generation platinum drug designed to have an extended spectrum of antitumour activity and overcome platinum resistance mechanisms, has shown synergistic in vitro activity in combination with paclitaxel. The purpose of this ongoing Phase I trial is to evaluate the safety of ZD0473 in combination with paclitaxel, in patients with refractory solid malignancies.

Methods: Patients received a 3-hour iv infusion of paclitaxel, followed after 30 min by a 1-hour infusion of ZD0473, repeated every 3 weeks.

Results: To date, 17 patients (NSCLC [12 patients], mesothelioma [3], SCLC [2]) have been recruited and have received paclitaxel/ZD0473 combinations at doses of 135/60, 135/90, 135/120, 150/120, or 175/120 mg/m2. The median (range) of treatment cycles received to date is 3 (1-6), with 8 patients having received at least 4 cycles of treatment. During the first treatment cycle myelosuppression was mild: 1 patient had grade 3/4 anaemia; there were no incidences of grade 3/4 thrombocytopenia or neutropenia. Nine patients were withdrawn due to disease progression. So far, no patients have experienced dose-limiting toxicity. Stable disease was observed in 9 of the 13 evaluable patients, including 3 patients with NSCLC who experienced a reduction in tumour size of ~10%. The median number of treatment cycles received by patients with stable disease was 4 (range 2-6).

Conclusion: The ZD0473 and paclitaxel combination is well tolerated and shows encouraging stable disease in patients with solid tumours.

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A phase I study of weekly Oxaliplatin (OXA) + continous infusion (CI) fluorouracil (FU) in patients with advanced colorectal cancer (CCR)

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A combination of OXA and FU is frequently used as 1st or 2nd line treatment for advanced CCR. However, the optimal schedule for this combination has not been defined. Weekly administration of OXA may result in decreased acute toxicity and increased dose intensity compared to bi- or tri-weekly administration. The purpose of this study was thus to identify the MTD of weekly OXA (4 dose levels: 60-70-80-90 mg/m2 on days 1, 8, 15) in combination with a fixed daily dose of CI FU (200mg/m2/die d1à21) + Leucovorin (LV), with cycles repeated every 4 weeks. Since April 2000, 20 patients with progressive advanced CCR, previously treated with or ineligible for 5-FU and CPT-11 were accrued (13 males, 7 females; median age 68 years; median ECOG PS 1; median CEA 31.5 ng/ml).

Overall, 56 cycles were delivered corresponding to 163 weeks of chemotherapy. The median number of cycles administered to each patient was 2 (range 1-6) and the median number of weeks of chemotherapy was 6 (range 3-18). Fifteen of 163 weeks of chemotherapy were delayed because of toxicity while 6 of 163 weeks were delivered at a reduced dose. Considering the first 2 cycles of treatment (2 months), no grade III-IV toxicity was observed up to dose level 4 (OXA 90 mg/m2). Three patients presented grade I thrombocytopenia lasting 19, 14 and 14 days, respectively. Three out of 6 patients treated at dose level 4 (OXA 90 mg/m2) required a major change in the treatment program (discontinuation, delay longer than 14 days or dose reduction) because of constitutional symptoms (asthenia, weight loss and unbearable peripheral sensory neuropathy). This was thus deemed to be the MTD for OXA in this combination. Among 15 patients with measurable disease completing at least one treatment cycle 1 PR, 4 MR, 7 SD and 3 P were obtained. Overall, disease progression was abrogated in 12 of 18 evaluable patients. Three patients with initially unresectable liver metastases underwent secondary resection with curative intent.

These results demonstrate that the combination of weekly OXA and low-dose CI FU is feasible and well tolerated. This regimen allows to deliver a higher dose intensity of OXA compared to bi-weekly or tri-weekly schedules and shows a promising antitumor actvity in heavily pretreated patients. The study is now continuing to assess the possibility of incorporating LV (20 mg/m2, d1, 8, 15) at the OXA dose level below the MTD (80 mg/m2).

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A phase I, dose-escalation study of the novel antifolate zd9331 in combination with cisplatin in patients with refractory solid malignancies

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Introduction: ZD9331 is a new antifolate cytotoxic that inhibits thymidylate synthase and does not require polyglutamation for its activity.

Objectives: To determine the maximum tolerated dose (MTD) for ZD9331 in combination with cisplatin and to assess the tolerability, pharmacokinetic and antitumor activity of the combination.

Methods: Thirteen patients with refractory solid tumors have been entered to date. ZD9331 was administered as a 30-min iv infusion on days 1 and 8 of a 21-day cycle. Cisplatin was administered after ZD9331 as a 30- to 60-min infusion on day 1. The MTD was defined as that which caused dose-limiting toxicity (DLT) in ~2/6 patients.

Results: Patients entered on one of three dose levels: ZD9331/cisplatin 100/50 (n=3), 130/50 (n=6) and 130/75 (n=4) mg/m2. Baseline performance status (PS) was good (PS 0 in 3 patients, PS 1 in 10 patients), and most patients had received prior chemotherapy. The majority of patients had thoracic malignancies. DLT was observed in 2 patients at 130/75. Both had grade 3/4 neutropenia requiring the day 8 dose of ZD9331 to be withheld. A third patient at this dose level experienced similar toxicity on his second cycle of treatment. Other toxicities include thrombocytopenia, anemia, fatigue, nausea, vomiting, and stomatitis. Accrual to the 130/50 dose level continues. Of the 13 patients entered, there has been 1 partial response in a patient with mesothelioma. Patients with mesothelioma and breast cancer also have stable disease.

Conclusions: The combination of ZD9331 and cisplatin is well tolerated and has antitumor activity.

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Phase I study of weekly paclitaxel and liposomal doxorubicin in patients with advanced solid tumours

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Objectives: Paclitaxel has a broad spectrum of toxicity against the most common human tumours. Weekly administration of paclitaxel may improve the toxicity profil of the drug increasing its efficacy. Liposomal doxorubicin (Caelyx) has shown similar to conventional doxorubicin's activity with much more favorable toxicity profil. A phase I study was conducted to determine the maximum tolerate dose (MTD) and the dose limiting toxicities (DLTs) of the combination of the two drugs administered weekly in patients with advanced solid tumours.

Patients and Methods: Escalating doses of Caelyx (6–12 mg/m^2) were administered as a 1 h IV infusion and a fixed dose (80 mg/m^2) of paclitaxel as a 3 h IV infusion on the same day for 4 consecutive weeks in a 6 week cycle. Nineteen previously treated patients with histologically confirmed advanced stage solid tumours were enrolled.

Results: The MTD was reached at the dose-level Caelyx 10 mg/m^2 + paclitaxel 80 mg/m^2. The DLTs were evaluated after the first cycle and consisted in all cases of grade 3 neutropenia resulting in treatment delay. A total of 55 cycles have been administered: Grade 2–3 neutropenia was observed in 7 (14%) cycles and grade 4 anemia in 1 (2%) cycle. Non hematologic toxicity included grade 2–3 nausea-vomiting in 5 (9%), grade 2–3 diarrhea in 4 (7.2%), grade 2–4 fatigue in 7 (12.7%) and grade 2 mucositis in 1 (1.8%) of the cycles. No cardiotoxicity, as determined by the development of CHF or more than 10% reduction on LVEF was observed. Among 12 evaluable patients, 1 PR was observed in a patient with ovarian cancer.

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A phase I study of the caelyx - Oxaliplatin combination in patients with advanced solid tumors

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Background: Caelyx is a liposomal doxorubicin formulation with low toxicity and high activity in various tumors. Oxaliplatin (L-OHP) is a new platinum analog with improved toxicity profile and only partial cross resistance with cisplatin and carboplatin. We conducted a phase I study to evaluate the MTD and DLT of the Caelyx-L-OHP combination.

Patients and Treatment: Caelyx was administered on day 1 as an 1-hour IV infusion at escalating doses of 25–35 mg/m^2 followed by L-OHP as a 2-hour IV infusion at doses of 80–100 mg/m^2. Cycles were repeated every 3 weeks without growth factors. Eighteen patients with advanced stage carcinomas have been entered. Median age 60, PS (WHO) 0:6, 1:9, 2:3. Treatment was 1st line for 5 (28%), 2nd line for 7 (39%) and 3rd line for 6 (33%) pts. DLT was evaluated during the first cycle of treatment and included any grade 4 hematologic toxicity, neutropenia grade 3–4 with

fever, non-hematologic toxicity grade 3–4 and any treatment delay due to toxicity.

Results: All patients were evaluable for toxicity and the DLT dose level has not yet been reached. A total of 61 cycles have been administered (median 2 cycles/pt), with 5 (8%) cycles complicated by grade 2 neutropenia, 3 (5%) grade 2–4 anemia, no grade 2–4 thrombocytopenia, 12 (20%) grade 2–3 asthenia and 2 (3%) grade 3 neurotoxicity. Seven cycles (11%) have been delayed due to toxicity. No febrile neutropenia has been observed.

Dose level	Caelyx	L-OHP	Pts	DLT	Toxicities
1	25	80	3	–	–
2	30	80	3	–	–
3	30	90	3	–	–
4	35	90	6	2	G2 neutropenia (Tx delay)
5	35	100	3	1	G3 neurotoxicity

Conclusion: The combination of Caelyx and L-OHP is well tolerated with acceptable toxicity. The study is ongoing to determine the MTD.

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Gemcitabine, Docetaxel and Carboplatin triplet: a phase I dose-finding study with and without filgrastim (G-CSF) support

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Gemcitabine(G), docetaxel(D), and carboplatin(C) have a wide spectrum of activity against solid tumors. This phase I study was designed to determine the maximally tolerated dose (MTD) and dose-limiting toxicity (DLT) of G+D+C chemotherapy administered with and without G-CSF support. G(day1,8) + D(day1) + C(day1) were administered every 21 days. Twenty patients (7F, 13M), median age 57 (28-77 years), with a variety of solid tumors have been treated. At dose level I(G 600mg/m2 + D 65/mg/m2 + C AUC=5), the first 2 pts experienced DLT

(grade [gr] 4 thrombocytopenia, with one febrile neutropenia [FN] and fatal sepsis). Dose level 0 was then established with reduction of the D dose (55mg/m2); 1/6 evaluable pts experienced DLT (gr. 4 thrombocytopenia & FN). Gr. 4 neutropenia was frequently observed at this level, but was generally short lasting. With G-CSF, dose level I was safely administered (0/3 DLT). At dose level II + G-CSF, 2/6 evaluable patients experienced DLT with gr. 4 thrombocytopenia. Of 12 evaluable pts, there were 4 partial responses, two in patients with pancreatic cancer, one in a patient with SCLC, and one in a patient with unknown primary. Eight patients are not evaluable for response (5 with DLT, 1 death from progressive disease within 1 week of treatment, 1 refused further treatment after D1, and 1 patient is currently being treated). This regimen is associated with notable myelosuppression, but is otherwise fairly well tolerated and is highly active. The recommended phase II doses in this combination regimen without G-CSF, are D 55 mg/m2, G 600 mg/m2 and C AUC=5. With the addition of G-CSF, the recommended phase II doses are D 65 mg/m2, G 600 mg/m2 and C AUC=5. Supported in part by Eli-Lilly, Aventis and Amgen.

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A Phase I/II study of dose-escalated docetaxel given two weekly in combination with a fixed dose of G-CSF

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Docetaxel has an established activity in different cancer types. Dose limiting toxicity is neutropenia and asthenia, which is reason to investigate the toxicity of different treatment schedules and the effect of specific support.

Purpose: To determine the MTD of docetaxel q 2wks in combination with G-CSF.

Patients and Methods: 25 patients with progressive and advanced malignancies and an anticipated sensitivity to docetaxel were included. Tumor distribution: breast cancer(15) bladder cancer(6),lung cancer(2),stomach cancer(1) and ovarian cancer(4). All patients were pretreated, one patient with paclitaxel. Further patient characteristics: 20 female/5 male; median age 52 years; PS was 0, 1 or 2. Docetaxel was administered q 2wks in a 1hr infusion. The dosis of docetaxel was escalated from 60 (7 patients), to 70 (7 patients) to 80 (11 patients) mg/m2. G-CSF (Lenograstim) 263 mcg s.c.was given from day 2-12. On day -1, 0 and +1 dexamethason 8 mg was taken two times daily orally. A minimum of 6 cycles was scheduled, unless disease progression or unacceptable toxicity occurred earlier. Every 3 cycles evaluation of response was performed.

Results: 16 patients completed at least 6 cycles; 6 stopped earlier because of progressive disease, 2 stopped after 4 courses because of toxicity (1SD,1PR), and 1 because of sepsis, most probably not related with docetaxel therapy. Hematological toxicity grade 3-4 was not observed in any patient during 160 cycles docetaxel. Alopecia was present in all patients after 3 cycles and nail changes cumulated with further treatment. At level 60 mg/m2 1/7 patient experienced asthenia grade 3 after 3 cycles, but completed 6 cycles. At level 70 mg/m2 1/7 patient experienced asthenia grade 2-3, but completed 6 cycles, and another patient stopped after 2 cycles because of sepsis. At level 80 mg/m2 4 patients (1PR/1SD/2PD) stopped therapy after 2, 3, 4, and 4 cycles, one patient because of toxicity. The other 7 patients except one experienced grade 2-3 asthenia, 2 developed edema in the arm at the mastectomy side, and 2 peripheral edema. These toxicities became evident after 6 cycles and prohibited further dose escalation. 9/15 patients with breast cancer and 2/2 with lung cancer had a PR; the patients with other tumor types did not response.

Conclusions: 2-weekly schedule of docetaxel supported by G-CSF resulted in a MTD of 80 mg/m2 consisting of asthenia and edema which became apparent particularly after 6 cycles.

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A Phase I Study of combined modality Fever-Range, Long-Duration, Low-Temperature Whole-Body Hyperthermia (LL-WBH) optimally-timed with Cisplatin (CIS)-Gemcitabine (GEM) & Interferon-a (IFN-a)

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Background: We have shown in an in vivo model that antitumor efficacy & normal tissue toxicity are highly time & sequence dependent when combining CIS with GEM, or either drug with whole-body hyperthermia.

Purpose: From our pre-clinical data, we designed a clinical protocol combining optimally timed & sequenced CIS with LL-WBH + GEM + low dose IFN-a. This Phase I study was designed to determine the MTD of cisplatin in the regimen of LL-WBH + GEM + IFN-a.

Patients and Methods: A total of 22 Pts. with drug resistant, advanced-bulky or metastatic cancers (median age 60y, [range 25-78y], 10 females/12 males were treated. 19 pts are evaluable; 4 pts recently started treatment). The therapeutic regimen was an escalating dose of CIS (50 to 80 mg/M2) d1, LL-WBH (40.0 ± 0.2 °C for 6h) + GEM (600 mg/M2 over 60 min during LL-WBH) d3, and GEM d10 + daily s.c. IFN-a (1 x 106 i.u.). Cycles were repeated at d28. LL-WBH was induced using the Heckel radiant heat device.

Results: The number of treatment cycles were 1-9 (median 3). Time to reach target core temperature was median 75 min. (range 60-185 min). Grade III thrombocytopenia occurred in 2/3 pts at CIS 70 mg/M2, 2/3 pts developed grade II thrombocytopenia after 3 cycles at CIS 70 mg/M2. Three pts experienced grade 1 leukopenia, 1 pt a grade III ototoxicity at CIS 70 mg/M2. We established the MTD of CIS to be 60 mg/M2. In 19 evaluable pts we documented 14 objective responses: 10 PRs (3 pancreas, 2 gastric, 1 renal, 1 lung, 1 adrenal, 1 bladder, 1 sarcoma), (3/10 PRs were >90%) and 4 SDs lasting > 5 mos.

Conclusions: i) the recommended phase-II dose of CIS in this multi-modality regimen is 60 mg/M2. ii) The thermobiochemotherapy regimen is safe, and well tolerated. iii) Although not a primary endpoint of analysis, the regimen induces clinical benefit in a high proportion of pts with advanced, chemotherapy-resistant tumors. iv). We will begin Phase II trials in a) pts with pancreatic; b) lung; and c) gastric cancer.

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Dose escalation and pharmacokinetic study of capecitabine and irinotecan (CPT-11) in gastro-intestinal (GI) tumors

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Capecitabine (Xeloda) is an oral tumor-activated fluoropyrimidine and has demonstrated superior activity and improved safety compared to the Mayo regimen in metastatic colorectal cancer (CRC). CPT11, a topoisomerase I inhibitor is an active drug in GI tumors. Capecitabine and CPT11 demon-