These survival benefits were observed even though the study design resulted in 65% of control patients receiving H at disease progression. Cardiac dysfunction (CD) in the H + T arms occurred in 11% of patients aged <60 years and 21% of those aged >60 years. All CD events in those aged >60 years improved to grade 1 with treatment and H was continued. Conclusions: Patients with HER2-positive MBC who are more than 60 years of age appear to have a worse overall outcome than patients aged <60 years. This could be related to poor baseline prognostic characteristics. However, the survival benefit due to the addition of H to C in the older age group was significant. These data indicate that there is no reason to withhold first-line H + C therapy in older (age >60 years) patients with MBC.

693 POSTER

Capecitabine (Xeloda) in 162 patients with paclitaxel-pretreated mbc: updated results and analysis of dose modification

J. Blum[1], S. Jones[1], A. Buzdar[2]. *On behalf of the Xeloda Breast Cancer Study Group; [1] US Oncology and Baylor-Charles A. Sammons Cancer Center, Dallas, USA; [2] M.D. Anderson Cancer Center, Houston, USA*

Background: Capecitabine, a novel, oral, thymidine phosphorylase (TP)-activated fluoropyrimidine, exploits the high activity of TP in tumor cells to generate 5-FU preferentially at the tumor site. In the pivotal trial evaluating capecitabine in 162 heavily pretreated MBC patients, the response rate was 20% (29% in a subgroup of 42 patients resistant to both doxorubicin and paclitaxel), median time to progression (TTP) was 3.0 months and median overall survival (OS) was 12.8 months [Blum et al, JCO 1999]. Myelosuppression and alopecia were rare. We report updated results of this trial and an analysis of the impact of dose modification on efficacy.

Methods: 162 patients received capecitabine 1,250mg/m2 twice daily, days 1-14 every 21 days. The standard capecitabine dose modification scheme was applied if patients experienced grade 2 or more severe toxicities. A retrospective analysis was conducted to evaluate the impact of dose modification on efficacy.

Results: Median OS after 143 events is 11.6 months. Median TTP is 3.0 months. 54 patients (33%) required capecitabine dose reduction for adverse events. The dose was reduced to 75% of the starting dose after a median of 1.6 months in 45/162 patients (27%). A retrospective analysis demonstrated that patients requiring dose reduction for adverse events experienced no significant increase in risk of progression (hazard ratio 1.07, Wald test p=0.73) compared with those not requiring dose reduction.

Conclusions: Capecitabine monotherapy has shown considerable activity in heavily pretreated MBC. Dose modification from the standard starting dose to each patient's individually tolerable dose does not reduce efficacy. Given these results, capecitabine at a starting dose of 1,250mg/m2 twice daily, days 1-14, should be considered the reference treatment for patients whose disease has progressed with prior taxane therapy.

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Relationship of estrogen receptor (ER) status to clinical benefit in clinical trials of herceptin

R.D. Mass[2], C. Vogel[1], M. Murphy[2], M. Cobleigh[3], D. Slamon[4]. *On behalf of the Herceptin Multinational Investigator Study Group; [1] South Point Medical Center, Plantation, FL, USA; [2] Genentech, Inc, South San Francisco, CA, USA; [3] Rush-Presbytarian-St Lukeis Medical Center, Chicago, IL, USA; [4] UCLA School of Medicine, Los Angeles, CA, USA*

Background: HER2 proto-oncogene amplification and/or HER2 receptor overexpression is associated with poor prognosis in breast cancer. It has been reported that there is an inverse correlation between HER2 receptor levels and ER levels. It has also been suggested that targeting HER2 using Herceptin (H) may restore sensitivity to hormonal therapy in patients who have developed resistance. Therefore, we analysed the relationship of ER status to outcomes in the pivotal H trials and a trial of first-line H monotherapy. These trials demonstrated that H monotherapy is active as first- and second-line therapy for metastatic breast cancer and that H plus chemotherapy significantly improves survival. Methods: 805 HER2-positive patients (2+/3+ by IHC) were enrolled in these three clinical trials. A retrospective analysis was undertaken to compare the outcomes of ER+ and ER- patients treated with H. Tumors positive for the progesterone receptor (PR) respond to hormone therapy similarly to tumors that are ER+; therefore, ER-/PR+ tumors are included with ER+ tumors for the purpose of this analysis. Results: 50% of the 805 patients enrolled were ER+, 40% were ER-, and 10% were ER unknown. Outcomes are shown below.

First-line monotherapy (ER+ vs ER-): RR, 25 vs 29%; TTP, 3.8 vs 3.4 months; survival, 26 vs 20 months

Second/third-line monotherapy (ER+ vs ER-): RR, 16 vs 16%; TTP, 3.2 vs 3.0 months; survival, 14.2 vs 12.4 months

H + chemotherapy (ER+ vs ER-): RR, 53 vs 49%; TTP, 6.6 vs 7.0 months; survival, 25.4 vs 24.1 months

Conclusions: The above data support the conclusion that ER-/HER2+ patients and ER+/HER2+ patients have similar clinical outcomes when treated with H alone or H + chemotherapy. Therefore, ER status should not preclude testing for HER2 status and does not predict benefit from H in HER2+ patients.

695 POSTER

Results of two open label Multicentre phase II pilot studies with Herceptin in combination with docetaxel and platinum salts (Cis or Carboplatin) (TCH) as Therapy for Advanced Breast Cancer (ABC) in women with tumors over-expressing the HER2-neu proto-oncogene

J.-M. Nabholtz[1], T. Pienkowski[2], D. Nothfelt[3], W. Eiermann[2], E. Quan[3], P. Fumoleau[2], R. Patel[3], J. Crown[2], D. Toppmeyer[3], D. Slamon[4]. *[1] BCIRG, Univ of California Los Angeles, Oncology, Los Angeles, USA; [2] BCIRG; [3] UCLA Community Network; [4] UCLA, Jonsson Cancer Cntr, Heme Onc, Los Angeles, USA*

Preclinical data indicate that docetaxel (T) and/or platinum salts (C) are highly synergistic with Herceptin (H). This synergy, taken together with the activity of these drugs in ABC, and the need to develop non-anthracycline containing regimens with H, led to our performing two pilot studies to evaluate the safety and efficacy of T and H in combination with cisplatin (TCisH) or carboplatin (TCarboH). Both studies enrolled ABC patients whose tumors were positive for the HER2 alteration by immunohistochemistry (IHC) or fluorescent in-situ hybridization (FISH), with retrospective analysis by FISH planned on all primary tumors. T (75 mg/m2) and C (cis 75mg/m2, Carbo, AUC of 6) were given on day 1, and then q3wks up to 8 cycles. H was given on day 1 cycle 1 (4mg/kg) then continued weekly at 2mg/kg for 1 year or until progression.

Results: Enrollment is complete with 61 TCisH pts and 60 TCarboH pts. Interim results are on 34 TCisH pts (162 cycles) and 27 TCarboH pts (159 cycles). Pt characteristics for TCisH and TCarboH respectively were: prior adj chemo 56% and 67%, visceral mets 76% and 78%, liver mets 38% and 26%, lung mets 35% and 56%, bone mets 44% and 41%, and 3 or more organs involved 32% and 26%. Febrile neutropenia was 9% on TCisH and 11% on TCarboH, there was one grade 3 infection on TCarboH. G3-4 non-hematological toxicities for TCisH and TCarboH respectively were: nausea 12% and 7%, vomiting 6% and 4%, diarrhea 9% and 4%, stomatitis 3% and 11%, and neurosensory 3% and 0%. There were no G3-4 renal or ototoxicities. Grade 1-2 ototoxicities were seen in 18% of TCisH pts. One pt in each study developed CHF (1 prior cardiac history). Responses were seen in 26/34 (3 CRs, 23 PRs, ORR 76%) of TCisH pts HER2 positive by IHC, and in 10/14 (3 CRs, 7 PRs, ORR 71%) TCarboH patients HER2 positive by FISH.

Conclusion: These pilot studies show that the TCH combinations are feasible and are active in ABC, and justify their study in random assignment trials. BCIRG is conducting such studies in both the metastatic and adjuvant settings. Final results for all patients will be presented.

696 POSTER

Fractionated half'body irradiation (HBI) for widespread bone metastases (WSBM) from breast cancer: A randomized phase III trial of the international atomic energy agency (IAEA)

O.M. Salazar[1], Sandhu[1], N.W. daMotta[2], M.A. Perez-Escutia[3], E. Lanzos[3], A. Mouelle-Stone[4], A. Moscol[5], M. Zaharia[5], S. Zaman[6], V. Levin[7]. *[1] Oakwood HS, Detroit, USA; [2] Hosp. Santa Rita, P. Alegre, Brazil; [3] Hosp. Doce Octubre, Madrid, Spain; [4] Hosp. General, Douala, Cameroon; [5] Cancer Inst., Lima, Peru; [6] Inst. Nucl. Med. & Oncol., Lahore, Pakistan; [7] IAEA, Vienna, Austria*

Purpose: Find the fastest and most effective method to economically deliver fractionated HBI for WSBM from breast cancer.

Methods: Phase III trial with 3 arms for WSBM: (A) Control-Convent, daily fract. (15 Gy/5 fx/5 days); (B) Hyperfract. (8 Gy/2 fx/1 d); (C) Accel. Fract. (12 Gy/4 fx/2 d). Of 156 pts. entered, 72 (46%) had breast cancer primaries; 27, 25 and 20 pts. were random. to arms (A), (B) & (C) and constitute the subject of this analysis. All pts had initial and subseq. pain &

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)

I. Vergote[1], B. Thürlimann[2]. [1] *Dept of Gynaecological Oncology, Uni. Hospitals, Leuven, Belguim;* [2] *Swiss Group for Clinical Cancer Research, Switzerland*

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

L. Gianni[1], W. Eiermann[2], D. Borquez[3], J. Albanell[4], R. Molina[4], B. Vanhauwere[5], J. Baselga[4]. [1] *Istituto Nazionale Tumori, Milan, Italy;* [2] *Frauenklinik vom Roten Creuz, Munich, Germany;* [3] *West Deutsches Tumor Zentrum, University of Essen, Essen, Germany;* [4] *Hospital Universitario Vall d'Hebron, Barcelona, Spain;* [5] *F. Hoffmann-La Roche, Basel, Switzerland*

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

P. Reichardt[1], G. von Minckwitz[2], H.J. Lück[3], P.C. Thuss-Patience[1], W. Jonat[4], H. Kölbl[5], D. Kiebak[6], W. Kuhn[7], F. Floemer[8], S. Frings[9]. [1] *Charite, Hämatologie/Onkologie, Berlin, Germany;* [2] *Universitätsklinikum, Frauenklinik, Frankfurt, Germany;* [3] *Medizinische Hochschule, Frauenklinik, Hannover, Germany;* [4] *Universitätsklinikum, Frauenklinik, Kiel, Germany;* [5] *Universitätsklinikum, Frauenklinik, Halle, Germany*

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

V. Trillet-Lenoir[1], T. Delozier[2], M. Lichinister[3], D. Gédouln[4], P. Bougnoux[5]. [1] *Medical Oncology, Centre Hospitalier Lyon-Sud, Pierre Bénite;* [2] *Centre François Baclesse, Caen;* [4] *Centre Eugène Marquis, Rennes;* [5] *Hôpital Bretonneau, Tours, France;* [3] *Cancer Research Center MAS of Russia, Moscow, Russia*

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