Age at baseline (yrs)	Predicted proportion of patients with FN (95% CI)			
	Disease stage I–III at baseline		Disease stage IV at baseline	
	PPP (N = 930)	CP (N = 646)	PPP (N = 361)	CP (N = 273)
40	3% (2%, 6%)	22% (12%, 36%)	5% (2%, 9%)	28% (16%, 45%)
50	4% (2%, 8%)	25% (15%, 40%)	6% (3%, 11%)	32% (19%, 49%)
60	5% (3%, 9%)	29% (17%, 45%)	7% (3%, 13%)	37% (22%, 54%)
70	6% (3%, 11%)	33% (20%, 50%)	8% (4%, 15%)	41% (25%, 60%)

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Patients' views of distress & interference with daily activities due to side effects in the TACT (Taxotere as Adjuvant ChemoTherapy) trial

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Introduction: TACT trial randomised 4162 women with early breast cancer to FEC-T (FEC × 4 → taxotere × 4) or Control (FEC × 8 or Epirubicin × 4 → CMF × 4). Quality of Life (QL) was an important secondary endpoint. In addition to a formal QL assessment (EORTC C30 & BR23), patients' (pts) self assessment of distress (D) & interference with daily activities (IDA) caused by toxicities during & after chemotherapy (CT) in the two arms were recorded & reported here.

Methods: Pts completed a diary card, rating each of 15 possible toxicity items as either 'did not suffer from', 'not at all', 'a little', 'quite a bit', 'very much' as D & IDA for cycles (C) 1, 5, & 8 and at 9, 12, 18 & 24 months (M). The proportion of pts at each time point rating toxicities as D &a IDA (quite a bit/very much) were compared between FEC-T & Control, a significance level of p = 0.01 allowed for multiple testing.

Results: 829 (418 FEC-T; 411 Control) pts entered the QL study. Diary Cards were completed by 458 at C1, 410 at C8, 633 at 12M & 539 at 24M. Median age was 49yrs (range 27–71).

At C1 rates of D & IDA did not differ significantly between FEC-T & Control and only vomiting, nausea & tiredness were reported as causing D & IDA by >10% pts.

During CT (C5&8) Control pts reported nausea & vomiting as causing significantly more D & IDA than FEC-T pts (approximately 3-fold difference in frequencies).

During C5&8 FEC-T pts reported pain in muscles/joints, tingling hands/feet, sore mouth & nail changes as significantly causing more D & IDA than Controls. Tiredness was reported as causing D & IDA by ⩾40% of all pts during CT, with a significant difference at C8 (Control: D 40% & IDA 43%, FEC-T: D 53% & IDA 61%).

Overall, tiredness, constipation, mouth ulcers, sore mouth, breathlessness & painful gritty eyes, caused D to >10% pts on C5&8 but only tiredness, sore mouth, breathlessness, pain in muscles/joints caused IDA for >10% pts.

After CT, toxicity rates decreased substantially; but at 24M tiredness & pain in muscles/joints were still reported as causing D & IDA by 13–22% pts, with no difference between regimens.

Conclusion: CT side effects caused more D than IDA, during CT. The majority of side effects resolved following CT but >13% pts reported a longer term impact of D & IDA from tiredness & pain in muscles/joints. More pts reported toxicities in FEC-T than control, a finding worth noting given that no overall difference in efficacy between FEC-T & control in terms of DFS was observed.

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Acupuncture for the treatment of hot flushes in breast cancer women treated with an estrogen antagonist

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Background: The object of this study was to investigate the efficacy of acupuncture in women operated for breast cancer suffering from hot flushes, a side effect of anti-estrogen medication.

Materials and Methods: In a prospective, controlled trial, 59 women suffering from hot flushes following breast cancer surgery undergoing adjuvant estrogen-antagonist treatment were randomised to either 10 weeks of traditional Chinese acupuncture or sham acupuncture. Number of hot flushes at night and daytime were recorded for 4 weeks prior to treatment, during treatment and during a 12 week follow up period. A validated health score (Kupperman index) was conducted at baseline, after 15 treatment sessions and 12 weeks post-treatment.

Results: During thetreatment period and the following 12 weeks, a 50% reduction of hot flushes both during the day and night was seen in the active treatment group, paralleled with a similar improvement in Kupperman index. Although a smaller treatment effect was observed in the sham acupuncture group during treatment, this effect could not be detected during the next 12 weeks.

Conclusion: Acupuncture seems to provide effective relief of hot flushes both day and night in women operated for breast cancer, treated post operativly with anti-estrogens. This treatment effect seems to coincide with a general health improvement measured with the validated Kupperman index.

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Safety and efficacy of the novel antiemetic neurokinin-1 (NK-1) receptor antagonist, casopitant, in women with breast cancer (BC) receiving moderately emetogenic chemotherapy (MEC) – subgroup analysis from a randomized, double-blind, placebo-controlled phase II trial

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Background: Casopitant is a potent, selective, NK-1 receptor antagonist that increased the rate of control of chemotherapy-induced nausea and vomiting (CINV) when added to an ondansetron/dexamethasone (OND/DEX) prophylactic regimen administered to patients (pts) with solid tumors receiving MEC in a phase II trial (J Clin Oncol. 2006;24:471s. #8512). The current analysis examines the safety and efficacy in the subgroup of women with BC.

Methods: Pts received OND 8 mg PO BID D1–3 + DEX 8 mg IV D1 with either active control, casopitant 50 mg, 100 mg, or 150 mg PO D1–3. Additionally, 2 exploratory arms were included to evaluate alternate dosing of casopitant and OND (150 mg D1 only (with OND/DEX) and casopitant 150 mg D1–3 with OND 16 mg/d). Pts with BC received MEC consisting of ⩾1 of the following (mg/m^2): cyclophosphamide (C) 500–1500 with other MEC; C 750–1500 if given alone or with non- or minimally emetogenic agents; doxorubicin (A) ⩾60; or epirubicin (E) ⩾90. Adjuvant regimens were not permitted. The primary endpoints were complete response (CR; no vomiting, retching, rescue medications, or premature withdrawal) and rate of significant nausea (⩾25 mm on VAS) during the first 120 hrs after chemotherapy.

	120 h CR rate (%)					
	Active control	Casopitant				
		50 mg	100 mg	150 mg	150 mg D1*	150 mg + OND 16 mg/d*
Primary analysis (N = 723)	69	81	79	84	79	84
Pts with BC (N = 176)	26 (69)	38 (82)	32 (75)	23 (87)	30 (73)	27 (81)

*Exploratory arms, not included in primary analysis.
† P = 0.012.

Results: Of the 176 pts with BC receiving MEC, the majority received a combination of AC or EC (n = 102) or a taxane (n = 37). In the primary

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