analysis, casopitant produced a statistically significant improvement in CR rates; in this subanalysis the results are similar to the overall results, however, the number of pts with BC in each arm is too small to draw similar conclusions (Table). There were no significant differences among groups in the rate of significant nausea in the primary analysis. All casopitant doses were generally well tolerated. Commonly reported AEs in pts with BC were nausea (24%), alopecia (17%), neutropenia (16%), anorexia (13%), and fatigue (12%).

Conclusion: CINV due to AC or taxane therapy in pts receiving OND/DEX was similar to that seen in previous studies of pts receiving MEC. Addition of casopitant demonstrated improved control of CINV, including delayed events, when added to a standard OND/DEX prophylaxis regimen in a phase II trial. This benefit appears to be maintained in women with BC receiving commonly administered AC and taxane-based MEC. A large phase III study in pts receiving cyclophosphamide plus an anthracycline has been completed and results will soon be published.

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Application of preventive measures minimizes the occurrence of osteonecrosis of the jaw (ONJ) in bisphosphonate treated breast cancer patients with bone metastases

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Background: ONJ is an uncommon adverse event reported in patients (pts) receiving cancer treatment including bisphosphonates (BPs). Dental problems were identified as the most important risk factors for developing ONJ. Screening of the oral cavity, dental examination, and good oral hygiene were suggested as preventive measures. We therefore investigated the occurrence rate of ONJ before and after the implementation of dental preventive measures.

Material and Methods: Since April 2005, 111 consecutive breast cancer (BC) pts treated with BPs (Group POST), underwent a baseline dental assessment (dentist's visit ± panoramic jaw radiograph) and dental care when required. Regular dental examinations were routinely performed during BPs treatment. From Jan 1999 to Feb 2007, a retrospective review of 591 consecutive BC pts with bone metastases (Group PRE) treated with BPs in our clinic, who did not receive any preventive measures were evaluated. Occurrence of ONJ was calculated both as number of cases by number pts at risk and as incidence rates (IR). Differences between the two groups (PRE and POST) were analyzed using the one-tailed Fisher's exact test and presented as incidence rate difference (IRD) with a 95% CI.

Results: In total, we analyzed 702 BC pts. The type of BP administered was: Zoledronic Acid (ZOL) in 175 pts, Pamidronate (PAM) in 432 pts, PAM followed by ZOL in 69 pts, and Clodronate (CLO) in 26 pts. Overall, 19 (3.21%) ONJ cases were observed in the PRE group vs 1 case (0.9%) in the POST group ($p = 0.148$). Considering pts exposed to ZOL/PAM+ZOL, the application of dental assessment lead to a significant reduction in the ONJ rate (PRE 7.9% vs. POST 1.3%, $p = 0.03$). The IR of ONJ in all 702 patients was 0.025/yr for group PRE and 0.009/yr for group POST (IR difference = 0.016, 95% CI from 0.005 to −0.04).

Conclusions: The treatment with BPs is often necessary in patients with bone metastases. In this study the, application of preventive measures before starting and during BP treatment produced a substantial 63% reduction of the incidence of ONJ.

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Zoledronic acid (ZA) prevents aromatase inhibitor (AI)-associated bone loss in postmenopausal women with early breast cancer – 36-month follow-up of the Z-FAST study

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Background: AI therapy improves disease-free survival in postmenopausal women (PMW) with ER+ and/or PgR+ early breast cancer (EBC) compared with tamoxifen. However, AIs result in near-complete ablation of estrogen production, leading to accelerated bone loss and increased fracture risk. The Zometa/Femara Adjuvant Synergy Trial (Z-FAST) evaluates the efficacy and safety of ZA in preventing AI-associated bone loss in PMW with EBC receiving adjuvant letrozole therapy.

Material and Methods: 602 PMW with stage I-IIIa ER+ and/or PgR+ BC beginning letrozole (2.5 mg qd × 5 yr) were randomized to upfront ZA (4 mg IV q 6 mo) vs delayed ZA (after T-score decreases to < −2 or a clinical fracture unrelated to trauma). All patients (pts) received calcium and vitamin D. The primary endpoint, percent change in lumbar spine (L1-L4; LS) bone mineral density (BMD) at 12 mo, has been reported (ASCO 2005). The results of 36-mo follow-up and fracture data are reported here.

Results: Baseline characteristics were well balanced between groups. At 36 mo, pts receiving upfront ZA (n = 189) had a mean LS BMD increase of 3.72% vs a mean decrease of 2.95% in the delayed group (n = 188), for an absolute difference of 6.7%; $P < 0.0001$. Total hip (TH) BMD also increased in the upfront group (mean +1.64%; n = 189) and decreased in the delayed group (mean −3.51%; n = 187), for an absolute difference of 5.2% ($P < 0.0001$). Excluding BMD data from pts who started ZA in the delayed group, the overall between-group differences at LS and TH were 8.2% and 6.7%, respectively. Among pts who had baseline T-scores between −1 and −2 and 36-mo data: normal T-score (> −1) was achieved in 40.4% of pts in the upfront vs 7.6% of pts in the delayed group; 2.1% of upfront-group pts and 13.4% of delayed-group pts became severely osteopenic (T-score < −2). Fractures occurred in 17 (5.7%) pts in the upfront and 19 (6.3%) of pts in the delayed ZA group (not statistically powered for significance). Administration of ZA 4 mg IV q 6 mo for up to 36 mo was generally safe and well tolerated. No serious renal adverse events or confirmed osteonecrosis of the jaw cases were reported.

Conclusions: After 36 mo follow-up, Z-FAST results show a progressive increase in the overall difference between the upfront and delayed ZA treatment groups for the percent change in BMD at both LS and TH throughout the course of the study. These data demonstrate that ZA 4 mg IV q 6 mo prevents bone loss associated with adjuvant AI therapy in PMW with EBC.

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Anthracycline extravasation in breast cancer patients. Effective treatment with dexrazoxane* in three multicenter trials

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Background: In international multicenter studies dexrazoxane (Savene®) prevented tissue necrosis in 53/54 (98%) of evaluable patients (pts) with biopsy proven anthracycline extravasation (AEV) in two studies and in 7/7 patients in a third ongoing study. More than half the patients had breast cancer and results for this population are reported below.

Patients and Methods: TT01 and TT02 were open-label, single-arm, multicenter studies enrolling pts with biopsy proven anthracycline extravasation (AEV) from 24 EU centres. Primary objective was to avoid tissue necrosis leading to surgery. A three-day schedule of IV dexrazoxane (1,000, 1,000, and 500 mg/m^2 on days one, two and three, respectively) was used, starting no later than 6 hr after the AEV.

TT04 is an ongoing prospective, open-label, single-arm, multicenter study in pts with AEV with the primary objective to establish pharmacokinetics (PK) of IV dexrazoxane (Savene®) in the three-day schedule.

Results: 34 evaluable breast cancer patients, all with epirubicin extravasation, entered the three studies. In 33 of the 34 evaluable patients the treatment prevented development of necrosis requiring surgery. The one failure was a patient with a very large (253 cm^2) epirubicin extravasation. The three-day regimen was well tolerated with reversible CTC grade 3−4 leucopenia/neutropenia (in part also due to the concurrent chemotherapy) in 49% and thrombocytopenia in 9% of the pts. Nadir occurred days 10−14. 4% had reversible increase of liver enzymes. Six patients had possibly related SAEs: fever, infection, diarrhoea. Among sequelae mild pain was seen in 19% and mild sensory disturbances in 12%.

In the PK analysis (n = 6) the average half lives ($T\frac{1}{2}$ ± SD) were 2.1±0.4, 2.2±0.3, and 2.2±1.3 h, day 1, 2 and 3, respectively. Average AUC 0−t ± SD were 187±61 (t = 24 h), 170±58 (t = 24 hr), and 60±24 mg hr/ml (t = 4 hr), on day 1, 2 and 3, respectively. Pre-dose concentrations days 2 and 3 were ⩽ limits of quantitation.

Conclusion: Dexrazoxane (Savene®) was highly effective against anthracycline extravasation and well tolerated in breast cancer patients. There was no accumulation of dexrazoxane and consistent half life during the three-day schedule.

* Savene/Totect: registered trademarks in EU/USA, respectively