narcotic scores (PNS). Init. Perf. status (PS)0–1 in 50 pts and 3–4 in 22 pts; the upper, mid & lower halves of the body were treated in 39, 31 & 2 pts.

Results: Pain relief seen in 96% pts [50%CR & 46% PR] within 3–7 days. Aver. surv. [OS, MST, pain-free (PFS)] was 203, 177 & 144 days respect. Quality of life (QOL) assessed by % remaining life pain-free (71%) plus sig. improv, in PS & PNS after HBI. Very acceptable tox. (39% norte, 49% mild/mod. & 13% severe but transitory). Upper HBI was more toxic.

Conclusion: All Rx arms similar in pain relief, time-to-response, OS, PFS, QOL and overall tox. Arm (A) has sig. longer MST (225 days) than arms (B)&(C) [174 days]. Arm (B) had less CR's (24%) and higher severe tox. (20%). Study indicates that schedules (B)&(C) are faster, more convenient, more economical and equally effective than more protracted HBI for palliating WSBM from breast cancer.

697 POSTER

First-line endocrine therapy in postmenopausal (PM) patients (pts) with advanced breast cancer (ABC) and visceral metastases (mets): Anastrozole (AN) versus tamoxifen (TAM)

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Purpose: Based on the combined analysis of two large, randomized, controlled clinical trials, AN 1 mg once daily (od) was superior to TAM 20 mg od in pts with ABC known to have hormone-sensitive tumours, in terms of time to progression (TTP) (p = 0.022). We have carried out a sub-group analysis to investigate the effectiveness of AN vs TAM overall in pts with and without visceral mets and in those pts with hormone-sensitive tumours.

Methods: Clinical benefit (CB; complete response + partial response + stable disease ≥ 24 weeks) was assessed for pts in each sub group. Visceral mets includes pts with pulmonary and intra-abdominal mets.

Results: CB following AN or TAM in the overall population and in pts with hormone-sensitive tumours (ER/PR) are shown in the table below.

	AN 1 mg od (n = 511)	TAM 20 mg od (n = 510)
Overall popn with visceral mets (N)	186	211
Gaining CB (no. of pts [%])	92 [49.5]	99 [46.9]
Median duration of CB (months)	15.3	16.6
Overall popn with no visceral mets (N)	321	297
Gaining CB (no. pts [%])	200 [62.3]	166 [55.9]
Median duration of CB (months)	16.4	14.5
ER/PR +ve popn with visceral mets (N)	131	154
Gaining CB (no. pts [%])	68 [51.9]	64 [41.6]
Median duration of CB (months)	15.7	16.6
ER/PR +ve popn with no visceral mets (N)	172	150
Gaining CB (no. pts [%])	113 [65.7]	88 [58.7]
Median duration of CB (months)	16.9	14.5

Conclusions: AN is highly effective in ABC PM pts with visceral mets and indicate that endocrine treatment, preferably with AN, should be considered as a first option in pts with hormone-sensitive non-life threatening visceral disease.

698 POSTER

Cardiac safety and antitumor activity of doxorubicin and taxol followed by weekly taxol (AT&T) when herceptin is initiated with AT or with T alone in women with HER2-positive advanced breast cancer

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Background: The combination of H with AT is attractive based on: 1) the activity of AT; 2) the survival improvement observed when H is added to A or T in HER2-positive metastatic breast cancer. The risk of cardiac toxicity when H is added to A restricts its use. Therefore, we performed a pilot study to compare the efficacy and cardiac tolerability of AT followed by T when H was started with AT or with T alone and to investigate pharmacokinetic interactions.

Methods: All patients received 3-weekly AT (60/150mg/m2) for 3 cycles followed by weekly T 80mg/m2 for 9 cycles. The initial 16 patients (cohort 1) received weekly H (4mg/m2 initial dose followed by 2mg/m2) until progression starting with AT; H was initiated with T in the other 16 (cohort 2). Cardiac function was assessed prospectively by echocardiography every 3 weeks. Pharmacokinetic interactions were evaluated by administering H 24 hours after AT in cycle 1 and before AT in cycle 2.

Results: All 32 HER2-positive patients have been recruited and are evaluable. Mean age was 49.7 and 55.4 years in cohorts 1 and 2, respectively. Response rate was 87.5% (1 CR, 13 PR) in cohort 1 and 75% (2 CR, 10 PR) in cohort 2. High ECD levels decreased at response in both cohorts whether or not Herceptin was present. Cardiac function was CTC G1 in 4 and G2 in 3 patients in cohort 1; 6/7 recovered normal function. At median follow-up of 12 months none had developed cardiac symptoms. In cohort 2, 1 patient developed CTC G1 and later recovered. No unexpected side effects were observed. Analysis in cohort 1 showed that pharmacokinetics of T, T metabolites and A were similar without and with Herceptin.

Conclusion: Comparison of the cohorts suggests that response rates are similar whether H is administered with AT or with T. No patient has developed clinical heart failure, but delaying Herceptin until A therapy is complete appears to cause fewer decreases in LVEF. AT&T plus H is highly active without irreversible or clinical cardiac effects.

699 POSTER

Capecitabine: The new standard in metastatic breast cancer failing anthracycline and taxane-containing chemotherapy? Mature results of a large multicenter phase II trial

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Capecitabine (C) is a rationally designed, oral, tumor-activated fluoropyrimidine carbamate. It is converted to 5-FU preferentially at the tumor site exploiting the higher levels of thymidine phosphorylase found in malignant cells compared to normal tissue. C has shown promising efficacy in metastatic breast cancer (MBC) compared to CMF in untreated or paclitaxel in pretreated patients (pts).

In this ongoing study we investigate the activity and toxicity of C in MBC after pretreatment with either paclitaxel or docetaxel. Treatment consists of C 1,250mg/m2 b.i.d. orally for 14 days followed by 7 days rest (=1 cycle).

Results: 136 pts have been entered so far. The median age is 56 years (range 32-77), and the median Karnofsky-index is 90% (range 60-100). Pretreatment included anthracycline-based chemotherapy in 93% and taxanes in 100%. 136 and 125 pts are evaluable for toxicity and response, respectively. Median number of cycles administered is 3 (range 1-21). Toxicity was generally low with grade 1 or 2 hand-foot syndrome (40%), nausea/vomiting (43%), diarrhea (22%), stomatitis (15%) and lethargy (16%). Grade 3/4 toxicity consisted of hand-foot syndrome in 12%, nausea/vomiting in 4%, and diarrhea in 5% of pts. Responses so far included 2 CR (2%), and 21 PR (17%). Disease stabilization occurred in another 48% of pts, accounting for an overall tumor control rate of 67%. Progressive disease as best response was seen in 41 pts (33%).

Conclusions: Capecitabine produces a high tumor control rate with low toxicity in an outpatient setting in heavily pretreated metastatic breast cancer. Our results, confirming previously reported data, suggest that capecitabine should be considered as a reference treatment in anthracycline and taxane refractory breast cancer.

Supported by F. Hoffmann-La Roche

700 POSTER

A phase II study of oral vinorelbine (NVBo) in first line locally advanced/metastatic breast cancer (ABC) chemotherapy. Final results

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Purpose: Oral Vinorelbine (NVBo) is a soft-gelatin capsule formulation with absolute bioavailability of 43 ± 14% (AACR 1997, 4009). Its pharmacokinetic behavior in fed and fasting patients is similar. We conducted a phase II study

to evaluate the activity and safety profile of NVBo as first-line treatment in advanced breast cancer (ABC).

Methods: From 11/97 to 07/00, 64 patients (pts) were entered: median age 63 years, 91% PS 0–1, 30% stage IV disease at diagnosis, and 61% with visceral metastases (lung: 34%, liver: 34%). In 73% of pts, at least 2 organs were involved; prior hormonotherapy (70%) and/or neoadjuvant/adjuvant chemotherapy (31%). NVBo was given at the dose of 60 mg/m^2/week for the first 3 administrations and then increased to 80 mg/m^2 in absence of severe neutropenia defined as one episode of grade 4 or ≥ lepisode of grade 3 neutropenia.

Results: 794 administrations were given (median 9/pt). Relative median dose intensity was 91%. The majority of pts (58/64) underwent dose increase from 60 to 80 mg/m^2. Similarly to NVB i.v, the main toxicity of NVBo was neutropenia (70% of pts and 20% of administrations); grade 4 was seen in 17% of pts and 1.8% of administrations and was complicated in 4 pts (6%). Gastrointestinal events were frequent but of mild to moderate intensity. Grade 3–4 events included nausea (3% of pts), vomiting and diarrhoea in (5%) each. No primary prophylactic antiemetic therapy was recommended. Only one patient experienced one episode of grade3 neuroconstipation. After independent review of efficacy results, 58 patients were evaluable for response (WHO criteria).

	ITT patients (N = 64)	Evaluable patients (N = 58)
CR	4	4
PR	15	14
OR CI 95%	29.7 [18–41]	31 [19–43]
Duration of response (weeks) median	39.2	
PFS (weeks) median [range]	17.4 [2.3–127.6]	

Conclusion: Oral vinorelbine as a single agent is effective. Efficacy results of this study fall in the range of those reported in all the published phase II studies of i.v vinorelbine. The safety profile of oral vinorelbine was qualitatively comparable to the one of NVB i.v. Therefore, oral vinorelbine is a good alternative to i.v vinorelbine in patients with ABC.

701 POSTER

Fluorescence in situ hybridization (FISH) may accurately select patients likely to benefit from herceptin monotherapy

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Background: Herceptin (H) is a humanized anti-HER2 monoclonal antibody and the first oncogene-targeted therapy for HER2-positive patients. HER2 gene amplification and subsequent overexpression of the HER2 protein on the cell surface occurs in approximately 25% of human breast cancers. This alteration is associated with poor prognosis. Patients enrolled in the clinical trials that led to the approval of H were selected using immunohistochemistry (IHC) against the HER2 protein, with those scoring 2+ or 3+ being eligible. Recent data suggest that FISH is an accurate method of choosing patients for H therapy. Methods: A retrospective analysis of FISH status in two trials of H monotherapy was performed: H0650g, in which patients received H as the first non-hormonal treatment for metastatic disease; and H0649g, in which patients received H following one or two chemotherapy regimens for metastatic disease. Results: FISH data were available for 111 patients enrolled in H0650g and 209 of those in H0649g. Of these 82 (73.9%) and 173 (82.8%), respectively, were FISH positive. Outcomes are shown below.

H0650g (first-line monotherapy): RR, 34 vs 7 vs 26% (FISH+ vs FISH- vs IHC+); TTP, 4.9 vs 1.7 vs 3.5 months; overall survival, 24.5 vs 24.4 vs 24.4 months

H0649g (second/third-line monotherapy: RR, 19 vs 0 vs 15% (FISH+ vs FISH- vs IHC+); TTP, 3.2 vs 1.9 vs 3.1 months; overall survival, 14.2 vs 8.8 vs 12.8 months

Conclusions: These results demonstrate that FISH is an accurate method of selecting patients for H therapy. The results further indicate that in optimally selected patients, H is an active therapy for the treatment of HER2-positive breast cancer, particularly when used as first-line therapy for metastatic disease.

702 POSTER

Insulin-like growth factor (IGF) components in postmenopausal metastatic breast cancer (MBC) patient having progressed on tamoxifen: different effect of exemestane (EXE) or megestrol acetate (MA)

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IGF-1 and IGF binding protein (IGFBP)-3 are modifyied in MBC pts receiving hormone therapy. IGF-1, IGF-2 and IGFBP-3 were prospectively evaluated on MBC pts enrolled in a large randomized study of EXE vs MA having progressed on tamoxifen (Kauffman M. et al., JCO 2000). A total of 53 pts were randomized to EXE 25 mg/day (23 evaluable pts) or MA 160 mg/day (28 evaluable pts) and treated until PD. The two groups were well-balanced; all were ER-/PgR-positive. Tumor response and clinical benefit (CR + PR + SD) 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. Only IGF-1 significantly increased at week 8 and the increase was higher with MA than with EXE. No correlation was found with tumor response. Estrone (E1) and estradiol correlate negatively with IGF-1 (EXE) and with IGF-1 and -2 (MA) ($p < 0.05$). E1-sulphate correlates negatively with IGF-1 (MA) ($p < 0.01$). IGF-1 increases on EXE were lower than on MA. Only the 8 wks data are reported due to pts drop-out for PD.

		Baseline (Geometric mean)	Week 8 (Geometric mean)	Probability (Wilcoxon's test) (Between treatments)	(vs. baseline)
IGF-1	EXE	88	136	<0.05	<0.01
(ng/mL)	MA	85	194		<0.01
IGF-2	EXE	108	109	Not significant (NS)	NS
(ng/mL)	MA	102	107		NS
IGFBP-3	EXE	4.6	5.1	NS	NS
(μg/mL)	MA	4.7	4.9		NS

The present study confirm previous findings indicating an effect of steroidal aromatase inhibitors on the IGF system in MBC pts.

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703 POSTER

Fractionated Navelbine and Doxorubicin (NA) as front line chemotherapy in metastatic breast cancer (MBC)

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The activity of Navelbine 25 mg/m2 and doxorubicin 25 mg/m2 [NA] (days 1 and 8 every 21 days for up to 9 cycles) was evaluated in women receiving front line chemotherapy for MBC. All pts had received no prior chemotherapy for metastatic disease and were PS 0-2. Pts with history of brain metastases or significant liver dysfunction were excluded. Prior adjuvant chemotherapy was completed >3 months prior to trial entry and no pt had received < 300 mg/m2 prior anthracycline therapy. All pts had measurable disease. 41 patients were entered on study between May 1999 and May 2000 with a median age of 54 years (range 31-74) and 39 pts received chemotherapy and were assessed for response. 13 pts had received prior adjuvant chemotherapy. The majority of patients presented with multiple sites of disease, with metastases in liver 19pts; lung 9pts; soft tissues 27pts and bone 8pts.

The NA combination was active with 4 CR, 16 PR in 39 pts with a further 12 pts having stable disease for > 3months. Responses were seen at all metastatic sites, median response duration 6.5 mths (range 3.5-11mths). Median survival of 13 months and 17/39 pts remain alive, a minimum of 11 mths after commencing chemotherapy

The treatment was well tolerated in the majority of pts, 200 cycles of therapy administered (median 6 cycles; range 1-9). There were 46 episodes of grade * neutropenia (23% cycles). 45 cycles were delayed but only 6 dose reductions, primarily because of myelosuppression, with day 8 treatment omitted on 7/200 cycles.