		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.

708 POSTER

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.

709 POSTER

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.

710 POSTER

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.

711 POSTER

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).

Patients and Methods: Pts with locally advanced (LA) or metastatic breast cancer (MBC) and ≤ 1 prior neo/adjuvant regimen discontinued ≤ 12 months before study entry were eligible. A maximum of 8 cy could be given (A total dose ≤ 480mg/m2) without routine G-CSF support.

Results: Sixty-six cy (median 4, range 1-6) have been given so far to 19 pts (11 with LA and 8 with MBC) with 8 pts still under treatment. Four dose levels have been tested from T30/A20/X1650 mg/m2, up to the maximum tolerated dose (MTD) of T35/A25/X2000 mg/m2 (6 pts). DLTs after the 1st cy at MTD were FN (4 pts), G3 diarrhoea (1 pt) and delayed absolute neutrophil count (ANC) recovery (1 pt). Overall, G4 neutropenia occurred in 26% of cy with 6 episodes of FN (9%), ≥ G2 diarrhoea and mucositis complicated 21% and 18% of cy, respectively. Eleven pts (58%) required either dose reductions (32%), treatment delays (16%) or both (10%), as a consequence of ≥ G2 GI toxicity in 3 pts (28%), haematological toxicity or the combination of both in 4 pts each (36%). The preliminary ORR in 18 evaluable pts who received at least 2 cycles is 50% (45% in LA disease, 50% in MBC) with stable disease in 39% of pts.

Conclusions: The TAX regimen proved to be safe and active in ABC. The cumulative toxicity profile needs however to be better defined, mainly on its impact on quality of life and on feasibility to deliver adequate total doses of the combination. A direct comparison with TEF might be a reasonable project to select the most cost-effective regimen in the individual patient.

712 POSTER

Cardiac safety and efficacy of TLC D99 (D99) and trastuzumab in patients with advanced breast cancer

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Purpose: D99 (Myocet™) is a liposomal doxorubicin (D) with significantly reduced cardiotoxicity compared to conventional D. Trastuzumab (T) is intrinsically cardiotoxic, but has additive or synergistic efficacy with D against breast cancer. To determine the safety of D99 + T, and to obtain preliminary efficacy data in advanced breast cancer (ABC), we performed this phase I/II study in patients (pts) with HER2+ tumors: 2–3+ by immunohistochemistry or gene amplification by fluorescence in-situ hybridization.

Methods: Left ventricular ejection fraction (LVEF) by multigated acquisition scan at baseline and after every even cycle; protocol-defined cardiotoxicity = LVEF reduction by 20 points or more to a value within the normal range; by 10 points or more to below the normal range; or congestive heart failure. Regimen: D99: 60 mg/m^2 intravenously (IV) every 3 weeks; T: 4 mg/kg IV week 1 followed by 2 mg/kg IV weekly. Eligibility: ABC; one or fewer prior T regimens; 2 or fewer cytotoxic regimens for ABC; prior adjuvant D permitted (up to 240 mg/m^2).

Results: n = 29; 136 cycles of therapy given. 13 pts had adjuvant D; 11 pts had prior chemotherapy for ABC; 4 had T. Median #cycles/pt: 6 (range 1–11). 23 pts had cumulative D + D99 dose of 360 mg/m^2 or greater (range 120–780 mg/m^2). No cardiotoxicity has been seen to date; 14% pts had grade 3 neutropenia (0 grade 4); other toxicities have been manageable. 20/29 pts evaluable for measurable response (secondary objective): 1 complete response, 11 partial responses, 60% overall response (95% confidence interval: 36–81%). 3 stable disease; 6 progressive disease (2 who had previously progressed on T); 2 pts with non-measurable disease normalized tumor markers; 6 pts are not yet evaluable for response.

Conclusions: D99 + T appears to be a well tolerated, active regimen in pts with HER2+ tumors. No cardiotoxicity has been observed to date among 29 pts treated with D99 + T, 45% of whom had prior D. A 60% overall major response rate was observed in these pts in a 1st-3rd-line setting. Accruals are continuing to a maximum of 40; additional trials are planned.

713 POSTER

Efficacy and safety of navelbine oral (NVBO) in first line metastatic breast cancer (MBC)

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Purpose: Navelbine intravenous (NVBi.v.) is highly active in MBC. Given the ease of administration (adm) and greater patient convenience of oral chemotherapy, a capsule of Navelbine has been developed. Here are the preliminary results of an open-label, multicenter phase II study of NVBo in the first-line treatment of MBC.

Methods: NVBo was administered at a dose of 60 mg/m2/w for the first 3 adm and subsequently increased to 80 mg/m2/w if no severe neutropenia occurred. From 12/97 to 08/00, 72 patients (pts) were enrolled. Pts characteristics at entry were: median age 63.4 years, 23.6% stage IIIb/IV at diagnosis, 47.2%, visceral involvement and 56.9% with ≥2 organs involved.

Results: A median of 10 adm per pt of NVBo were given. Relative median dose intensity was 88.6%. All responses were reviewed by an independent panel: 2 CR and 15 PR were validated giving a RR of 23.6% [95% CI=14-33] in the intent-to-treat (ITT) population (n=72) and 27% [95% CI=16-38] in the evaluable population (n=63).

Pts were stratified at study entry by 3 strata (S): S1= prior adjuvant hormonotherapy, S2= prior adjuvant chemotherapy, S3= no prior adjuvant therapy.

For the S3 RR was only 14.3% and 15% in the ITT (n=21) and the evaluable (n=20) populations, respectively. Actually, this group consisted mainly of pts with very poor prognosis features: 52.4% with stage IIIb/IV, 71.4% with DFI ≤2 years and 57.1% with ≥3 organs involved. This is in contrast with the 2 other strata in which a smaller proportion of pts presented such bad prognosis factors.

In S1 RR were 27.8% and 31.3%, in the ITT (n=18) and evaluable (n=16) populations, respectively. And in S2 RR were 27.3% and 33.3%, in the ITT (n=33) and evaluable (n=27) populations, respectively.

G4 neutropenia was reported in 28.6% of pts (3.3% of adm). One febrile neutropenia and 2 neutropenic infections were reported. G3-4 nausea, vomiting and diarrhoea were observed in 12.8%, 10% and 8.5% of pts, respectively. No primary prophylactic antiemetic was recommended. Neurotoxicity was minimal. No toxic death nor unexpected adverse event were reported. These results show the efficacy of NVBo is comparable to NVBi.v. and its safety profile is qualitatively similar.

Navelbine Oral represents a good alternative to NVBi.v. Accrual is ongoing. Updated results will be presented at the meeting.

714 POSTER

Activity and feasibility of a ten-day schedule of single agent vinorelbine (VNR) in advanced, pretreated breast cancer (BC): a phase II study

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Purpose: VNR has been shown to be active against advanced BC as both 1st-line and salvage treatment, with acceptable toxicity. Previous published studies reported the need of G-CSF support when intravenous (i.v.) VNR was given weekly at 25-30 mg/m2, with neutropenia being dose-limiting. Our prior single-centre experience also confirmed a high incidence of leukoneutropenia in 10 earlier treated patients (pts) given a weekly regimen; thus we designed a phase II study to test the activity and tolerability of a ten-day schedule of single agent VNR in the advanced setting.

Patients and Methods: Thirty consecutive pts aged 35-72 years (median 49) with histologically confirmed, evaluable advanced BC entered the trial. All pts had received prior anthracyclines for the metastatic disease, and 25 of them had also been treated with taxane (23 with paclitaxel and 2 with docetaxel). The number of prior chemotherapy regimens ranged from 1 to 4 (median 2, mean 3); 27 pts had previously received hormonal treatment. The most represented metastatic sites were visceral (liver 47%, lung 27%); 13 pts had bone lesions, alone or combined with loco-regional disease. VNR was given i.v. at a dose of 25 mg/m2 over 10 minutes, every 10 days, on ambulatory basis. Treatment was continued either for 6 months, until disease progression or unacceptable toxicity.

Results: A total of 192 cycles were given (median 9, range 4-18 per patient); the median DI was 22.5 mg/m2/wk. One complete (CR) and 10 partial responses (PR) were achieved, for an overall objective response (OR) rate of 37% (95% confidence interval, 20% to 55%). Five out of 24 pts (21%) whose disease progressed while receiving anthracycline (clear resistance) had a PR, and 24% taxane-pretreated pts had an OR, including the CR at the bone level. Additional 7 MRs and 6 SDs were found. Median TTP was 19 weeks (range, 12-36) and median survival time was 38 weeks. Treatment compliance was good, with mild non-haematological toxicity (WHO gr.1 peripheral neuropathy in 12 pts, gr.1 phlebitis in 9, grade 1-2 constipation in 13); gr.3 neutropenia, lasting 7-12 days, occurred in 4 pts (23% of cycles).

Conclusions: Our results confirm that VNR is able to produce major responses in advanced BC, also in heavily pretreated pts. Specifically,