to the occurrence of CNS metastases: either dead of breast cancer without proven CNS metastases or dead of other causes.

Results: A total of 124 pts (21%) developed CNS metastases, 411 pts (71%) died of breast cancer, 16 pts (3%) of other causes (cardiac toxicity (12 pts) other toxicity (4 pts), 28 pts (5%) are still alive. Median follow-up was 135 mts (range 0-183+mts). Median time to CNS involvement after start of chemotherapy: 12 mts (range 0-55mts). Following factors predicted CNS metastases: elevated pre-treatment LDH (1-2x upper normal limit (UNL) and >2 x UNL) liver, lung and lymph node metastases and estrogen receptor negative/unknown tumor (ERneg/unknown). Elevated LDH was a predictive factor for all three event, while lung and liver metastases and ERneg/unknown tumor were predictive factor dead of breast cancer too. Increased LDH was the most influential factor identified. CI in pts without any CNS risk factors was 9%. With 'LDH elevated 1-2xUNL' as only risk factor the CI rosed to 20% and up to 55% when 'LDH elevated>2xUNL'. For pts with lung metastases as only risk factor the CI was 18%, and reached 36%in combination with 'LDH elevated 1-2xUNL.

Conclusion: Elevated pre-treatment LDH was the strongest predictive factor for occurrence of CNS metastases in pts treated for metastastic breast cancer. Liver, lung and lymph node metastases were predictive factors too. The risk differed considerably between risk groups, and for some the risk of development of CNS metastases was greather than the risk for dying of breast cancer outside the CNS.

439 POSTER

Correlation between efficacy of single-agent Trastuzumab (T) and molecular markers in HER-2 positive advanced breast cancer patients.

R. Giuliani[1], V. Durbecq[1], D. Larsimont[1], L. Dirix[2], J.-L. Canon[3], V. Richard[4], J.-Y. Leroy[1], C. Ferrara[1], M.J. Piccart[1], A. Di Leo[1]. *[1] Jules Bordet Institute, Translational Research Unit, Brussels, Belgium; [2] AZ St Augustinus, Medical Oncology, Wilrijk, Belgium; [3] RHMS, Medical Oncology, Baudour, Belgium*

Background: HER-2 overexpression is the only known marker predictive of response to T. Nevertheless, 60% of patients with HER-2 amplified breast cancer will not benefit from T. The activation status of either the horizontal network (ErbB family receptors: EGFR, HER-2, HER-3, HER-4), or of the vertical signalling pathway (Akt, MAP kinases), might play a relevant role in this context.

Material and methods: Medical files from 247 patients registered in two national compassionate use programs have been reviewed. The targeted population of our study is represented by 89 patients for whom an assessment of the response to single-agent T was adequately documented. The following biological markers have been evaluated by immunohistochemestry on archival tumor samples from the same patients: EGFR, pEGFR, HER-2, pHER-2, HER-3, HER-4, pAkt, and pMAPK.

Results: Median age of the study population was 55.5 years (range 26-82 years). Median number of metatastic sites was 2 (range 1-4). Sixty-four of 89 patients (71.9%) had visceral disease (liver and/or lung). Fifty-one patients (57.3%) received previous hormonotherapy for metastatic disease (range 1-5 lines, median 2), and 84 of 89 patients (94.3%) were pretreated with chemotherapy (range 1-5 lines, median 2). A median of 16 T weekly cycles have been administrated to 89 patients, with a range of 6-87 cycles. After an independent response review, two complete and nine partial responses have been confirmed (overall response rate12.4%). Twenty-nine patients (32.6%) had stable disease as best response (*6 mos in 14 patients). Thirty-seven patients (41.5%) had progressive disease. In 12 patients (13.5%) clinical response and/or biological markers were not evaluable. Median time to progression for the 77 evaluable patients was 3 mos (range 1-34 mos), and median overall survival was 18 mos (range 2-38 mos). Analysis of biological markers on archival samples is currently ongoing.

Conclusions: The study hypothesis is that the activity of T is increased in the subgroup of tumors carrying HER-2 pathway activation, i.e.: HER-2 +, pHER-2 +, pMAPK, and/or pAkt +. Full results will be available for the meeting.

440 POSTER

Superiority of Tandem High-Dose (HDC) Over conventionally-dosed Chemotherapy(CDC) in Patients (Pts) with Metastatic Breast Cancer (MBC): Updated Results of the International Randomised Breast Cancer Dose-Intensity Study (IBDIS)

J. Crown[1], S. Leyvraz[2], M. Verrill[3], V. Guillem[4], A. Efremedis[5], J. Garcia Conde-Bru[6], R. Welsh[7], A,. Montes[8], R. Leonard[9], J. Baselga[10]. *[1] St. Vincent's University Hospital, Medical Oncology, Dublin, Ireland; [2] CHUV, Medical Oncology, Lausanne, Switzerland; [3] Newcastle General Hospital, Medical Oncology, Newcastle upon Tyne, UK; [4] Duran y Reynals, Medical Oncology, Barcelona, Spain; [5] Instituto Valenciano de Oncologia, Medical Oncology, Valencia, Spain; [6] St. Savas Hospital, Medical Oncology, Athens, Greece; [7] Clinico Universitario, Medical Oncology, Valencia, Spain; [8] Christie Hospital, Medical Oncology, Manchester, UK; [9] Western General Hospital, Medical Oncology, Edinburgh, UK; [10] Vall d'Hebron, Medical Oncology, Barcelona, Spain*

In non-RCT, late-intensification HDC (usually single-cycle), produced promising outcomes in pts who had responded to CDC. This was not confirmed in PRCTs. We hypothesised that multi-cycle HDC with minimal CDC might be more logical, and we compared this approach to CDC in our PRCT.

Methods: Pts without prior CDC for MBC were randomised to CDC: Doxorubicin/Docetaxel (AT) x 4 (50/75-all doses in mg/m^2), followed by all i.v. CMF x 4 (600/40/600 days 1&8), or HDC: AT X 3, then ifosphamide/carboplatin/etoposide (12,000/AUC 18/1200), and 28 days later Thiotepa/Cyclophosphamide (800/6,000). Lenograstim was administered after all AT and HDC cycles, haematopoietic progenitors were leukapheresed after AT #2 and infused after both HDC cycles.

Results: Following ASCO 1999, and the Bezwoda incident, accrual failed, with 110 of a planned 264 enrolled. There were 6 deaths on treatment (4 HDC). The median follow-up is now 45 (range 68-21) months. The study is positive for its primary endpoint which is three-year event (relapse, or treatment-related death)-free survival (27% HDC, 20% CDC p=0.02, median EFS HDC-437 v 290 days respectively, p=0.014, RR 0.59), and for progression-free survival (468 v 300 days respectively p=.009). Med overall survivals were 961 and 812 days respectively (p=0.18). A 100% blinded audit is underway.

Conclusion: Despite the premature termination of accrual, HDC was superior to CDC in MBC. HDC remains a valid investigational strategy.

441 POSTER

A phase I study of oral vinorelbine and paclitaxel in metastatic breast cancer (MBC)

T. Pienkowski[1], N. Tubiana[2], R. Delva[3], U. Vanhoefer[4]. *[1] Centrum Onkologi Instytut, Department of Breast Cancer and Reconstructive Sur, Warsaw, Poland; [2] Hôpital Dupuytren, Limoges, France; [3] Centre Paul Papin, ANGERS, France; [4] Universitaesklinikum-Essen, Essen, Germany*

Background: The combination of intravenous (IV) vinorelbine (VRL) generally given on days 1 and 8 of an every three-cycle and paclitaxel (PTX) is an effective option for the treatment of MBC. In an effort to improve patient convenience, IV VRL was replaced by its oral form used at equivalent doses.

Material and methods: We sought to determine the maximal tolerated dose (MTD) evaluated during the first cycle of oral VRL given on days 1 and 8 and PTX infused over 3 hours on day 1 every 3 weeks, maximum of 6 cycles. The dose of oral VRL was escalated from 60 to 80 mg/m2 in 10 mg/m2 increments. PTX was administered at 110 and then 135 mg/m2. Eligibility criteria included first-line chemotherapy of MBC. Three to 6 patients per cohort were treated.

Results: Twenty two patients were treated in the first 4 cohorts (oral VRL / PTX): 60/110, 70/110, 80/110, 80/135. In cohort 4, seven patients were treated, one patient being non evaluable for MTD; and 3 of them presented a dose-limiting toxicity (DLT) consisting of febrile neutropenia and neutropenic infection. Therefore 80/135 was the MTD. Because 36% of oral VRL administrations on day 8 were delayed to day 15 at 80/110, two additional cohorts were tested: in cohort 5, oral VRL 60 mg/m2 on days 1 and 15 and PTX 135 mg/m2 on day 1 and in cohort 6, oral VRL 80 mg/m2 on days 1 and 15 and PTX 110 mg/m2 on day 1, every 3 weeks. In cohort 5, six out of 8 patients had DLTs: omission of oral VRL on day 15 for 5 patients, grade 4 neutropenia > 7 days for another one. Therefore the recommended dose (RD) for further clinical testing was oral VRL 80 mg/m2 on days 1 and 15 and PTX 110 mg/m2 on day 1 of an every 3 week cycle. Three of the 8 evaluable patients treated at the RD had a partial response.

The co-administration of PTX and oral VRL is unlikely to drug-drug interact on pharmacokinetics.

Conclusion: This phase I study has determined the doses of oral VRL and PTX to be used in combination. The recommended regimen of oral VRL 80 mg/m2 on days 1 and 15 and PTX 110 mg/m2 on day 1 given every 3 weeks is being tested in phase II.

442 POSTER

Fulvestrant ('Faslodex') demonstrates clinical benefit in heavily pre-treated patients with metastatic breast cancer

G.G. Steger, R. Bartsch, C. Wenzel, D. Hussian, U. Pluschnig, R.M. Mader, C.C. Zielinski. *University Hospital, Department of Medicine I, Vienna, Austria*

Background: Fulvestrant (Faslodex') is an Oestrogen Receptor Downregulator that was recently shown to be at least as effective as the selective aromatase inhibitor anastrozole in the second-line, palliative treatment of advanced tamoxifen-resistant metastatic breast cancer. We evaluated Fulvestrant in postmenopausal patients with ER-positive and/or progesterone receptor-positive metastativ breast cancer after failure on at least two previous hormonal agents (adjuvant and/or advanced disease).

Materials and methods: Sixty-one patients (median 61 years of age; range 39 - 81) whose disease had progressed following prior hormonal therapy were treated with a once-monthly intramuscular injection of Fulvestrant 250 mg as part of a Named Patient' programme (AstraZeneca, Austria). Previous hormonal agents included tamoxifen (adjuvant or advanced), anastrozole (first- or second-line advanced) and exemestane (second- or third-line advanced). Twenty-two patients received Fulvestrant as second-line therapy for advanced disease, 27 patients as third-line and 12 patients as fourth-line therapy. While only 23 (38%) patients had received adjuvant chemotherapy, 38 patients (62%) had received chemotherapy for advanced disease. Thirty-three patients (54%) had bone and/or soft tissue metastases only, 9 patients (15%) had visceral metastases only and 18 patients (30%) had both.

Results: patients were evaluated every 3 months and treatment continued until disease progression. To date, 52 patients are evaluable and the median time of observation is 5.5 months (range 4 - 19+ months). We observed a partial response (PR) in 4 patients (8%), stable disease (SD) = 6 months in 25 patients (48%) and disease progression in 23 patients (44%) giving a clinical benefit rate (PR + SD) of 56%. Of the 4 patients who had a PR, 2 patients showed a reduction in the size of visceral metastases and 2 patients showed a reduction in bone/soft tissue metastases. To date, median time to progression is 5 months (range 4 - 11+ months). Fulvestrant was well tolerated and no WHO grade 3/4 toxicities were observed. Adverse events comprised WHO grade 1 nausea in 1 patient, hot flushes in 2 patients and grade 2 unspecific abdominal pains in 1 patient.

Conclusions: Fulvestrant is a promising new endocrine agent with a very favourable toxicity profile in patients with heavily pre-treated advanced breast cancer. The observed clinical benefit rate of 56% with Fulvestrant, even when used third- or fourth-line, necessitates further clinical evaluation.

443 POSTER

Safety and tolerability of oral ibandronate therapy in patients with metastatic bone disease

I. Diel[1], M. Pecherstorfer[2], J.J. Body[3], D. Tripathy[4], B. Bergstrom[5]. *[1] CGG-Klinik GmbH, Mannheim, Germany; [2] Wilhelminenspital, Vienna, Austria; [3] University Libre de Bruxelles, Brussels, Belgium; [4] University of Texas Southwestern Medical Center, Dallas, USA; [5] F. Hoffmann-LaRoche Inc, Nutley, USA*

Background: In recent years, bisphosphonates have become the therapy of choice for metastatic bone disease (MBD). However, the use of existing oral bisphosphonates is limited by their association with gastrointestinal side effects. There are also concerns over the renal safety profile of bisphosphonates as a drug class. Ibandronate is a new, highly-potent, third-generation bisphosphonate that has been developed in both intravenous (i.v.) and oral formulations for MBD management. The safety profile of oral ibandronate has been investigated in phase III clinical studies.

Patients and methods: A pooled analysis of data from two randomized, double-blind, placebo-controlled trials evaluated the safety and tolerability of oral ibandronate in women with MBD from breast cancer. Patients received oral ibandronate 50mg (n=287) or placebo (n=277) daily, in addition to their existing anti-cancer therapy for 96 weeks. Adverse events (AEs) were monitored throughout the study period. Renal toxicity was assessed via urea creatinine clearance.

Results: The percentage of patients experiencing any AE was similar between the oral ibandronate 50mg and placebo groups (94.4% vs 95.3%). The most frequently recorded AE was malignancy progression (affecting 67.5% and 70.8% of patients, respectively). There was a slightly higher incidence of drug-related AEs with ibandronate (26.6%) than placebo (17.7%), primarily due to more reports of hypocalcaemia in the ibandronate group (a common side effect of bisphosphonate therapy). Serious drug related AEs were experienced by 1.0% of patients receiving ibandronate compared with 1.4% of patients in the placebo group.

The incidence of upper gastrointestinal AEs in the pooled dataset was similar with oral ibandronate 50mg and placebo (dyspepsia 10.4% vs 8.3%, esophagitis 2.0% vs 2.2%, ulcer/hemorrhage 0.3% vs 0.7%). The incidence of renal adverse events was also comparable between the ibandronate (4.5%) and placebo (4.0%) groups. There were no reports of serious renal adverse events (renal failure) with oral ibandronate therapy, and there was a similar number of patients with decreased creatinine clearance in the ibandronate (n=4) and placebo (n=3) groups.

Conclusions: Oral ibandronate 50mg/day was well tolerated in patients with MBD from breast cancer, with a similar adverse event profile to placebo, except for hypocalcemia and dyspepsia (more frequent than placebo and >5% incidence). The results suggest that oral ibandronate has less gastrointestinal toxicity than existing oral bisphosphonate therapy (clodronate) and has no clinically significant renal toxicity, unlike existing i.v. bisphosphonates (zoledronate and pamidronate). Oral ibandronate may therefore offer a well tolerated and convenient alternative to existing bisphosphonates for MBD management.

444 POSTER

Predictive outcome assessment and monitoring by serum testing for HER-2/neu, EGFR, uPA and CA 27.29 in metastatic breast cancer

D. Lüftner[1], P. Henschke[1], R. Geppert[1], W. Carney[2], K.D. Wernecke[3], K. Possinger[1]. *[1] Medizinische Klinik II, Charité, Campus Mitte, Berlin, Germany; [2] Oncogene Science, Bayer Diagnostics, Cambridge, Germany; [3] Institut für Medizinische Biometrie, Charité, Campus Virchow, Berlin, Germany*

Purpose: To determine the predictive and monitoring value of serum measurements of HER-2/neu, EGFR, uPA and CA 27.29 for outcome assessment of palliative chemotherapy in breast cancer by multivariate analysis.

Patients and methods: Longitudinal sera of 111 breast cancer patients with stage IV disease under cytotoxic therapy were collected and tested for the serum levels of HER-2/neu (normal: <15 ng/ml), EGFR (normal range: 52-76 ng/ml) and uPA (normal range: 857-1830 pg/ml) using enzyme-linked immunosorbent assays (Bayer/Oncogene Science,Tarrytown, USA). CA 27.29 (normal: <30 U/ml) was measured using an automated chemiluminescence immunoassay.

Results: HER-2/neu levels ranged from 5-2373 ng/ml with a median at baseline of 17.4 ng/ml. EGFR ranged from 30-136 ng/ml with a median of 57 ng/ml at baseline. uPA ranged from 411-5086 pg/ml with a baseline median of 1433 pg/ml. CA27.29 ranged from 8-12612 U/ml with a baseline median of 103 U/ml. Among all demographic, tumor specific and biochemical data in the multivariate analysis, the remission status, the number of involved organs and the serum HER-2/neu concentration were the only parameters to show a statistical significant influence on time to progression in multivariate analysis ($p=0.008$, $p=0.006$ and $p<0.001$, respectively). Patients with a serum HER-2/neu level >18 ng/ml showed a shorter progression-free survival (19 weeks) than patients with a normal serum HER-2/neu level (34 weeks). The serum concentrations of EGFR, uPA and CA 27.29 did not provide any predictive information for time to progression. We found that serum EGFR concentrations of postmenopausal patients were significantly lower than those of premenopausal patients (56.5 ng/ml versus 64.7 ng/ml, respectively). EGFR levels fell statistically significantly with age ($p=0.017$) and did not correlate with tumor mass. Decreased EGFR levels <50 ng/ml were observed in one third of stage IV breast cancer patients. HER-2/neu negative patients by FISH analysis presented decreased EGFR levels <50 ng/ml statistically significantly less often ($p=0.044$) than HER-2/neu positive patients by FISH. Serum courses of HER-2/neu, uPA and CA 27.29 reflected remission status.

Conclusions: Increased levels of serum HER-2/neu predict lack of benefit from systemic chemotherapy in metastatic breast cancer as precisely as remission status or number of involved organ systems. The biological meaning of decreased EGFR levels in metastatic breast cancer remains to be eludicated.