in 11 pts and 1 in 1 pt. A total of 147 cycles of ND was administered. 24 pts were evaluable for efficacy with 6 CRs and 11 PRs leading to an overall response rate of 71%. All patients were treated with C after the completion of 6 cycles ND. A total of 130 cycles of C were delivered. 13 CRs and 7 PRs were observed for an overall response rate of 83%. Median time to progression and median survival were 28 and 33 months respectively. No Grade IV toxicity was observed during treatment with ND. Grade III neutropenia was observed in 3 pts (12%) with febrile neutropenia in 1 pt. Grade II-III anemia was seen in 3 & 1 pts. Most frequent non hematological toxicities were: nausea/vomiting, Grade I in 20 pts (80%) and Grade II in 5 pts (20%), Gr III alopecia in 23 pts (92%), nail disorder in 5 pts (20%), cutaneous erythema in 3 pts (12%) and oedema in 2 pts (8%). While on capecitabine, the toxicities were: Gr II HFS in 1 pt, Gr II anemia in 2 pts & Gr I neutropenia in 3 pts.

Conclusion: VD followed by C is an effective regimen as first line treatment of MBC with a favorable toxicity profile and very encouraging response rates.

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Preliminary results of a Phase II study of low dose weekly paclitaxel (TXL) plus high dose tremifene (TOR) in patients with metastatic breast cancer (MBC)

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Background: No synergistic effect has been reported for the combination of chemotherapy and endocrine therapy. However, a recent *in vitro* report demonstrated that tremifene (TOR) inhibits the excretion of intracellular paclitaxel (TXL) due to P-glycoprotein (P-gp) expression in an anthracycline resistant cell line treated with TOR and TXL simultaneously. In this study, we report the results of a phase II study of low dose weekly TXL and high dose TOR as treatment for metastatic breast cancer (MBC) patients.

Patient and Methods: Eighteen patients were included in the study and treated as described. Eligibility criteria for inclusion in the study included ECOG PS 0–2 and adequate hematological, renal and hepatic function. The primary endpoint was the response rate (RR), and the secondary endpoint was toxicity. TXL (80 mg/m^2) was administrated by intravenous infusion over 60 minutes on days 1, 8, and 15 of a 28 day treatment cycle. Patients were subjected to at least 6 cycles. At the same time, TOR (120 mg/body) was administrated orally, once a day without a break. Prior chemotherapy regimens were as follows: oral 5-FU agents; 3 cases, anthracycline; 2 cases, taxanes; 1 case, and hormonal therapy; 1 case. The metastatic sites: bone 2, lung 5, brain 1, liver 3, lymph node 2 and others 5 cases. Hormone receptor (HR) status was positive in 8 cases, negative in 7 cases, and unknown in 3 cases. The average administration cycle was 6.2 cycles.

Results: Nine responders were observed (4 CR, 5 PR), so the response rate was 50.0% (95% CI 26.9–73.1%). Time to progression was 8.8 months. Only one case experienced grade 3 neutropenia. No cases showed withdrawal.

Discussion: Despite the small number of patients, our results show that weekly TXL administration in conjunction with high dose TOR may be an effective treatment for MBC patients. The recruitment of patients is ongoing and an updated report of response and analysis of P-gp expression as predictive factor will be presented.

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In vitro models of breast cancer lymph node metastasis

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Introduction: Lymph node metastasis is a common feature of many cancers. It is associated with considerable morbidity and is often linked to poor prognosis. As part as the European Framework 6 Consortium METABRE, we used the parental cell line MDA-MB-435 and two metastatic sublines, LN1 and LV1, derived from lymph node and liver metastases respectively, as a model to study organ-specific metastasis and to compare the mechanisms of lymphatic and hematogenous metastasis. When injected into mammary fat pads of athymic mice, LN1 (but not LV1) produced spontaneous lymph nodes metastases, whereas when injected intravenously all three lines generated experimental lymph node metastases as well as lung metastases. These distinct patterns of spread – due respectively to direct (intralymphatic) and indirect (hematogenous) colonisation of nodes – will enable us to explore determinants of both mechanisms independently.

Methods: In an attempt to study the mechanism of lymph node metastasis *in vitro*, we initially compared the migration and invasion potential of these cell lines in Transwell® assays under different conditions. The filter inserts were either uncoated or coated with collagen IV, and the lower chamber contained either standard culture medium supplemented with 5% FCS, lymphatic endothelial cells (LECs) or LEC-conditioned medium.

Results: MDA-MB-435 parental cells and LV1 in all cases migrated more readily than LN1, suggesting that under these conditions, we were unable to detect any organotropism due to the presence of LECs or secreted products.

Future work: We are now exploring 3D models in which fluorescently tagged tumour cells are co-cultured with Matrigel® supplemented with fibroblasts above a layer of LECs, in order better to mimic the *in vivo* environment. Additionally, future studies will compare spontaneous and experimental lymph node metastasis from MDA-MB-435 cell lines and a second model (GI 101 and sublines) using gene expression microarrays, in order to explore the potential different mechanisms involved in these two routes of dissemination.

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Pilot study of gemcitabine (G) plus trastuzumab (H) in metastatic breast cancer patients with erb-2 overexpression previously treated with anthracyclines (A) and taxanes (T)

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Trastuzumab and Gemcitabine have demonstrated a survival benefit in combination with other drugs in metastatic breast cancer (MBC) patients (pts). Preclinical data suggests a synergism between both agents. We performed this pilot study to evaluate the clinical benefit (CR+PR+SD) and safety of the GH combination in MBC pts.

Patients with histological confirmation of MBC previously treated with anthracyclines and taxanes, erb-2/neu overexpression (IHQ +++ or ++ and positive FISH), measurable disease (RECIST), age >18 years old, ECOG performance status ⩾ 2, left ventricular ejection fraction > 50%, and adequate bone marrow, renal and hepatic function were included in the study. Treatment consisted of gemcitabine 1200 mg/m^2 days 1, 8 every three weeks up to eight cycles. Trastuzumab was administered weekly at a dose of 2 mg/kg, with a loading dose of 4 mg/kg.

Seventeen pts were recruited.

The median age was 57.3 years old (range 35–72); ECOG PS 0–1, 82%; PS 2, 18%. Histology included ductal carcinoma (88%) and lobular carcinoma (6%). All patients received previously A and T; 15 pts received neo/adjuvant treatment, and 6 first line (4 of them received both). 59% of patients had visceral disease (47% in the liver and 23.5% in lung). Total number of cycles received were 86, with a median number of 5 cycles per patient (range 1–8). Median relative dose intensity for G was 95%. In terms of haematological toxicity per patient (N = 17): neutropenia G 3–4 (47%) without any febrile neutropenia, and anemia grade 3 (6%). Non-hematologic toxicity was generally mild with grade 3–4 fatigue and transaminase elevation in 17% and 13% of pts respectively. The clinical benefit rate (N = 15) was 59% (95% confidence interval (CI) 33–81.5), with 4 PR and 6 SD; six pts progressed during treatment.

These results reveal an encouraging activity and toxicity in a group of patients with an unfavorable prognosis. Further evaluation of this regimen is warranted.

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Efficacy and tolerability of taxanes or vinorelbine chemotherapy with trastuzumab as a first combination in Her-2 overexpressing patients with metastatic breast cancer

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Background: Data from clinical trials showed that treatment with trastuzumab and chemotherapy in patients (pts) with Her-2 overexpressing metastatic breast cancer (mbc) significantly increases response rate, time to progression, duration response and reduces mortality in comparison with conventional chemotherapy. Preclinical data suggest synergistic antitumor activity beetwen either taxanes or vinorelbine with trastuzumab.