Metastatic sites were: bone (54%), skin (32%), lymph nodes (27%), lung (20%), pleura (7%), liver (2%) and other sites (1%).

Treatment results: All p were evaluable for response. Overall response (OR): 151 p (34.7%), Complete Response (CR): 57 p (13.1%), No Changes (NC): 116 p (26.6%), and Progressive Disease (PD): 169 p (38.8%). At the end of the study, 28 of the 57 p (49%) remained in CR, after a median follow-up for response of 10 m (2–153). The median CR duration was 73 m (95% CI: 50–96).

After a median follow-up for survival of 21 m (2–216), 248 p (56%) have died.

Median overall survival (and 95% CI) was 36 m (31–41) for the whole series, 128 m (86–170) for CR; 39 m (35–43) for PR, 46 m (39–53) for NC and 14 m (12–16) for PD.

Differences in survival with statistical significance were found between CR vs PR, CR vs NC, CR vs PD, PR vs PD and NC vs PD.

We conclude that long disease-free and overall survival can be seen in selected patients who obtain CR after HT as first line therapy.

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NAVELBINE (NVB) PLUS MITOMYCIN (MMC) OR MITOXANTRONE (MTZ): A RANDOMIZED TRIAL IN ANTHRACYCLINE BREAST CANCER RESISTANT (ABCR) PATIENTS. PRELIMINARY REPORT

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NVB, a new semisynthetic Vinca alkaloid is one of the most useful new drugs in breast cancer. The response rate (RR) in pretreated patients (pts) is between 17% and 35%. Combination chemotherapy in ABCR pts with NVB and MMC provided a RR of 46% (R. Santos et al., EJC 29A: 78, 1993, Suppl. 6 n° 407), or with MTZ, RR 40% (Silvestro P. *et al.*, EJC 29 A: 85, 1993, Suppl. 6 n° 449) in two phase II studies. Both combinations are associated with high RR and tolerable toxicity (T), but they have not been compared in a randomized trial. Between 8–1993 and 12–1994, 69 pts. with ABCR non suitable for hormonotherapy were randomized to A: NVB 25 mg/m^2 IV days 1–8 plus MMC 7 mg/m^2 IV day 1, or B: NVB as above plus MTZ 8 mg/m^2 IV day 1. A and B each 28 days, until progression or toxicity grade 4. Number of patients: A: 35; B: 34. Median age: A 55 y; B 54.4 y. Premenopausal: A: 8; B: 5. Adjuvant chemotherapy: A: 26; B: 23. Previous homonotherapy: A: 6; B: 4; Metastatic sites: soft tissue: A: 30; B: 28,; Lung: A: 9; B: 8; Liver: A: 10; B: 10; Number of metastatic sites: One: A: 13; B: 10; Two: A: 16; B: 21; Three: A: 6; B: 3. *Results:* RR: A: 14/35 (48%); CR: 0; PR: 14. B: 18/34 (58%), CR: 1; PR: 17. Median survival A: 7.24 months; B: 6.94 months. T: a total of 128 cycles in arm A and 127 cycles in arm B are comparable. Hematological grade 3–4 were seen in 18 cycles of A and 13 cycles of B and one phlebitis grade 3 in arm B. There were no drug related deaths. *Conclusion:* 1—Both second line schedules are active in ABCR (A: 48%, B: 58%, p:NS). 2—T was manageable. 3—To this date there are no differences in survival. Study is still ongoing.

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PACLITAXEL BY 3-H ON DAY 1 & 8 EVERY THREE-WEEKS IN WOMEN WITH ANTHRACYCLINE-RESISTANT METASTATIC BREAST CANCER

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Frequent administration by 3-h infusion should result in prolonged and intense tumor exposure to active concentrations of P. In May 1994 we started a trial to assess feasibility, maximum tolerated dose (MTD) and antitumor activity of P on day 1 and 8 q 3 wk schedule. After standard premedication P was infused in 3-h starting at 100 mg/m^2. Dose escalation by 25 mg/m^2 steps in subsequent cohorts of patients (pts) was planned. Twenty pts with metastatic breast cancer were accrued so far (10 at 100, and 10 at 125 mg/m^2). Median age was 50 (22–59) and ECOG PS 0 (0–2). Thirteen pts had relapsed and 7 progressed within median 7 months (1–20) of prior anthracyclines. Fourteen pts and 70 cycles are presently evaluable for rexicily and 13 pts for activity. Main toxicities according to WHO scale were:

dose	patients	neutropenia		neuropathy		myalgias	
(mg/m^2)	(n.)	III	IV	I	II	I	II
100	10	3	1	6	1	2	2
125	4	2	-	2	1	2	-

All patients had grade 3 alopecia. Nansea was rare. Dominant sites of measurable disease in 13 pts were: lung (n = 7), liver (n = 2), pleura (n = 1), and soft tissue (n = 4). Three CR and 8 PR (84%, C.I.: 55–98%) were observed. Sites of response were lung (6/7), liver (2/2), soft tissue (3/3), and bone (3/4). Median duration of response is 5 months (2$^+$–10$^+$). Four pts had CNS progression while still responding on extra-CNS sites. These preliminary data indicate that the new schedule of P is feasible and very active. The accrual continues to define the MTD and assess the actual duration of responses.

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PHASE I/II STUDY WITH PACLITAXEL IN COMBINATION WITH WEEKLY HIGH DOSE 5-FU/FOLINIC ACID IN THE TREATMENT OF METASTATIC BREAST CANCER

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Introduction: Based on the results of a phase II study with a weekly (x6) schedule of a 24 h infusion of high dose 5-FU/Folinic acid (HDFU/FA) demonstrating high efficacy (RR 41% 13/32 pts) and low toxicity in intensively pretreated metastatic breast cancer patients (pts), we added Paclitaxel (P) to HDFU/FA in a phase I/II trial. P was chosen because of its activity in pretreated metastatic breast cancer pts, different mode of action than HDFU/FA and the lack of overlapping hematologic toxicities between the combination partners. Since 9/93, 51 pts with at least one prior chemotherapy regimen were entered.

Treatment: Pts were treated with HD5-FU (24 h infusion)/FA (2 h infusion prior to FU) weekly for six weeks (d1, 8, 15, 22, 29, 36) and P (3 h infusion) was administered additionally on day 1 and day 22. Each cycle comprised of six weeks followed by two weeks rest. Number of cycles depending on response and toxicity. All pts were treated under outpatient conditions using i.v. port systems and portable pumps. During Phase I we chose the following dose levels (dl): Fixed doses of FA dl1–4 500 mg/m^2 followed by HDFU 24 h infusion dl1: 1.5, dl2: 1.8, dl3 and dl4: 2.0 g/m^2. .3 h infusion of P, given prior to HD5-FU/FA on d.1 and d.22 dl1–dl3: 135, dl4: 175 mg/m^2. Dl 4 was chosen to be further evaluated during phase II.

Patient Characteristics: 51 pts entered this ongoing trial. Up to now 48 pts were evaluable for response and toxicity. 12 ps entered dl1–3 (4 pts each dl) and 39 pts dl4; age 47 yrs (26–63). WHO PS 1 (0–2), metastatic disease sites 2 (1–4). All pts had bidimensionally measurable disease.

Pretreatment: Pts had adjuvant chemotherapy 17/51, prior chemotherapy for metastatic disease 12/51, chemotherapy both adjuvant and for metastatic disease 22/51; prior treatment with anthracyclines 34/51, resistance to anthracyclines with disease progression while treatment prior to study entry 29/51.

Toxicity: (n = 51). No dose limiting toxicities occurred during dl1–3. 153 treatment cycles at dl4 had the following toxicities (WHO grade) in (n) cycles: leucopenia 3°/4° (28); mucositis 2° (49); diarrhea 2° (35), 3° (15); hand-foot syndrome 2° (85); PNP 2° (41); nausea/vomiting 2° (37); myalgia 2° (66).

Results: (n = 48). CR 4% (2/48), PR 58% (28/48), SD 34% (16/48), PD 4% (2/48). RR (Response rate) 62%, 95% confidence interval 48–76%. Responses (PR) at dl1–3: 2/4 patients. Response concerning 29 patients with anthracycline refractory disease (26 pts were evaluable for response so far): RR 58% (15/26), 95% confidence interval 38–78%. Time to maximum response 2 months (1–5), remission duration 8+ months (2–11). Median survival time not yet reached.

Conclusions: The combination of P with weekly HDFU/FA is well tolerated and indicates high efficacy also in anthracycline refractory metastatic breast cancer. In addition the regimen can safely be administered under outpatient conditions.