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

changes and the occurrence and distribution of tumour-infiltrating mononuclear cells.

Results: Among patients with regional disease, 50% showed a high degree of regressive changes (more than 75 percent of the section area) after biochemotherapy. Patients with histopathological response could be identified pretreatment by analysing the numbers of tumour infiltrating CD4+ lymphocytes in FNA. There was a statistically significant correlation between the occurrence of these cells and a high degree of regressive changes post treatment, p=0.01. A Kaplan-Meyer analysis of patients with regional metastses showed a tendency to a longer overall survival in patients with a high degree of regressive changes. Similar results were found in a smaller group of patients with systemic disease.

Conclusion: Biochemotherapy showed a remarkable efficacy with a high degree of tumour regression in 50% of the patients with regional disease. There was a close correlation between extensive regressive tumour changes and the amount of tumour infiltrating CD4+ lymphocytes pre-treatment. Patients with regressive changes of more than 75% of the analysed biopsies were also found to have a tendency to a longer overall survival. Thus immunohistochemical analysis of tumour biopsies shortly after immunotherapy seems to be a good surrogate endpoint and this technique also allows a detailed analysis of anti-tumour reactivity and escape mechanisms.

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Immunomagnetic detection of micrometastatic cells in bone marrow predicts survival of patients with malignant melanoma and osteosarcoma

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Purpose: We have previously reported simple and sensitive methods for detection and characterization of micrometastatic tumor cells, based on the use of immunomagnetic and fluorescent microparticles. The aim of this work was to relate results obtained with our method on samples from patients with advanced malignant melanoma and with osteosarcoma to clinical parameters to examine the clinical potential of the method for predicting prognosis.

Methods: The methods were used on blood and bone marrow samples obtained from 152 melanoma patients and from 39 patients with primary osteosarcoma. Twentyfive (16.3%) melanoma patients had positive samples. This group showed a significantly shorter survival, both from primary operation (p = 0.031) and from time sampling (p = 0.042), than those without micrometastasis. Multiple variat analysis revealed that presence of melonoma cells was, together with the number of metastatic sites, the most important parameter of survival. In osteosarcoma, 50–100% of 39 patients had tumor cells in their bone marrow, increasing with disease stage. In a number of the patients the findings in repeated samples correlated to the effect of preoperative chemotherapy. The malignant nature of the immunomagnetically selected cells could be confirmed by binding of fluorescent antibody-coated particles targeting other tumor-associated antigens, and in a few cases by culturing the cells in vitro and in nude mice.

Conclusion: The results demonstrate the validity and clinical potential of using these methods for prognostication and response monitoring in these type of malignancies.

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Sentinel node biopsy improves regional node staging in melanoma patients

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Elective lymph node dissection (ELND) has been performed widely in the past for patients with melanoma who have been considered to be at high risk for local or systemic recurrence. Sentinel node biopsy (SNB) has largely replaced this technique in many major cancer centres in order to reduce postoperative morbidity and to minimise unnecessary dissections. Whether SNB, with subsequent lymph node dissection when micrometastatic disease is found in a SN, has any benefit in terms of survival remains unclear. Whilst some SNs are not removed due to technical failures, SNB has been shown to improve staging in breast cancer patients when compared to standard axillary lymphadenectomy. In melanoma patients such an improvement has never been demonstrated, therefore a large matched-paired patient study was conducted to compare nodal staging accuracy and survival in patients treated with either SNB or ELND.

All patients treated at the Sydney Melanoma Unit (SMU) between 1983 and 2000 for a primary tumour ~ 1.5 mm in thickness and who underwent a SNB (n=775) or an ELND (n=1026) were evaluated. Two groups of 659 ELND and 659 SNB patients treated over the same time period were matched for age, sex and thickness of the primary melanoma, and compared for node involvement.

The most important predictors of node positivity in multivariate analysis of the matched pairs were tumour thickness (p<0.0001), ulceration (p=0.001), and age (p=0.002). The overall number of patients with positive nodes after ELND was 11.4% and after SNB 16.1%, which was a statistically significant difference (p=0.004). Overall survival after 3 years of follow-up was comparable for both groups.

Thus it is concluded that SNB identifies proportionally more lymph nodes containing metastatic melanoma than ELND in this retrospective matched-paired cohort analysis. Detailed pathological examination, recent improvements in immunohistochemical techniques and accurate identification of the lymph node field(s) by preoperative lymphoscintigraphy are all likely to be responsible for this increased accuracy. Irrespective of any effects on survival which may be demonstrated by presently ongoing clinical trials, SNB in combination with preoperative lymphoscintigraphy is desirable for all patients entering trials of adjuvant therapy in order to create more closely equivalent patient groups.

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Histamine dihydrochloride administered with Interleukin-2 increases survival duration in patients with ocular melanoma with liver metastases

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Background: Ocular melanoma (OM) is the most common intra-ocular malignancy, and it metastasizes to the liver in about two-thirds of patients (pts). This portends a poor prognosis and a median survival of only 2 to 7 months. Therapy for metastatic cutaneous melanoma (CM) has been largely ineffective in pts with OM, and these pts are usually excluded from clinical trials for metastatic CM. Results of a large, randomized phase III trial of a novel combination of IL-2 and histamine dihydrochloride (HDC) compared with IL-2 alone have recently been reported [Agarwala et al. Cancer Invest 19 (suppl 1): 81, 2001], and a significant survival benefit in pts with melanoma metastatic to the liver treated with the combination of HDC and IL-2 was noted. Methods: To examine the potential role of IL-2 and HDC specifically in pts with OM with liver metastases (OM-LM), a retrospective analysis of 35 pts with OM-LM enrolled in a randomized trial and in on-going phase II trial of combination IL-2 and HDC was performed. Pts received IL-2 (9 MIU/m2, bid, sc, days 1-2, weeks 1,3; and 2 MIU/m2, bid, sc, days 1-5, weeks 2, 4) with or without HDC (1.0 mg, bid, sc, days 1-5, weeks 1-4) for 4 weeks of a 6-week cycle. Results: 13 pts received IL-2 alone, and 22 pts received the combination of IL-2 and HDC. In the group receiving HDC + IL-2, the median age was 55 years (range 31-79), 7 (32%) pts were male, and high LDH levels (> ULN) were present in 6/15 (40%) pts. In the group receiving IL-2 only, median age was 64 years (range 25-75), 9 (69%) pts were male, and high LDH levels were present in 6/12 (50%) pts. The median survival for pts with OM-LM receiving IL-2 + HD was 229 days compared to 119 days for pts receiving IL-2 alone (p=0.0051). Conclusions: These results suggest that the benefit noted for pts with CM metastatic to the liver in the randomized phase III trial of IL-2 + HDC vs IL-2 alone was not restricted to CM but extended to those with OM-LM. Further trials in this subset of patients are planned.

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Early evaluation of tumour response to STI 571 with FDG-PET in patients with soft tissue sarcomas (STS)

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Evaluation of treatment response is currently based on changes in tumour volume measured on CT. New anti-cancer drugs often induce tumour growth