In patients who had received anthracycline-containing adjuvant CT, the cumulative doses had not to exceed 180 mg/m$^2$ for doxorubicin, 360 mg/m$^2$ for EPI, and 72 mg/m$^2$ for mitoxantrone. Patients received a maximum of 6 cycles.

**Results:** Between October 2000 and March 2002, 49 patients have been enrolled. Median age was 55 years; 88% had visceral involvement (51% liver; 37% lung) and 37% had at least 3 organs involved. The most common toxicity was neutropenia with 65% of patients with grade 3-4, 8% of febrile neutropenia and 12% of neutropenic infection. The main non haematological toxicities included nausea (86% of patients), vomiting (59%) and fatigue (77%) but they were rarely severe. No cardiac toxicity except one transient episode of arrhythmia was seen. Twenty five patients responded, yielding a response rate of 51% in the intent-to-treat population and 55% in the 44 evaluable patients. Median duration of response was 8.5 months. With a median followup of 9.5 months, the median progression-free survival has not been reached.

**Conclusion:** VRL alterning oral and IV in combination with EPI is an effective and convenient therapeutic option for MBC. Its activity and safety profile are similar to those reported for the fully IV regimen.

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## A phase II study of first-line combination chemotherapy with docetaxel and gemcitabine in anthracycline-pretreated, Her-2 negative metastatic breast cancer (MBC)

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**Background:** The combination of docetaxel (D) and gemcitabine (G) is particularly attractive as both agents are not completely cross-resistant and have been shown to be active in anthracycline-pretreated MBC. This phase II study evaluated the efficacy and safety of D and G in anthracycline-pretreated patients with MBC not overexpressing *Her-2/neu*.

**Materials and methods:** Patients with MBC (n=36) not overexpressing *Her-2/neu* and pretreated with an anthracycline-based adjuvant or neoadjuvant chemotherapy received D 75 mg/m$^2$ on Day 1 and G 1000 mg/m$^2$ on Day 1 and Day 8 every 3 weeks as first-line chemotherapy. The predominant metastatic sites were visceral (liver 36% and lung 30%); 10 (28%) patients had soft tissue metastases and 2 (6%) patients had bone lesions alone.

**Results:** All patients were evaluable for toxicity and 35 for response. A total of 184 cycles were given to 36 patients (median 6 cycles, range 1-6). A complete response was recorded in 8 (23%) patients and a partial response in 11 (31%) patients for an overall response rate of 54%. With a median follow-up of 11 (range 3-22) months, median time to progression was 8 (range 2-21) months. Median overall survival has not been reached so far. The predominant toxicity was leucopenia, however, no febrile neutropenia occurred. Haematological toxicity WHO grade 1-4 occurred as follows (% of patients/% of cycles): leucopenia grade 1, 14%/22%; grade 2, 33%/34%; grade 3, 47%/30% and grade 4, 6%/2%; thrombocytopenia grade 1, 28%/14%; grade 2, 8%/2%; grade 3, 14%/3%; grade 4, 0%/0%; anaemia grade 1, 47%/34%; grade 2, 19%/6%; grade 3, 3%/1%; grade 4, 3%/1%. The most common grade 1 or 2 nonhaematological toxicities per cycle were nausea and vomiting 21%, mucositis and stomatitis 20%, diarrhoea 15%, asthenia 28%, neurological symptoms 22%, pain 22%, nail and cutaneous disorders 21%, and dyspnoea 8%. Grade 3 or 4 toxicity per cycle included dyspnoea 3%, pain 2%, asthenia 2%, nausea and vomiting 2%, and constipation 1%.

**Conclusion:** The D-G combination regimen was active and well tolerated as first-line treatment of anthracycline-pretreated MBC not overexpressing *HER-2/neu*.

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## Caelyx (pegylated liposomal doxorubicin hcl) and conventional doxorubicin have significantly different adverse event profiles

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In a previously reported randomized, phase III trial in first-line treatment of 509 women with metastatic breast cancer, CAELYX™ and conventional doxorubicin were shown to have comparable efficacy with respect to progression-free survival. There was a significantly greater risk of cardiotoxicity with conventional doxorubicin compared with CAELYX™ (P<.001). In order to ascertain whether there were other significant differences in toxicity between the 2 agents, a post-hoc analysis was performed using data from the trial. Twenty types of adverse events were reported in ≥5% of patients in either arm. Palmar-plantar erythrodysesthesia was the most frequently reported adverse event related to CAELYX™ treatment (48% of patients overall; NCI-CTC Grade 3 in 17%, and Grade 4 in 0%), whereas alopecia was the most frequently reported adverse event associated with conventional doxorubicin, (reported in 66% of patients overall; pronounced or total hair loss reported in 54%). Adverse events related to the skin or mucosa were significantly more prevalent in the CAELYX™ arm and included mucositis (CAELYX™ = 59 events, conventional doxorubicin = 33 events; $P$ = 0.0026), stomatitis (CAELYX™ = 55 events, conventional doxorubicin = 38 events; $P$ = 0.0487), palmar-plantar erythrodysesthesia (CAELYX™ = 123 events, conventional doxorubicin = 5 events; $P$<.0001), rash (CAELYX™ = 25 events, conventional doxorubicin = 4 events; $P$<.0001), erythema (CAELYX™ = 18 events, conventional doxorubicin = 3 events; $P$ = 0.0008), and abnormal pigmentation (CAELYX™ = 21 events, conventional doxorubicin = 6 events; $P$ = 0.0029). Alopecia (CAELYX™ = 51 events, conventional doxorubicin = 169 events; $P$<.0001), nausea (CAELYX™ = 94 events, conventional doxorubicin = 136 events; $P$ = 0.0002), vomiting (CAELYX™ = 48 events, conventional doxorubicin = 78 events; $P$ = 0.0022), and neutropenia (CAELYX™ = 10 events, conventional doxorubicin = 25 events; $P$ = 0.0089) were more often associated with conventional doxorubicin treatment. In this posthoc analysis there were no other significant differences in adverse event frequency between the 2 groups. CAELYX™ and conventional doxorubicin have distinct toxicity profiles. Skin and mucosal toxicity are the most common type of adverse events associated with CAELYX™ whereas conventional doxorubicin is associated with significantly more alopecia, nausea, vomiting, and neutropenia.

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## Multicenter phase II study of sequential hormonotherapy with Anastrozol/Exemestane (ARIM-AROM) in metastatic breast disease. Preliminary data of Goim 2107 study.

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The study was oriented to evaluate the overall response as primary endpoint, TTP, clinical benefit, toxicity and overall survival as secondary end-point.

**Eligibility criteria:** Advanced breast cancer or primary tumour or locally advanced not resectable, with positive or unknown ER/PgR, with interrupted TMX treatment and physiological, pharmacological, radiotherapeutic or surgical menopause.

**Treatment:** Anastrozol 1 mg/die up to progression, followed by Exemestane, 25 mg/die up to 2nd progression.

**Recruitment time:** 12 months.

**Patient characteristics:** 99 pts were recruited, median age 67 (range 36-93) with bone metastases (55%), skin and lymphonodes (27%), liver (33%) and PS 0 (58%), PS 1 (35%), PS 2 (17%) and 42 months median DFS.

**Results:** 73 valuable pts; CR 5 (7%), PR 18 (24,5%), OR 23 (31,5%), NC 24 (33%), PD 21 (29%). In 18 pts treated in second line with exemestane were registered 2 PR and 4 NC >4 months.

**Conclusion:** These actual data are on line with literature results. Very promising seem preliminary not shown data of median response duration and clinical benefit. The next update will be at the end of June 2003.

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## Weekly paclitaxel plus trastuzumab in metastatic breast cancer (MBC): a multicentre German trial

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**Background:** Three-weekly paclitaxel plus weekly trastuzumab therapy has proven clinical benefit in metastatic breast cancer (MBC) (Slamon D, et al. New Engl J Med 2001:344;783-92). The current trial investigates the efficacy and safety of weekly administration of both paclitaxel and trastuzumab in MBC.

**Patients and Methods:** In total, 150 patients with HER2-overexpressing MBC (IHC 3+ [DAKO HercepTest] or IHC2+/FISH+) will be enrolled from approximately 30 centres throughout Germany. Patients previously treated with adjuvant chemotherapy and/or a single course of therapy for MBC are eligible for enrolment. Patients will receive two 6-week courses of paclitaxel (90mg/m$^2$/week i.v.), separated by a 2-week break. Concurrently they will receive weekly trastuzumab (4mg/kg i.v. loading dose followed by 2mg/kg/week i.v.); trastuzumab will be given for at least 48 weeks, or until disease progression.

**Results:** Currently 76 patients have been enrolled; data on 58 patients is discussed here. 89% had tumours with IHC 3+ overexpression, 11% had IHC2+/FISH+ tumours. The median number of sites of metastasis was two, with predominant sites being the lungs (60%), liver (39%) and bone (40%). 67% of patients have received adjuvant therapy and 38% have been given one previous course of chemotherapy for MBC; all patients have received previous anthracycline therapy. Median treatment duration with paclitaxel plus trastuzumab was 24 weeks. 49 patients are available for assessment of response and the overall response rate is 69% (n=34), including complete response in 20% of patients (n=10). The weekly regimen was generally well tolerated. The most commonly reported adverse events of grade e 2 were leucopenia (28%) and anaemia (36%). Non-haematological toxicities included myalgia, peripheral neuropathy, nausea and vomiting, which were mainly mild to moderate in severity.

**Conclusions:** The preliminary data are promising and suggest that the increased dose-intensity of weekly paclitaxel in combination with trastuzumab compares favourably with the reported 3-weekly paclitaxel plus trastuzumab data. Recruitment to the trial is ongoing and updated efficacy and safety data will be presented.

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## Weekly paclitaxel: an effective and well tolerated treatment for advanced breast cancer

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**Backgound;** Paclitaxel has shown to be an active single agent in the treatment of metastatic breast cancer with response rates over 60% as first-line and up to 30% as second line therapy. However, the treatment is mostly palliative and thus the treatment should be as mildly toxic as possible and be convenient to patients. Therefore we initiated this national multi-institutional study with weekly paclitaxel in patients with metastatic breast cancer.

**Patients and methods:** Ninety-one patients (pts) progressing either after hormonal (42%) or cytostatic treatment (57%) for advanced breast cancer were included into this study. For 44% of pts weekly paclitaxel was first line, for 42% second and for 13,6% third line cytostatic treatment for advanced breast cancer. The median age of the pts was 53.8 years (range, 34-74). Twenty (22%) were pre- and 71 postmenopausal (78%). Thirty-five (38.5%) had lung and 47 (51.6%) liver metastases (mts) and 42 (46.7%) bone mts. Only 15 (16.5%) had skin mts and four (4.4%) had ascites. Fifty-eight pts (63.7%) had >1 metastatic sites. Patients should be ambulant. They should have measurable or evaluable disease and sufficient renal, liver and bone marrow functions. Brain metastases were excluded.

**Treatment schedule** Paclitaxel, 90 mg/m$^2$ with dexamethasone premedication, was given weekly i.v. three times. The treatment cycle was 4 weeks. Median of 5 cycles (range 1-13) was delivered. Four pts received only one cycle and 30 pts over 6 cycles.

**Results:** Ten complete (11.6%) and 37 partial (43%) responses were achieved giving an overall response rate of 54.6%. Twenty-seven stable (30.5%) and 13 progressive (15.1) diseases were recorded in 86 evaluable patients. Median time to progression was 7.5 months (range 6.5-8.5 mo) and median survival time was 20.1 months (range 13.7-26.5 mo) The treatment was in general well tolerated. Grade 3-4 neutropenia occurred in 13.3% of pts, but only 2 grade 3 and one grade 4 septic episodes were recorded. No grade 3-4 thrombocytopenia and only one grade 3 anaemia were recorded. Grade two alopecia occurred in 79.8% of the pts and neuropathy grade 1 in 41.6%, grade 2 in 16.9% and grade 3 in 11.2% of pts. Only one patient had severe myalgia/artalgia. Treatment was stopped due to progression in half of the patients and due to patients' wish in 16.9% and due to toxicity in one third of the pts.

**Conclusion** According to this second largest study published of weekly paclitaxel it is concluded that weekly paclitaxel is an effective and well tolerated treatment for advanced breast cancer yielding response rate 55% with a median survival of 20 months.

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## Reduction of the incidence of central nervous metastases in patients treated with high dose epirubicin and high dose cyclophosphamide compared to high dose epirubicin alone for metastastic breast cancer.

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**Background:** Central nervous metastases (CM) occur frequently in patients (pts) with metastatic breast cancer.

**Material and methods.** Data from 116 antracycline naive pts with metastastic breast cancer were retrieved. All entered a phase III trial between January 1992 to November 1995, comparing (A) epirubicin 130 mg/m$^2$ (59 pts) every three weeks, with (B) epirubicin 130 mg/m$^2$ and cyclophosphamide 2500 mg/m$^2$ (57 pts) alternately every three weeks for a total of eight cycles as first line chemotherapy for metastatic breast cancer. Distribution of pts with lung or liver metastases, oestrogen receptor status, number of metastastic sites, and pre-treatment lactate dehydrogenase level in (A) and (B) was all identical. Retrospectively pts with CM has been listed. Statistical analyses included Kaplan-Meiers plots, Log rang test and Chi-square test.

**Result.** Twenty six (22%) of all pts developed CM; twenty (34%) treated with (A), and six (11%) with (B), p=0.0058. Median time to CM: (A) 20 mths (8-87 mths), (B) 7 mts (3-18 mts). Median survival: (A) 20 mths (2-92+ mths), (B) 22 mths (0-110+ mths), p-value = 0.6330. The median survival for CM pts after the CNS diagnosis: 2 mts (0-33 mts). The follow-up time was 108 mts (0-110+ mts). In CM pts response status after treatment was; CR 4 (15%), PR 10 (39%), NC 10 (39%), and PD 2 (7%).

**Conclusion.** Treatment with high dose epirubicin alternately with high dose cyclophosphamide reduces the incidence of CNS metastases significantly, but whitout any influence on the survival.

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## Oral capecitabine monotherapy in taxane & anthracycline pre-treated metastatic breast cancer (mbc): Suffolk Oncology Centre experience

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**Background:** Therapeutic options in taxane & anthracycline pre-treated mbc patients (pts) are limited. Capecitabine, an oral fluoropyrimidine prodrug has shown activity in MBC. We present our experience with oral capecitabine as monotherapy in taxane and anthracycline pre-treated mbc pts from Suffolk Oncology Centre.

**Material and Methods:** 26 pts with mbc, (25 females and 1male) mean age 50 yrs (range 31-64 yrs) WHO PS 0-2 were treated with oral capecitabine monotherapy from 1999-2002. Informed written consent was obtained prior to treatment. All pts had taxanes (paclitaxel or docetaxel) for mbc prior to capecitabine. 14/26 had 2 or more chemotherapy regimes for mbc. Her-2neu status: 4+ve, 10ve, 12 unknown. ER status: 13+ve, 4 ve 9 unknown. Sites of metastases: Soft tissues 14/26, Liver 10/26, lung 8/26, bone 13/26 and brain 3/26. 62% had 2 or more sites of metastases. Capecitabine dose/schedule was 2.0-2.5 gm/m2/day for 14 days, given three weekly. Median number of cycles 4.5 (range 1-13). Response was assessed as per WHO criteria and toxicity as per CTC grading.

**Results:** 25 pts were assessable for response and 26 pts for toxicity. Overall response rates (ORR): complete response (CR) 0, partial response (PR) 25% (95% CI 8-42) and stable disease (SD) 40% (95% CI 18-62). 5/16 and 3/16 best responses were in soft tissues and liver, respectively. Overall survival: (from start of capecitabine) median 5.25 months and mean 6 months (95% CI 4.6-7.4). Time to progression: median 3 months, mean 3.4 months (95% CI 2.1-4.8). Toxicity 25% had grade 3 toxicity (palmar plantar erythema 3 pts and diarrhoea 2 pts), 60% had grade 2 or more fatigue and only 13% had grade 2 anemia. There were no neutropenic septic events or treatment related deaths.

**Conclusions:** Post taxane mbc has a poor prognosis. Oral capecitabine monotherapy has activity in this subgroup with ORR of 25% and SD of 40%. The best responses were achieved in soft tissues. Oral capecitabine is well tolerated with acceptable toxicity profile in this population.