Results: Thirty-two patients with advanced solid tumors have been treated using the 7/7 schedule for a total of 42 courses; 41 patients have been treated using the 21/7 schedule for a total of 36 courses. The MTD of TMZ was 150 mg/m2 per day on the 7/7 schedule. For patients on the 21/7 schedule, the MTD was 100 mg/m2 per day for minimally pretreated patients and 85 mg/m2 per day for heavily pretreated patients. The DLT for both schedules was myelosuppression with both thrombocytopenia and neutropenia. Significant dose-related depletion of AGAT levels was observed with both extended schedules. Pharmacokinetic studies indicated that TMZ does not accumulate with extended dosing with a mean clearance of 163 ml/hr/kg (range: 152-195 ml/hr/kg) and a mean terminal phase half-life of 1.76 hours (range: 1.52-2.45 hours).

Conclusion: Extended dosing with TMZ is safe at doses of up to 150 mg/m2 per day utilizing a 7-days on/7-days off schedule and 85-100 mg/m2 per day with the 21-days on/7-days off schedule, allowing at least a 2.8 fold increase in drug exposure per treatment cycle compared with the daily x5 schedule. Furthermore extended TMZ dosing depletes AGAT levels which may potentiate TMZ activity.

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Phase I and pharmacokinetic study of ET-743, a minor groove DNA binder, administered weekly to patients with advanced cancer

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Purpose: Ecteinascidin 743 (ET-743), a DNA minor groove binder that inhibits transcription, has demonstrated impressive preliminary activity in patients with doxorubicin-refractory soft-tissue sarcomas and breast cancer and is currently undergoing phase II/III evaluations as a single-infusion every 3-weeks. On this schedule, neutropenia, transaminitis, nausea and vomiting preclude administration of doses exceeding 1500 ug/m2. Since transaminitis appears to be related to peak concentration, and dose fractionation in animal models appears to be associated with a lower incidence of transaminitis, this study is evaluating the feasibility of administering ET-743 as a 3-hour IV infusion weekly for 3 weeks every 4 weeks, as well as the pharmaockinetics of the agent on this schedule.

Methods: 16 patients (median age, 53, [range 22-77]) have received a total of 32 courses of ET-743 at 4 dose levels: 300, 400, 525, and 650 microg/m2/wk. The total dose/course at the third and fourth dose levels are 1575 and 1950 ug/m2 respectively. The activity of the P450 isoenzyme CYP3A, which is the principal metabolizing enzyme involved in drug disposition, is being quantified using the Erythromycin Breath Test, and these data are being related to individual toxicologic and pharmacokinetic profiles.

Results: One heavily-pretreated (HP) patient at the 650 ug/m2/wk dose level developed a dose-limiting event characterized by grade 3 neutropenia, the resolution of which delayed retreatment for 3 weeks. No other clinically significant toxicities have occurred. Thus far, two heavily-pretreated patients with metastatic liposarcoma and ovarian carcinoma experienced a minor response and prolonged disease stabilization, respectively. Preliminary pharmacokinetic analysis in patients at dose levels 1 and 2 suggest that plasma concentration-time profiles are best fit by a biexponential model, with an initial disposition phase half-life of 0.18-0.34 h and terminal half-life of 34-47 h. AUC ranged from 4.8 to 8.5 ng*h/mL and the Vss was large, ranging from 1005-2052 L/m2.

Conclusion: ET-743 administered on a weekly x 3 every-4-week schedule is well tolerated and achieves a dose-intensity approaching to single-dose every-3-week schedules. Further accrual is ongoing at the 650 ug/m2/wk dose level. The tolerability of this schedule and preliminary evidence of biological activity suggest that this administration schedule may portend an improved therapeutic index.

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Phase I (PI) trials with aplidine (APL), a new marine derived anticancer compound

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APL is a cyclodepsipeptide isolated from the Mediterranean tunicate A. albicans that blocks the cell cycle progression at G1 in a non MDR/p53 dependent manner, targets protein palmitoyl thioesterase and decreases the expression of the VEGF type 1 receptor gene and the secretion of VEGF.

A total of 162 patients (pts) have been entered into four PI trials assessing the following intravenous (iv) infusion schedules: 01: 24 hours (h) weekly (w); 02: 1 h w; 03: 24 h every 2 w and 04: 1 h daily x 5 days every 3 w. The results are listed below. Doses are expressed in mg/m2. MTD = maximal tolerated dose/RD = recommended D/DLT = D limiting toxicity.

Trial	# pts	MTD (RD)	DLT
01	35	4.5 (3.7)	Muscular, Hepatic
02	41	3.6 (3.2, ong.)	Muscular
03	53	6 (5)	Muscular
04	33	1.35 (1.2, ong.)	Diarrhea, Rash

APL induced muscular toxicity(MT) is characterized by muscle cramps or increases of creatine kinase with normal MB fraction or dose-limiting myalgia and weakness; the pathological assessment shows thick filament disappearance. At the RDs the toxicity profile is limited to G1 emesis, G1 muscular weakness and G1-3 asthenia. Bone marrow toxicity, mucositis or hair loss have not been noted. Toxic deaths have not been reported. A review of potential mechanisms of the APL MT led to the incorporation of L-Carnitine into the trial O3, enabling a further increase of the RD up to 7 mg/m2 (tumor protection ruled-out in experimental in vitro models). Activity has been noted in medullary thyroid, colorectal and renal ca, neuroendocrine tumors and melanoma from doses below the MTD. The pharmacokinetic (PK) plasma profile (LC/MS/MS) indicates linearity, high plasma CL (median (m) 252 mL/min/m2), a m elimination half life = 23.8 h and a m Volume of distribution = 413 L/m2. There is blood cell accumulation (m blood:plasma ratio 3.0). In fact, initial whole blood PK data shows lower CL; m 64 mL/min/m2, m elimination half-life =24.6 h, and a m Volume of distribution 111 L/m2. Pharmacologically appropriate plasma levels (>1ng/ml) are achievable below the RDs. APL is clinically feasible in pretreated adult pts with advanced disease. Phase II studies incorporating the protracted iv infusion every other week are under implementation.

Melanoma and sarcoma

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On the efficacy of biochemotherapy in metastatic malignant melanoma. An immunohistochemical evaluation

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Purpose: Metastatic malignant melanoma is despite various treatment strategies still associated with a poor prognosis. There is a great need to better understand the mechanisms of action of immunotherapeutic drugs and how tumours escape the action of these drugs. In the present study tumour-infiltrating CD4+ lymphocytes were determined in fine needle aspirates (FNA) pretreatment and the therapeutic efficacy was evaluated in metastases resected after treatment using histopathological criteria of tumour regression.

Methods: Thirtytwo patients with metastatic malignant melanoma (18 with regional disease and 14 with systemic disease) were treated with biochemotherapy (Cisplatinum 30mg/m2 d.1-3, DTIC 250mg/m2 d.1-3 iv and IFN-a2b 10 million IU sc three days a week, q 28d). Pretreatment fine needle aspirates were obtained from metastases to analyse the number of tumour-infiltrating CD4+ lymphocytes. After treatment biopsies from resected tumours were analysed regarding histopathological regressive