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-