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A phase III trial comparing vorozole (RIVIZOR™) versus aminoglutethimide in the treatment of advanced postmenopausal breast cancer

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Purpose: To evaluate clinical efficacy of vorozole, a third-generation aromatase inhibitor, with reference to aminoglutethimide (AG) in the treatment of advanced postmenopausal breast cancer.

Methods: In an open, multicentre, phase III trial design advanced postmenopausal breast cancer patients, progressing under tamoxifen, were centrally randomized to receive vorozole (2.5 mg o.d.) or AG (250 mg b.i.d.) plus hydrocortisone (30 mg o.d.). In the initial study analysis response rate was selected as a primary objective and was evaluated in accordance with EORTC Breast Cancer Cooperative Group criteria for measurable disease and WHO criteria for evaluable disease.

Results: The response rates in the intent-to-treat analysis were 23% on vorozole treatment and 18% on aminoglutethimide treatment ($p = 0.070$). 47% of patients on vorozole versus 37% of patients on aminoglutethimide were demonstrated to have clinical benefit (CR+PR+NC $\geq$ 6 months) from treatment ($p = 0.017$).

Conclusion: At initial analysis vorozole tended to yield a higher response rate and showed significantly higher clinical benefit when compared to AG. At ECCO a final study analysis including data on time to disease progression will be presented.

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Palliative management of breast carcinoma skin metastases using 6% miltefosine solution applied topically: Results of a compassionate use programme

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Miltefosine is an alkylphosphocholine derivative which has been shown to have activity against breast carcinoma. Applied topically, it has shown efficacy against cutaneous metastases of several tumour types. Due to the distressing nature of visible metastatic disease and difficulty of controlling skin nodules and lymphangitis in advanced breast carcinoma, a compassionate use programme was instituted to run parallel to the regulatory programme in the UK to assess efficacy and safety.

Over a 30 month period, 73 patients received miltefosine in this study. 60 are evaluable with treatment periods ranging from 4 to 68 weeks. 22 received >12 weeks. The solution was applied b.d. and response was considered to range from static disease to CR. A RR of 53.3% was obtained. In a subset treated in Edinburgh, the RR was 75%. Mean duration of response was 5 months [range 1 to 14] with mean duration of therapy 6.5 months. Adverse events occurred in 15 pts and were mainly skin related [dryness, atrophy, itch]. 2 pts were withdrawn due to intolerable pain on application.

Most patients felt that they had contributed to their treatment. Miltefosine has thus a significant effect in the palliative management of cutaneous breast cancer metastases and should be a useful tool in their management.

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Phase II dose-finding trial of CAELYX™ (Stealth® liposomal doxorubicin HCL) in the treatment of advanced breast cancer

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Recent advances in the design of liposomes as cytotoxic drug carriers have resulted in a new formulation of doxorubicin with improved pharmacokinetic and tumour localisation properties. This new generation of liposomes, referred to as Stealth® is characterised by a long circulation time with stable retention of drug, reduced hepatosplenic uptake, and enhanced tumour localisation in animal model systems. Between Sept. 94 and March 96, 71 patients with IIIb/IV breast cancer, most with multiple metastatic sites, KP $\geq$ 60 and who had either received no prior chemotherapy, or prior CMF were entered into a multicentre phase II trial. The trial design was to administer CAELYX as a 1 hour infusion at 60 mg/m^2 every 21 days. The protocol dose was reduced after the initial 13 patients to 45 mg/m^2 every 21 days and later to 45 mg/m^2 every 28 days to define better the optimum balance between efficacy and toxicity because of the occurrence of plantar erythrodysthesia in some patients. 64 patients completed at least 2 cycles of treatment and were available for response assessments. 4 CRs and 16 PRs overall response rate = 31% were seen, 20 patients had stable disease and 24 patients had progressive disease. Of the 22 assessable patients who had received prior chemotherapy, 7 (32%) had an objective response to CAELYX. The response duration was 9 months. In contrast to conventional doxorubicin, nausea, vomiting and alopecia was notably mild or absent. Myelosuppression was mild with 90% of cycles resulting in only grade 2 or less neutropenia. Palmar plantar erythrodysthesia appeared to be the dose limiting toxicity.

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Recurrent breast cancer: Thermo-radiotherapy once versus twice weekly hyperthermia – A prospective randomized study

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Purpose: A prospective randomized study was performed to compare hyperthermia (HT) *once vs. twice weekly* applied together with fractionated radiotherapy (RT).

Methods: External beam RT and HT was applied to 127 females with 191 histopathologically confirmed recurrent breast lesions. 41% had no metastases (M0), 38% a single or few bony mets (M1) and 24% multiple bony or visceral mets (M2). Mean lesion volume was 180 cm^3 and mean depth 15 mm. Conventional fractionated RT (mean dose: 42 Gy) was combined with randomized HT: *once* (A: n = 65 pts; 98 lesions) or *twice per week* (B: n = 62 pts; 93 lesions) for a total of 4 or 8 HT sessions per HT course. The patient and lesion parameters were equally distributed in both groups. Multiple invasive thermometers were used to assess the thermometry profile.

Results: Mean FU was 24 (3–90) months. Treatment toxicity was limited: 29% discomfort/pain 1°/2°, 20% acute skin/subcutaneous reactions and 6% catheter complications. Tumor response at 3 months FU was 55% CR and at 12 months 49% local tumor control (LC), 40% were deceased. At last FU, 30 (24%) patients were alive. 31% loco-regional relapses occurred: 22% outside, 6% at the edge and 3% within the treated HT-field. In univariate analysis no difference was found between the two treatment schedules with regard to all endpoints. In contrast, relapse interval, metastatic status, tumor volume, total RT dose and thermal parameters predicted CR and LC ($p < 0.05$). In multivariate analysis, metastatic status and minimum tumor temperature were independent prognostic factors ($p < 0.05$).

Conclusions: The two different HT fractionation schemes revealed no difference in the initial and long-term local tumor response and the observed treatment toxicity.

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Monitoring treatment of bone metastases

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Purpose: Pyridinoline, deoxypyridinoline, and the N-telopeptide (NTX) are markers of bone resorption. In cancer patients with bone metastases NTX is more often elevated than either PYD or DPD. Bisphosphonates are inhibitors of osteoclasts and decrease crosslink values. This study's purpose was to correlate urinary NTX levels with clinical events in patients receiving Pamidronate therapy.

Methods: 27 patients with lytic bone disease (25 breast cancer; 2 myeloma) were treated with Pamidronate 90 mg I.V. every month in addition to standard endocrine or chemotherapy. A 24-hour urine was collected at baseline, 1, 3, and 6 months. NTX values were determined by ELISA (Ostex International, Inc.)

Results: Of the 27 patients, 24 experienced a decrease in NTX (mean decrease of 44%, SD = 56%). Of these 27 subjects, 21 had initial values of NTX in the abnormal range (>65 BCE). Twelve of the 21 patients finished the study with normal NTX values. Therefore, two subgroups of patients were constructed: (I) the 12 patients whose NTX went from abnormal to normal and (II) the 9 patients whose NTX stayed abnormal. The observed proportions of patients with fractures, 5/12 (42%) vs. 8/9 (89%), were close to statistical significance ($p = 0.07$, Fisher's exact test). The observed

proportions of patients with disease progression in bone, 3/12 (25%) vs. 7/9 (78%) were statistically significant (p = 0.03, Fisher's exact test).

Conclusion: Measurement of NTX can be used to monitor the results of bisphosphonate therapy of bone metastases. The goal of treatment should be to normalize excretion of NTX.

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High-dose therapy with peripheral blood progenitor cell support (PBPC) for the treatment of advanced breast cancer

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Purpose: High-dose chemotherapy (HD-CT) and PBPC has been used with increasing frequency in the adjuvant setting for high risk patients with breast cancer (stage II and III). In a phase I and II trial we have studied a HD-CT regimen for the treatment of breast cancer in an attempt to improve antitumor activity.

Material and Methods: Since September 1992 60 patients with advanced breast cancer were treated with a tandem HD-CT and PBPC on these clinical trial. Two cycles of cytotoxic chemotherapy with ifosfamide (7500 mg/m^2) and epirubicine (120 mg/m^2) were administered. These drugs were given in equally divided doses over 3 days. PBPC were harvested during G-CSF-supported marrow recovery. We started leukaphereses as soon as distinct population of CD 34+ cells was detectable. Following tandem HD-CT consisted of 2 cycles with ifosfamide (12000 mg/m^2), carboplatin (900 mg/m^2) and epirubicine (180 mg/m^2) given equally over 5 days.

Results: The probability of disease free survival after 3 years was 79%. 8 patients have a relapse in the first year (median 8 months) after therapy. 4 of this patients have a locoregional relapse, 1 patient has bone and 3 visceral metastasis.

The OAS of the enrolled patients in this study is 85% (95% confidence interval between 41 and 100). Severe non hematological toxicities were not observed.

Conclusion: HD-CT for the treatment of advanced breast cancer is associated with prolonged event-free survival and it is well tolerated with low side effects and no mortality.

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Dose-intensified versus standard chemotherapy in high-risk breast cancer patients: Preliminary data of a randomized trial

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Purpose: Breast cancer patients with ≥10 tumor infiltrated axillary lymph nodes have high risk of early relapse and death. Because conventional adjuvant chemotherapy is not effective in this subgroup, several high dose regimens were proposed.

Methods: We treated breast cancer patients with ≥10 tumor infiltrated axillary lymph nodes or extracapsular nodal disease within a randomized adjuvant protocol:

Arm A (HDI-EC): epirubicin 190 mg/m^2 and cyclophosphamide 600 mg/m^2 IV, q2 wks. G-CSF 5 μg/kg SC daily (day 2–12). Total 4 courses.

Arm B (EC/CMF): epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 IV; 4 courses, q3 wks followed by 3 courses of CME 500/40/600 IV day 1 + 8, q4 wks.

Results: To date, 163 patients were randomized, 115 courses in 32 patients of HDI-EC were evaluated for toxicity. Median dose-intensity was 55 mg/m^2/week (planned 60). We observed leucopenia <10^9/L in 12% of the courses and one case of acute cardiac toxicity. In 63 patient diary cards 6 episodes of severe nausea and vomiting were reported, 25 courses were followed by mild nausea. No significant deterioration of quality of life during therapy (LQE, LASA) was reported. The median total time of treatment (including radiation therapy) were 14 weeks in HDI-EC resp. 26 weeks in EC/CMF. At a median follow-up of 29 months (10–43 months) we had 6 recurrences in 41 evaluated patients treated by HDI-EC.

Conclusion: We conclude that the described dose-intense regimen is a well-tolerated therapy for breast cancer patients with high risk of relapse. Prelimenary results suggest at least equal efficacy as compared to a standard regimen, but a substantial shorter time of treatment.

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Activity of gemcitabine in metastatic breast cancer (MBC) patients previously treated with anthracycline-containing regimens

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Purpose: GEMZAR® (Gemcitabine, GEM) produced an overall response rate of 25% in MBC (Carmichael, JCO 1995, 13, 2731–6). We initiated a phase II trial of gemcitabine, as 2nd line chemotherapy for MBC, at 5 French centres in July 1994.

Methods: Major inclusion criteria were: ≥6 months of response to 1 prior anthracycline-based regimen for MBC, measurable lesions, adequate renal, hepatic and bone marrow function. GEM 1200 mg/m^2 (30 min infusion) was administered on days 1, 8, 15 of a 28 day cycle.

Results: 47 patients (pts) were recruited and all were evaluable for toxicity. 43 pts were evaluable for response: 4 pts were ineligible (1 pt had not progressed after 1st line anthracycline; 3 pts had received only 1 or 2 doses of GEM). Patient characteristics: median age 56 years (33–75), median KPS 100 (70–100), prior adjuvant chemotherapy in 14 pts, and hormonal therapy in 42 pts. Metastatic sites were mainly liver 60% and soft tissues 51% (lung 34%, bone 28%, pelvis and peritoneum 4%). 4 CRs (5 soft tissues, 3 lung, 1 liver) and 8 PRs (2 lung, 4 liver, 4 soft tissues) were confirmed for an overall response rate of 28%. The main and limiting toxicity was asthenia with 4 pts withdrawn for grade 3/4. 2 pts presented with severe cutaneous allergy requiring treatment (1 pt discontinued). Ankle oedema was occasionally noted, but 3 pts presented with mild to severe cutaneous reaction associated with oedema and pain in previously irradiated fields (1 pt withdrawn). Haematological toxicity was mild with grade 4 neutropenia in only 2 pts and 1 grade 3 thrombocytopenia with subcutaneous haemorrhage. No patient had infection related to treatment. No patients were hospitalized due to adverse events.

Conclusion: Our study confirms the activity and low haematologic toxicity of GEM as a single agent in pretreated MBC and warrants future combination trials with other cytotoxic drugs.

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Phase II study of gemcitabine in patients with metastatic breast cancer

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Purpose: Gemcitabine (GEMZAR®) has single-agent activity in metastatic breast cancer. In a European study, gemcitabine 800 mg/m^2 weekly × 3 every 4 weeks produced a response rate of 25% in 40 evaluable patients (pts) with metastatic or locally advanced breast cancer.

Methods: The present study included stage IV breast cancer pts with histologically confirmed disseminated breast cancer who had not received chemotherapy for metastatic disease. Pts received gemcitabine 1200 mg/m^2 on days 1, 8 and 15 of a 28 day cycle. Inclusion criteria: bidimensionally measurable disease, Karnofsky PS ≥ 60, adequate bone marrow reserve.

Results: 39 pts were enrolled: 33 post-menopausal, 2 peri-menopausal and 4 pre-menopausal pts, aged 34–84 years (median age 58 years). 21 of the 39 pts had received prior chemotherapy in an adjuvant setting. 35 of 39 patients were evaluable for response (received ≥2 cycles of therapy). There were 4 complete responses and 9 partial responses for an overall response rate of 37.1% (95% CI – 23–57). 13 pts had stable disease and 9 pts had progressive disease. Currently the time to event data (calculated from first dose) are: median survival 17.8 months, median response duration >12.7 months, median time to progressive disease >7.4 months. Gemcitabine was well tolerated, the maximum WHO toxicity grades (G) and numbers of pts were neutropenia: G3–9 pts, thrombocytopenia: G3–2 pts, nausea/vomiting: G3–4 pts, dyspnoea: G4–1 pt. Other toxicities were hyperbilirubinaemia (1 pt), elevated liver enzymes (2 pts), cough and pleural effusion 2 pts. One case of grade 4 infection was reported No pts were hospitalized due to drug-related adverse events, and only 1 pt was discontinued due to a drug-related toxicity (neutropenia).

Conclusion: The encouraging activity and modest toxicity of gemcitabine in this group of patients deserve further exploration in combination chemotherapy regimens and as monotherapy in pts not able to tolerate more aggressive therapy.