of 63 was required to identify a clinical meaningful ORR ⩾15% based on Simon's Minimax 2-stage design.
Results: As of Apr 05, 64 pts (median age 51 years) were enrolled. Of these, 56% and 16% were ER+ and HER2+, respectively, and 82% had visceral disease. Fifty-two pts had prior adjuvant chemotherapy (A = 90%; T = 56%), and in the MBC setting, 62 pts were previously treated with A (26%), T (69%), capecitabine (66%), vinorelbine (23%), platinum (16%) and gemcitabine (15%). Preliminary efficacy data are available for 51 pts, seven (14%) of whom achieved partial responses and one had stable disease for 11 months. Grade 2/3 treatment-related adverse events (AEs) are listed below. No grade 4 AEs were reported.

Table 1: Most common AEs

	Percentage (N = 41)	
	Grade 2	Grade 3
Fatigue	32	5
Diarrhoea	20	7
Anorexia	17	0
Hypertension	10	5
Mouth pain	12	0
Hand–foot syndrome	5	7
Neutropenia*	15	39
Thrombocytopenia	17	15
Anaemia	12	2

*No patients with neutropenic fever

Seven (17%) of 41 pts required toxicity-related dose-reduction, and 13 (31%) required dose-interruption. Currently, 21 pts remain on treatment and only two have discontinued for toxicity.
Conclusions: This Phase II study demonstrates the clinical activity of sunitinib as a monotherapy in MBC pts unresponsive to prior chemotherapy or radiotherapy. Sunitinib has acceptable toxicity. Further studies should include pts with exposure to fewer prior regimens and sunitinib in combination therapy.

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A single institution randomized trial of taxotere (T) and xeloda (X) given in combination vs. taxotere (t) followed by xeloda (x) after progression as first line chemotherapy (CT) for metastatic breast cancer (MBC)

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Purpose: Xeloda and Taxotere have demonstrated preclinical antitumor synergy mediated by upregulation of thymidine phosphorylase. XT combination gave significantly superior overall survival, tumor response and TTP compared with T alone in patients with MBC (JCO 20: 2812, 20), but just one third of the patients receiving T continued with X after progression of the disease. We designed this study to evaluate the efficacy and toxicity of the combination of Taxotere and Xeloda compared with Taxotere followed by Xeloda after progression for Metastatic Breast Cancer (MBC).
Materials and methods: 100 patients (pts) with measurable MBC, prior adjuvant anthracyclines (100%) but no prior chemotherapy for MBC and KPS ⩾ 70 were randomized to receive: arm A = X 1,250 mg/m^2 twice daily d1–14 plus + T 75 mg/m^2 day 1; arm B = T 100 mg/m^2 day 1 followed after progression by X 1250 mg/m^2 twice daily d1–14, both given on a q3 week cycle. The two arms were well balanced for known prognostic factors: median age 58 (26–75) vs 51 (25–75) yrs, median KP 100 (70–100) both arms; hormone responsive disease 20% vs. 16%, dominant metastatic sites: viscera 70% vs. 68%, soft tissue 16% vs 13, bone 21% vs. 23%; number of involved organs: 1 = 58% vs. 52%, 2 = 30% vs. 34%, > 2 = 12% vs. 14%. We did not translate the results obtained from the use of Xeloda monotherapy into analysis of response rate and time to progression but we use them in analysis of overall survival and toxicity.
Results: See the table.
Grade 3 toxicity was more present in arm A: 70% vs. 56%; grade 4 was similarly distributed. The main toxicities were: Fatigue; 10% for both groups, Alopecia; 6% vs. 8%, Hand and foot syndrome; 24% vs. 2%, Nausea; 6% vs., 4%, Diarrhea; 16% vs. 8%, Stomatitis; 20% vs. 6%, Neutropenia; 14% for both groups, Neutropenic fever; 14% vs. 16%. We have had to reduce the dose for the 52% of the patients from the Arm A (Xeloda; 4%, Taxotere; 8%, both; 40%) and for the 30% patients from the Arm B.
Conclusion: XT provides significant TTP and OS advantage over T even after the 75% of the patient progressed on Taxotere had been cross-overed to Xeloda monotherapy.

	Group A	Group B	P value
Complete responses (%)	14	6	
Partial responses	54	34	
Overall responses	68	40	0.004
Time to progression (months)	9.3	7.66	0.0017
95%CI	(8.49–10.17)	(6.33–8.99)	
Overall survival (months)	22.00	19.00	0.006
95%CI	(20.85–23.15)	(17.85–20.15)	

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Safety comparison of oral ibandronate and intravenous zoledronic acid in metastatic breast cancer patients: Phase III data

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Background: Bisphosphonates are the standard of care for metastatic bone disease. Ibandronate is a third-generation, single-nitrogen bisphosphonate available in intravenous and oral formulations. In Phase III trials, both ibandronate formulations were well tolerated and had safety profiles comparable to placebo. In this study, oral ibandronate was compared directly with zoledronic acid in terms of safety assessments.
Materials and methods: This head-to-head, multicenter, randomized, open-label, parallel-group study recruited breast cancer patients with advanced disease and at least one confirmed osteolytic or mixed bone lesion. Patients were randomly assigned to receive oral ibandronate 50 mg/day (n = 137) or intravenous zoledronic acid 4 mg via 15-minute infusion every 4 weeks for 12 weeks (n = 137). All adverse events (AEs) were recorded throughout the study.
Results: In general, both bisphosphonates were well tolerated. However, the proportion of patients who experienced AEs was higher in the zoledronic acid group than the ibandronate group (76% versus 65%). In particular, there was a higher incidence of AEs during the first 3 days of the study for zoledronic acid than ibandronate (47% versus 8%). This was composed predominantly of acute-phase response AEs, including pyrexia, chills, flu-like illness, arthralgia, and myalgia, that were probably or possibly treatment-related. Throughout the entire study, a higher proportion of patients reported bone pain in the zoledronic acid group (21%) than the ibandronate group (12%), although the incidence of gastrointestinal (GI) AEs was slightly higher for ibandronate (23% compared with 18% for zoledronic acid). The incidence of serious AEs (ibandronate 5.8%; zoledronic acid 8.0%) and withdrawals (ibandronate 2.9%; zoledronic acid 5.1%) was lower for ibandronate.
Conclusion: In this first direct comparison of safety profiles, more patients treated with intravenous zoledronic acid experienced AEs than those treated with oral ibandronate. In particular, zoledronic acid was associated with a high incidence of an acute-phase response following initial treatment, a known side-effect with a disproportionate risk among intravenous bisphosphonates. The frequency of GI AEs was only slightly higher for oral ibandronate than intravenous zoledronic acid. Oral ibandronate represents an effective and well-tolerated treatment for metastatic bone disease with apparent AE advantages over intravenous zoledronic acid.

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Incidence and implications of HER2 and hormonal receptor overexpression in newly diagnosed metastatic breast cancer

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Background: Overexpression of the HER2 receptor protein predicts a worse prognosis and higher metastatic risk in patients (pts) with breast cancer. HER2 positivity also has a strong predictive value for the clinical benefit of trastuzumab (Herceptin®, H). The aim of this study was to assess the incidence of HER2 and ER/PR overexpression in patients with newly diagnosed metastatic breast cancer (MBC) and to compare the

characteristics and outcomes of pts with HER2-positive and HER2-negative disease.
Methods: From June 2000 to November 2001, 96 centres in France participated in a prospective epidemiological study (ESTHER) including 741 consecutive pts with newly diagnosed MBC. HER2 and hormonal receptor overexpression was assessed by immunohistochemistry (IHC). HER2 positivity was defined by an IHC 3+ score according to the FDA approved IHC scoring system.
Results: Of the 699 evaluable pts aged 25 to 83 (median 54.6) years, 67% were postmenopausal. In terms of tumour characteristics, 29.6% were HER2 positive; 61.4% were ER+, and 66.6% were either ER+ or PR+. Notably, 22.4% of ER+ tumours were also HER2 positive; hence ER/HER2 co-positivity was found in 13.8% of all MBC patients. HER2 overexpression was more frequent in invasive ductal carcinoma than in invasive lobular carcinoma (32.1% vs 16.5%; $p = 0.0033$, OR = 2.4), and was associated with a shorter time to relapse ($p = 0.0294$). Ninety-two percent of tumours were SBR grade 2 or 3; 70% had nodal involvement and 32% relapsed within 6 months of MBC diagnosis. However, HER2 overexpression was associated with neither SBR grade nor nodal involvement.
Conclusions and outlook: These findings confirm that HER2 positivity at presentation is frequent in MBC (close to 30% IHC 3+ staining) and is associated with a shorter time to relapse than HER2-negative disease. Importantly, nearly a quarter (22.4%) of ER+ tumours in MBC were also HER2 positive. This significant group of patients could possibly benefit from the addition of trastuzumab to their hormonal treatment. This is currently explored in the TAnDEM trial (anastrozole ± trastuzumab in ER/HER2 co-positive MBC), for which data are expected by end of 2005.

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Quality of life (QoL) improvements with capecitabine in patients with metastatic breast cancer (MBC)

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Background: The oral fluoropyrimidine capecitabine is highly active and well tolerated as single-agent therapy in patients with anthracycline- and/or taxane-pretreated MBC and extends survival when added to docetaxel in MBC. In addition to response rates and survival times, patient preference for oral therapy and QoL are increasingly important considerations in MBC.
Materials and methods: Women with anthracycline- and/or taxane-pretreated MBC received oral capecitabine 1250 mg/m^2 twice daily on days 1–14 every 3 weeks in a prospective noncomparative multicentre study. QoL was evaluated using EORTC QLQ C-30 (v3.0) and BR-23 questionnaires at 4 timepoints (before cycle 1, weeks 7 and 13, and treatment end). Linear models for repeated measures were used to analyse least square mean QoL data over time. Improvement was defined as a $\geqslant$ 10-point improvement and maintenance as a < 10-point improvement/worsening from baseline in functional or symptom scores at one or more visits.
Results: Baseline characteristics of the 1125 evaluable patients were: mean age 54.5±12.3 (range 22–90) years; Caucasian (80%); ECOG performance status 0–1 (74%). Patients receiving capecitabine had significant, sustained improvement ($p < 0.0001$ unless stated otherwise) over the study period in the following domains: global health status, role functioning, emotional functioning, social functioning ($p = 0.0004$), cognitive functioning ($p = 0.0257$), fatigue, nausea/vomiting, pain, insomnia, appetite loss, constipation, financial problems, body image, future perspective, systemic therapy side effects, breast symptoms, arm symptoms ($p = 0.0003$), and upset caused by hair loss. Depending on the domain, between 64% and 84% of patients reported improved or maintained QoL during capecitabine therapy.
Conclusions: Patients receiving capecitabine had a significant and sustained improvement in 13 of 14 QLQ C-30 domains and 6 of 8 QLQ BR-23 domains, including all QLQ BR-23 symptom scales that are known to be important to women with MBC. These findings highlight the importance of considering QoL and other measurable benefits of oral treatments alongside well-established clinical measures in patients with metastatic disease. The QoL benefits, together with other proven clinical outcomes, suggest that earlier use of capecitabine in MBC would be beneficial to patients.

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Preclinical study of continuous administration of trastuzumab as combination therapy after disease progression with trastuzumab monotherapy

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Purpose: Trastuzumab is an anticancer drug widely used for HER2-positive metastatic breast cancer. Recently, it has been suggested that prolonged administration of trastuzumab as combination therapies beyond progressive disease is of clinical relevance. In the present study, we tried to clarify whether trastuzumab treatment should be continued or not after showing no antitumor activity as monotherapy in xenograft models. After an initial trastuzumab monotherapy period (3 weeks), treatment was continued with a taxane alone or in combination with trastuzumab. We compared the antitumor activity of the combination therapy of trastuzumab with a taxane and that of the monotherapy of a taxane after trastuzumab showed no antitumor activity as monotherapy in two breast cancer xenograft models, KPL-4 or MDA-MB-361.
Results: Trastuzumab (40 mg/kg, ip, qw) showed a significant antitumor activity in KPL-4 breast cancer bearing mouse. Although the HER2 status (3+ in Herceptest®) of the tumor tissues was not changed during the treatment, trastuzumab as a monotherapy at the same dosage as the initial treatment showed no antitumor activity after 3 weeks treatment. However, trastuzumab in combination with taxol (60 mg/kg, iv, qw) showed a significantly more potent antitumor activity (tumor volume: 44 mm^3) compared to taxol monotherapy (tumor volume: 169 mm^3) after the initial trastuzumab treatment period. The same result was observed in the combination therapy with taxotere (15 mg/kg, iv, q3w). Comparable data were observed in MDA-MB-361 xenograft model when 30 mg/kg of trastuzumab and 60 mg/kg of taxol was used. We are further investigating underlying mechanisms of progression disease during the initial trastuzumab-treatment.
Conclusion: These results indicate that trastuzumab is able to potentiate the antitumor activity of taxanes even after not showing antitumor activity as a single agent. Taken together, these xenograft studies, suggest a clinical relevance of treatment with trastuzumab as combination therapy beyond progression disease.

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High incidence of brain metastases in HER2-overexpressing metastatic breast cancer (MBC) patients (pts) treated with trastuzumab and chemotherapy

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Background: In recent years an increased incidence of central nervous system (CNS) metastases in HER2-overexpressing MBC has been frequently reported. In our trial we reviewed the occurrence of CNS metastases in pts with HER2-overexpressing MBC underwent to therapy with trastuzumab and chemotherapy in two institutions.
Material and methods: Between April 1999 and December 2004 we treated with trastuzumab and chemotherapy 91 pts with HER2-overexpressing MBC. Median age of pts was 48 years (range:29–79). Tumor characteristics included: grading G3 in 60% of cases, ER–, PgR– in 47%. Disease-free interval was < 24 months in 52% of the pts and *24 months in 48%. Visceral metastatic disease was present in 70% of the pts. Trastuzumab + chemotherapy represented the 1st line of treatment in 53% of pts, 2nd line in 27% and *3th line in 20%.
Results: At a median follow up of 55 months (range:7–196) from the diagnosis and of 28.5 months (range 2–117) from the occurrence of metastatic disease, 36 pts (39.6%) developed CNS metastases, confirmed by TC or MRI scanning. Neurological symptoms were present in 89% of these pts. In 64% of these pts, brain metastases occurred during trastuzumab treatment. Out of the 36 pts developing CNS metastases, 47% were in response in other metastastic sites and brain represented the only site of progression. Following the diagnosis of brain metastases, 28 out of 36 pts (78%) have been treated with panencephalic radiotherapy; trastuzumab ± further chemotherapy was continued in 11 pts (30%) and 16 pts (36%) received only cytotoxic chemotherapy. Out of 91 pts, 39 (43%) died (95%CI: 32.5 to 53.7%). Median overall survival (OS) was 93.2 months (range 5.6–194) in the overall population; median OS was 69 months (range 6±168+) in pts with brain metastases and 112 months (range:7–194) in pts without brain metastases ($p = 0.08$).
Conclusions: We conclude that the occurrence of brain metastases is common event in the natural history of HER2-overexpressing MBC