations* (Wed, 26 Sep, 14:00−17:00)
## Breast cancer – advanced disease

**2104** POSTER

**Serum Levels of N-telopeptide (sNTX) and bone-specific alkaline phosphatase (BAP) in oncology patients (pts) who developed osteonecrosis of the jaw (ONJ) during therapy with intravenous bisphosphonates (IB)**

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**Background:** IB including pamidronate and zoledronic acid are routinely utilized in the treatment of pts with metastatic breast, lung and prostate carcinoma to bones, and multiple myeloma, since a decreased incidence of skeletal complications was reported with their use. (Hortobagyi et al, N Engl J Med 1996) ONJ is a serious complication of long-term therapy with IB, and its incidence is as high as 7.7% in pts on chronic IB therapy. (Bamias et al, J Clin Oncol 2005) sNTX and BAP are biochemical markers of bone turn-over and can be suppressed by IB. A major hypothesis for the etiology of ONJ is over-suppression of bone turn-over. (Woo et al, Ann Internal Med 2006) To test this hypothesis we tested sNTX and BAP before and after the diagnosis of ONJ.
**Materials and Methods:** We identified a database of 75 oncology pts who developed ONJ between 2003–2006 and were seen by our Dentistry Service. 28 eligible pts had stored serum samples at 3 time-points: one year prior to ONJ diagnosis, 6 months prior, and proximate to the time of ONJ diagnosis.
**Results:** Of 28 pts: 75% were female; median age was 60 (range 43−81); primary diagnosis included metastatic breast carcinoma 68%, metastatic prostate carcinoma 21%, and multiple myeloma 11%. Median months of IB prior to diagnosis of ONJ was 33 (range 3.4–118.7).
Laboratory normal ranges for sNTX and BAP are 5.5−19.5 nM BCE, and 14.2−42.7 Units/L, respectively. The median level of sNTX and BAP proximate to the time of ONJ diagnosis in our cohort was 11.4 nM BCE (range 7.6−23.2) and 21 Units/L (range 8–160), respectively. 96% and 86% of patients had normal levels of sNTX and BAP, respectively, at the time of ONJ diagnosis. There was no evidence of a downward trend of sNTX and BAP serum levels approaching (one year and 6 months prior) diagnosis of ONJ.
**Conclusions:** In this single-institution cohort of pts who developed ONJ on IB:
1. There was no evidence of very low absolute serum levels of sNTX and BAP and
2. There was no evidence of a downward trend in sNTX and BAP serum levels over the year prior to diagnosis.