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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