Results: All patients have progressed at the time of analysis. Five patients (38%) derived clinical benefit (CB) (compete response/partial response/stable disease for ⩾ 6 months) with a median duration of 9 (7–32) months. Details for the different subgroups are shown in the table.

Agents prior to G+E	N	CB(%)	Median duration of response (mo)
G+A	3	0	N/A
G+T, G+A	6	50	9 (9–32)
G+T, G+A, M	4	50	8 (7–9)

G = Goserelin; T = Tamoxifen; A = Anastrozole; E = Exemestane; M = Megestrol acetate.

Therapy was well tolerated and no patients withdrew due to side effects.

Conclusion: A combined use of goserelin and exemestane produces CB with long duration of response in significant proportion of premenopausal women with ER+ advanced breast cancer following prior use of other endocrine agents. The continued use of ovarian function suppression with goserelin alongside available endocrine agents allows further therapeutic opportunities (with much better side-effect profile than chemotherapy) in this setting. Further studies are warranted.

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Safety and efficacy of first-line docetaxel–gemcitabine in metastatic breast cancer

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Purpose: New combinations and strategies have been developed over the past 10 years including new drugs such as taxanes and Gemcitabine and this design demonstrates the feasibility of the most effective drugs, while minimizing toxicity.

Docetaxel (DXL) – Gemcitabine (GMZ) has shown significant activity against metastatic breast cancer (MBC) in a lot of studies.

Methods: From November 1998 to January 2000, 42 patients have been enrolled in the study and all patients had previously received adjuvant therapy.

Treatment: Patients received DXL: 75 mg/m^2 Day1 + GMZ: 1250 mg/m^2 Day 1 and Day 8, every 3 weeks without growth factor support. Median age was 57.5 years (range 27–74).

Results: Complete response was observed in 22.5% (9 patients) and partial response in 57.5% (24 patients) with an overall response rate of 80%. The probability of one-year survival was 83.5%. Main grade * toxicities were Neutropenia in 12.5% (5 patients) and Anaemia in 7.5% (3 patients). Nausea and vomiting grade 2–3 were in 19.2%.

Conclusion: DXL + GMZ is an active regimen in MBC. This scheme is of an easy administration, very well tolerated and effective in patients with MBC relapsing after an anthracycline based adjuvant treatment.

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Combination of vinorelbine alternating i.v. and oral in combination with docetaxel as 1st line chemotherapy of metastatic breast cancer

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Background: The combination of IV VRL and DTX was shown to be feasible and effective in MBC. In an effort to improve patient convenience a regimen alternating i.v. and oral VRL was investigated.

Methods: A phase II study was designed to evaluate the efficacy and the tolerance of i.v. VRL 20 mg/m^2 with DTX 60 mg/m^2 on day 1 and oral VRL 60 mg/m^2 on day 15 of a three-week cycle in first line treatment MBC for a maximum of 6 cycles (recommended dose established in phase I study, abstract n° 684, ASCO 2004).

Prior adjuvant CT was allowed if completed at least 12 months before study entry. At least one bidimensionnally measurable lesion (WHO criteria) was required.

Results: 49 patients (pts) were treated: with a median age of 53 years; 31 pts (63.3%) had received prior adjuvant chemotherapy; 44 pts (89.9%) had a KPS ⩾80%; and 38 pts (77.6%) had visceral involvement. A total of 261 cycles were given (median 6). Median relative dose intensities (RDI) of i.v. VRL and DTX were ⩾ 99% and median RDI of oral VRL was 76.4%. Neutropenia was the major dose-limiting event (grade (G) 4 in 51% of pts and 22.1% of cycles) but only complicated in 5 pts: 4 febrile neutropenia (8.2%) and one neutropenic infection (2%). In terms of non-haematological related toxicity, the most frequent events reported were alopecia (61.2%), fatigue (22.4%), weight loss (18.4%), stomatitis (16.3%) and constipation, diarrhoea and nausea (14.3% each). G3 events were stomatitis, vomiting and amenorrhea (4.1% each) and fatigue, constipation, diarrhoea, nausea, infection, syncope and abdominal pain (2% each). The single grade 4 event was dehydration. The combination was effective with 24 responses documented and validated by an independent panel review, yielding a response rate of 55.8% [95% CI: 40–71] in the 43 evaluable pts. Median progression-free survival was 5.5 months [95% CI: 4.2–7.2]. Median overall survival has not yet been reached with a median duration of follow-up of 9.7 months.

Conclusions: This combination with oral VRL on day 15 avoiding hospitalisation is effective and manageable. VRL i.v./oral D1/D15-DTX D1 every 3 weeks represents a convenient option to combine DTX and VRL for the palliative treatment of MBC.

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Trastuzumab (T) plus oral vinorelbine (OV) in patients with advanced breast cancer (ABC) overexpressing Her2/neu

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Background: Trastuzumab combined with i.v. Vinorelbine (ivV) is an active regimen for pts with ABC. We previously developed two effective chemotherapy (CT) regimens which included day 1 and 3 ivV (FLN, ViFUP). In order to further improve Quality of Life (QoL) of pts undergoing treatment for ABC, a new regimen using oV, day 1 and 3, plus q3wks T was tested (ToV).

Methods: Forty-one pts with ABC, HER2/neu 3+ or FISH positive, were enrolled to receive three different dose level of oV. Thirty-four pts (median age 48 yrs; 28–71) received 271 courses of T, 6 mg/kg (loading dose, 8 mg/kg) on d1, and oV 55 mg/m^2 on day 1 and 3, q3wks. Eight pts received previous CT for ABC. Three pts received 23 courses of oV at a dose of 75 mg/m^2 and 4 pts received 19 courses of oV 60 mg/m^2; for this dose level accrual is ongoing. Pts were treated until disease progression or unacceptable toxicity or treatment refusal.

Results: Thirty-four pts treated with oV 55 mg/m^2 were evaluable for response and toxicity and received a median of 8 courses (range,1–16). Treatment was well tolerated with no G3–4 NCI-CTC non-haematological toxicity but only G3 elevation of SGOT in 1 pt; G2 observed toxicity consisted of nausea (4 pts), diarrhoea (4 pts), mucositis (1 pt) and constipation (3 pts). Five pts had G3–4 neutropenia. Six pts required a ⩾25% oV dose reduction. Two pts had CR, 11 PR, 17 NC and 3 PD. Median TTP was 8.7 mos (1.6–21.4+) and median duration of response was 13 mos (2.4–20+). The combination with oV 75 mg/m^2 appeared unfeasible for G4 neutropenia in 2/3 pts, while the intermediate dose of oV 60 mg/m^2 was then selected to be evaluated and the first 4 treated pts do not show any relevant side effects.

Conclusions: The ToV combination is active and well tolerated. It allows once-every three weeks hospital admission and frees pts and care providers from the unpleasant effect of ivV. ToV 60 mg/m^2 is currently under evaluation with particular attention to QoL parameters and acceptance.

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Vinorelbine (V) plus docetaxel (D) followed by Capecitabine (C) as first-line treatment of metastatic breast cancer (MBC)

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Background: Vinorelbine (V), Docetaxel (D) and Capecitabine (C) were found to be active as single agent in metastatic breast cancer. In this trial, we evaluated the efficacy and tolerability of V and D combination followed by C in first line treatment of MBC.

Patients and Methods: Pts were eligible if they had recurrent or metastatic breast cancer, measurable disease, ECOG PS ⩽2, adequate organ function, ability to give informed consent and had received no chemotherapy for metastatic disease. All patients had received anthracycline-based chemotherapy in the adjuvant setting. Patients were treated with 6 cycles of V (25 mg/m^2) on days 1 and 8 and D (75 mg/m^2) on day 1 every 3 weeks. Patients who responded or had stable disease at the end of ND treatment, received 6 cycles of C (1250 mg/m^2 twice daily).

Results: From Feb 2001 to Dec 2002, 25 patients were enrolled. The median age was 41 years (range 34–61). The sites of metastasis were liver in 17 (27%), skin in 15 (24%), lymph nodes in 12 (19%), lung in 10 (16%) and soft tissue in 2 (3%) pts. Number of metastatic sites were: 3 in 13 pts, 2

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.