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Dose-finding study of docetaxel plus 5-fluorouracil (5-FU) in patients with metastatic breast cancer

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Purpose: To determine the dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended dose of docetaxel plus continuous infusion 5-FU in patients with metastatic breast cancer previously treated with an anthracycline-containing regimen. The maximum tolerated dose was defined as three or more DLT events in six patients. Additional objectives were to evaluate response rate and the duration of response. This was a multicentre, open-label, non-randomised study. The recommended doses in this combination regimen are to be used for further phase II/III evaluation.

Methods: 28 Patients were enrolled over the course of the study. Patients received docetaxel (60 mg/m2, 1-hour infusion q3 weeks on day 1), folinic acid (500 mg/m2, 2-hour infusion on Days 1 and 15) and 5-FU (1.8 g/m2, 24-hour infusion on Days 1 and 15). Patients then received either of the following doses of docetaxel (Day 1) and 5-FU (Days 1 and 15) during subsequent cycles: at dose level 1 (60 mg/m2, 1.8 g/m2); at level 2 (75 mg/m2, 1.8 g/m2); at level 3 (85 mg/m2, 1.8 g/m2); at level 4 (100 mg/m2, 1.8 g/m2); at level 5 (100 mg/m2, 2.1 g/m2). Anthracycline pre-treatment was given for adjuvant purposes (7/28 patients) or for palliative purposes (21/28 patients). Of the 28 patients enrolled, 17 received six or more treatment cycles. Treatment was stopped in the case of progressive disease (PD; 4/28 patients), stable disease (SD; 11/28 patients), partial response (PR; 9/28 patients) or DLT (4/28 patients).

Results: With respect to DLT: none was observed at level 1 (n=3); one serious infection related to a portacath and one diarrhoea NCI-CTC grade IV occurred at level 2 (n=6); one serious infection due to staphylococcal pneumonia at level 3 (n=7); one febrile neutropenia grade IV and one staphylococcal sepsis at level 4 (n=6); one serious infection related to a portacath and one erythema grade III/IV at level 5 (n=6). Four patients were not evaluable for tumour response because they only received two treatment cycles. Of the remaining 24 patients, there were 4 PD, 11 SD and 9 PR. The response duration for the patients with PR was 195 days.

Conclusion: Although the MTD was not reached, the recommended dose is docetaxel 100 mg/m2 and 5-FU 2.1 g/m2. This regimen displays promising antitumour efficacy and is suitable for further phase II/III evaluation in patients with metastatic breast cancer.

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Effect of cardiac dysfunction on treatment outcome in the herceptin pivotal trial

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Background: H, a humanized monoclonal antibody directed against HER2, increases time to progression, response rate, and survival in combination with first-line chemotherapy and induces durable responses as a single agent in women with HER2-positive metastatic breast cancer. In the pivotal trials of H, treatment was associated with cardiac dysfunction (CD) similar to the cardiomyopathy associated with anthracycline (A) administration. CD occurred at greatest frequency (28%) in patients simultaneously receiving A compared to 7% in patients receiving A alone. CD was less common and less severe in patients treated with paclitaxel (T) plus H: 11% of patients receiving T plus H and 1% of patients receiving T alone. The majority of patients (75%) improved with treatment for congestive heart failure, and 77% continued to receive T for a median of 25 weeks.

Methods: The effect of CD on treatment outcomes was evaluated in the 469 patients in the pivotal H combination chemotherapy trial (H0648g). For the purposes of this analysis, time to treatment failure (TTF) was defined as the time to disease progression or CD and CD-free as the time to symptomatic CHF (NYHA grade III or IV) or death.

Results: As shown below, H produced improvements in TTF and CD-free survival.

TTF (months) (95% CI):
H + C 6.5 (5.8,7.0); C 4.6 (4.4,5.3);
H + AC 6.6 (5.5,7.3); AC 6.0 (4.8,6.9);
H + T 6.6 (5.3,7.1); T 2.8 (2.0,4.3)

CD-free survival (months) (95% CI):
H + C 22.2 (17.7,25.4); C 20.0 (16.5,24.0);
H + AC 22.3 (16.6,25.7); AC 20.9 (16.8,28.6);
H + T 22.1(17.1,26.3); T18.4 (12.7,24.4)

Conclusions: Improvements in treatment outcomes when H was added to chemotherapy were observed despite the development of CD. These results suggest that risk/benefit considerations in the metastatic disease setting favor the use of H plus T.

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Phase II study of weekly docetaxel (Taxotere; txt) and trastuzumab (Herceptin; H) for patients with HER-2 overexpressing (HER2+) metastatic breast cancer (MBC)

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Combination of H with chemotherapy improves response rates, time to progression (TTP) and survival in patients (pts) with HER2+ MBC. Txt is one of the most effective treatments for MBC. Txt and H are synergistic in vitro. A phase II trial was designed to evaluate the efficacy and safety of weekly Txt + H in patients with HER2+ MBC. H was given on day 1 as a 4 mg/kg loading dose (cycle 1 only), followed by 2 mg/kg per week (wk). Txt was administered at 35 mg/m2/wk. One cycle is defined as 3 weekly administrations of Txt + H followed by 1 week of rest. HER-2 status was defined by immunohistochemistry (IHC, score 3+) or by flourescence in situ hybridization. Results are reported for all 30 patients enrolled in this study. Median age 45 (33-78) years. Twenty-six pts (87%) had received prior chemotherapy, either adjuvant or for MBC. A median of 6 (2-16) cycles was given per pt. Number of weekly doses delivered: 589. The median time on study was 24 (8-64) weeks. Hematological toxicity: grade 3/4 neutropenia (8 pts); 1 patient developed neutropenic fever; no grade 3/4 anemia or thrombocytopenia. Non-hematological toxicity (grade 3/4): catheter-related bacteremia (1 pt), diarrhea (1 pt), neuropathy (1 pt), fatigue (6 pts), pleural effusion (1 pt), asymptomatic transient LVEF decline below 50% (3 pts), pulmonary edema (1 pt). All 30 pts are evaluable for response to therapy. Eighteen pts (60%) had a partial response; 4 pts (13%) had a minor response; 4 pts (13%) had stable disease; and 4 pts (13%) had progressive disease (PD) as best response. FISH data are available for 23 pts (20+, 3-). The response rate in pts whose tumors were FISH+ was 65%. Three patients had brain metastases at the time of recurrence. In two of them the brain was the only site of disease. These patients were treated with whole brain irradiation and H was continued until PD. Twelve patients continue on study. The estimated median time to progression is 6 months. In summary, weekly Txt + H is a safe and effective regimen for pts with HER2+ MBC. Support: Genentech, Aventis

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Markers of bone turnover in metastatic breast cancer (MBC) patients having progressed on tamoxifen: Short term effect of further treatment with either exemestane (EXE) or megestrol acetate (MA)

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Bone turnover markers and their correlation with tumor response in pts on hormonal treatment for MBC has seldom been explored. We performed a prospective study on bone turnover markers on 53 pts enrolled in a large randomized study of (24 pts) EXE 25 mg/day vs (29 pts) MA 160 mg/day in MBC pts having progressed on tamoxifen (Kauffman M. et al., JCO 2000). The two groups were well-balanced and 40 pts had MBO spread to bone. The bone serum markers analyzed were bone alkaline phosphatase (BAP), and type-I collagen telopeptide (ICTP). Tumor response and clinical benefit (CR + PR + SD $\geq$ 24 wks) were 12.5% and 54.2% on EXE and 10.3% and 34.5% on MA. Pts were sampled at baseline, 8 wks, 24 wks and every 12 wks thereafter until PD. Only the 8-wks data (51 pts) are reported due to pts drop-out for PD as geometric mean.

No correlation was found with tumor response for BAP or ICTP. There was a significant correlation between the ICTP increase and E_1S suppression ($p < 0.01$ for EXE and $p < 0.05$ for MA), but not with BAP. In conclusion, bone turnover markers ate affected by estrogen suppression in MBC. The increase in ICTP, but not of BAP, on MA might suggest a modest catabolic

		Baseline	Week 8	p* (EXE vs MA)	p* (vs Baseline)
BAP	EXE (23)	24.9	30.1	NS	<0.01
(ng/mL)	MA (28)	23.8	24.2		NS
ICPT	EXE (23)	5.3	6.3	NS	<0.01
(ng/mL)	MA (28)	5.3	6.1		<0.05

p* Wilcoxon's test

effect, while the increase of both on EXE may suggest also the presence of an anabolic effect, possibly linked to the weak androgenic effect from the metabolite 17-hydro-exemestane.

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A phase II trial of zd0473 in patients with metastatic breast cancer. A National Cancer Institute of Canada clinical trials group study (NCIC CTG-IND 129)

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ZD0473 is a new generation platinum compound with significant activity against a wide range of cultured human tumour cell lines and against a panel of human ovarian xenografts, including cisplatin- and carboplatin-resistant cell lines. Phase I studies showed activity in several solid tumours including breast carcinoma, and at the recommended starting dose of 120 mg/m2 q 3 weeks (wks), the NCIC-CTG initiated a multicenter phase II study in metastatic breast cancer (MBC) in January 2000. Thirty-three patients (pts) have been enrolled. Thirty two pts are evaluable for toxicity and 25 for response at this time. Eligibility criteria included pts with no more than one prior chemotherapy for their MBC, performance status (ECOG 0-2), adequate organ function, measurable disease and informed consent. After the first11 pts experienced only minimal hematological toxicity, the starting dose was subsequently escalated to 150mg/m2 q 3 wks. Thirteen pts have received a total of 41 cycles at 120mg/m2, and 19 pts have received a total of 40 cycles at 150mg/m2. In the patients evaluable at this time, toxicity has been mainly hematological with grade 3 or 4 thrombocytopenia in 12/19 pts at 150mg/m2 and grade 3 thrombocytopenia in 3/13 pts at 120mg/m2. Grade 3 or 4 neutropenia occurred in 14 pts at the 150mg/m2 dose. At 120mg/m2, 2 pts had grade 3 or 4 neutropenia. Non-hematological toxicities have been generally mild to moderate and include nausea, vomiting, anorexia, fatigue, bleeding, taste disturbance, headache, constipation, alopecia and dyspnea. No complete responses have been seen but there has been one partial response and 13/25 pts have stable disease at this time. ZD0473 has modest activity as a single agent in MBC. Phase 1 combination studies with other agents including paclitaxel and docetaxel suggest increased activity which may be worthwhile in pursuing in the metastatic breast cancer setting.

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Gemcitabine, epirubicin and paclitaxel (GET) vs. 5-fluoro-uracil, epirubicin and cyclophosphamide (FEC) as first-line treatment in metastatic breast cancer: interim toxicity analysis of a randomised, multicenter phase iii trial of the Central European Cooperative Oncology Group (CECOG)

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Purpose: This phase III multicenter trial was initiated to compare the efficacy and toxicity of GET vs. FEC as first-line therapy in patients with metastatic breast cancer.

Patients and Methods: 84 female patients were enrolled into the study between October 1999 and March 2001. Out of those, 78 patients are available for analysis of toxicity. 33 patients were randomized to receive gemcitabine (1000 mg/m2, days 1+4), epirubicin (75 mg/m2, day 1) and paclitaxel (175 mg/m2, day 1), whereas 45 patients received 5-fluorouracil (500 mg/m2, day 1), epirubicin (75 mg/m2, day 1) and cyclophosphamide (500 mg/m2, day 1). Both regimens were administered in 21-day- courses up to a maximum number of 8 cycles. The median age of patients was 54 years (53 years in the GET and 55 years in the FEC arm) with a median of 6 administered cycles (range: 1-9) in both treatment arms.

Results: Myelotoxicity represented the major toxicity and included neutropenia of grades 3 & 4 occurring in 93.9% of patients receiving GET vs 73.3% of patients receiving FEC, thrombocytopenia of grades 3 & 4 in 27.3% vs 4.5% and anemia grades 3 & 4in 18.2% vs 11.4% of patients. Febrile neutropenia occurred in 3 patients treated with GET vs 2 patients receiving FEC. Peripheral neurotoxicity grades 1 & 2 were observed in 45.2% of patients in the GET arm vs 11.4% of patients in the FEC arm. No clinically apparent left ventricular dysfunction or failure were found in either group of patients.

Conclusion: While recruitment of patients is continuing, we conclude from this interim analysis that GET has a favourable and acceptable toxicity profile, as compared to the FEC regimen. These results warrant further clinical trials on the efficacy of the GET regimen.

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A phase II multicenter trial of weekly herceptin with navelbine in chemonaive patients with her2 positive metastatic breast cancer

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Background: Herceptin (H) is a well tolerated agent with documented efficacy in breast cancer and pre-clinical synergy with Navelbine (N). This combination has been found to be active in a single institution trial of largely pre-treated breast cancer patients (N at 25mg/m2/wk; Burstein et. al. ASCO 2000).

Purpose: We designed this phase II multicenter study to assess the efficacy and safety of H+N as first-line treatment for HER2 overexpressing metastatic breast cancer patients with measurable disease.

Patients and Methods: Eligible women were treated with weekly IV doses of H (4mg/kg loading dose, then 2mg/kg) and N (30mg/m2) without a break, with 4 weeks comprising a cycle.

Results: As of April 15, 2001, 37 of the planned 40 patients have been entered. Patient characteristics are: median age 51 years (range 30-82); prior adjuvant chemo 29%; prior hormonal therapy 32%; visceral metastases 58%. Twenty-nine patients are evaluable for response, having received at least 2 cycles. Two CRs and 19 PRs have been observed with an overall objective response rate of 72%, while 5 patients are stable and 3 progressed. Median time to response was 8 weeks. To date, a total of 188 cycles have been administered (median 4, range 1 to 26) with dose delays in 32% of the cycles Grade 4 toxicity was limited to neutropenia experienced by 25% of patients in 8% of cycles, while 51% of patients experienced Grade 3 neutropenia in 23% of cycles. Four patients were hospitalized with fever (1 neutropenic, 1 line sepsis, 1 with tuberculosis, 1 with pneumonia), 1 patient with hematura (due to over anti-coagulation from coumadin) and 1 patient with pulmonary embolism. Non-hematologic toxicity of fatigue was observed as grade 3 in one patient and grade 4 in another patient. No severe nausea, vomiting, cardiotoxicity, neurotoxicity, or alopecia has been reported.

Conclusion: These preliminary results suggest that H+N is well tolerated and very active in this patient population. Supported by grants from Genentech Inc. and GlaxoWellcome Inc.

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Dose-finding study of Docetaxel (T) and Doxorubicin (A) day 1 and 8 plus Capecitabine (X) day 1 to 14 (TAX) as first line treatment in advanced breast cancer (ABC)

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Background: Early results of T and Epirubicin (E) given on days 1 and 8 plus continuous infusion (c.i.) 5FU days 1 to 14 q 3wks (TEF) in 30 patients (pts) have shown that haematological toxicity was dose limiting (DLT) with G4 neutropenia and uncomplicated febrile neutropenia (FN) in 67% and 5% of cycles (cy) at the highest dose level (T40/E45/5FU200 mg/m2), respectively. Gastrointestinal (GI) toxicity seemed E-related (being the 5FU dose fixed at all dose levels) with ≥ G2 diarrhoea and mucositis in 6% and 18% of cy, respectively. In July 2000 a multicentric dose-finding study was launched to replace c.i. 5FU by X given days 1 to 14 with T and A on days 1 and 8 q 3wks (TAX).