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.