Methods: ZD1839 was given as a single, oral, daily dose from day 2 onwards, at one of two dose levels (250 or 500 mg). Gemcitabine (1250 mg/m2) was administered as a 30-min infusion on days 1 and 8, and cisplatin (80 mg/m2) as a 2-h infusion on day 1, after gemcitabine. Cycles were repeated every 3 weeks for a maximum of 6 cycles, or until disease progression, toxicity or patient (pt) refusal. Recruitment of 6-12 pts was planned at each ZD1839 dose level. Pharmacokinetic analyses were done during cycles 1 and 2.

Results: Between November 2000 and February 2001, 18 pts were enrolled (M:F 11:7; median [range] age, 59 [30-71] years; WHO performance status, 0 [4 pts], 1 [11] and 2 [3]). Primary tumours: non-small cell lung cancer (NSCLC) (8 pts), adenocarcinoma of unknown primary (ACUP) (3), oesophageal (3) and other (4). All pts were chemonaive for advanced or metastatic disease. Nine pts were included at each ZD1839 dose level and all pts were assessable for toxicity. Toxicity at the 250 mg dose level comprised: G1 skin rash (3 pts), G1 diarrhoea (3), G3 asthenia (1), G3 thrombocytopenia (1), G3 vomiting (1) and G4 asymptomatic short-lasting (2 days) elevated hepatic transaminases (1). At 500 mg, 4 pts experienced G3 diarrhoea and 1 pt had G4 asymptomatic elevation of hepatic transaminases. Skin rash was observed in 7 pts but was generally mild (G1 [3 pts], G2 [3] and G3 [1]). No other severe toxicity or treatment-related deaths were observed. Fifteen pts are evaluable for efficacy, to date (1 pt withdrew after 1 cycle, 1 pt had only pleural effusion and 1 pt too early). Six pts had PRs (NSCLC [4 pts], ACUP [1] and pancreatic [1]), 7 pts had SD, including 2 pts with MRs (mesothelioma and oesophagus) and 1 pt with an unconfirmed PR (NSCLC); 2 patients progressed. Pharmacokinetic results will be available by September 2001.

Conclusion: p The combination of ZD1839 with gemcitabine and cisplatin is feasible and well tolerated, and appears highly active. A three-arm, multicentre, Phase III trial of the same combination, in patients with advanced NSCLC, has completed accrual with >1000 patients having been enrolled.

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103 ORAL

A phase I dose escalation pharmacokinetic (PK) study of BAY 38-3441 administered as a short infusion once every three weeks

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Rationale: BAY 38-3441 is a camptothecin glycoconjugate that was designed to stabilize the lactone form of camptothecin in blood, thereby increasing the proportion of the lactone available for uptake by tumor cells.

Methods: BAY 38-3441 was administered as a single 30-minute intravenous infusion once every three weeks (q3wks) to patients with advanced refractory cancer. Patients received 20 (n = 3), 40 (n = 6), 67 (n = 3), 100 (n = 6), 140 (n = 3) and 210 (n = 3) mg/m^2/day q3wks BAY 38-3441. Plasma samples were taken at pre-defined time points for the determination of pharmacokinetic parameters, including C_{max}, AUC, t_{max}, $t_{1/2}$, and CL.

Results: Twenty-four patients (pts) with different solid tumor types have been accrued so far. The median age was 60 yrs (27–71), At 20 mg/m^2 1 pt developed brain metastases 16 days after dosing with BAY 38-3441. At 40 mg/m^2 1 pt with mCRC developed an increase of liver enzymes after the first dosing, but was considered disease-related rather than drug-related. At 67 mg/m^2 no TOX was observed. At 100 mg/m^2 1 pt developed bradycardia, hypotension, and loss of consciousness during drug infusion, and these conditions were considered possibly drug-related. No further TOX was seen. At 140 and 210 mg/m^2 no TOX has been observed so far. The following pharmacokinetic results were obtained.

PK parameters of BAY 56-3722 (free base of BAY 38-3441) and Camptothecin (means/SD)

Dose [mg/m^2]	20	40	67	100	140
BAY 56-3722					
C_{max} [mg/L]	1.85/1.47	4.27/1.33	9.38/1.27	7.39/1.36	13.1/1.63
AUC [mg*h/L]	1.50/1.71	4.83/2.20	20.3/2.02	8.52/1.73	16.2/3.03
$t_{1/2}$ [h]	1.10/1.69	2.65/1.44	9.20/2.51	4.31/1.69	10.2/1.28
CL [L/h]	19.2/1.67	13.8/2.16	5.26/1.85	21.4/1.60	13.3/3.16
Camptothecin					
C_{max} [µg/L]	3.39/1.58	16.8/2.50	15.3+	17.7/1.42	28.1/2.05
AUC (0-tn) [µg*h/L]	53.3/2.74	537/2.70	410+	346/2.34	591/3.88
$t_{1/2}$ [h]	22.9/1.33	33.4/1.23	–	26.8/2.74	37.8/1.67

+) median

Conclusion: BAY 38-3441 administered intravenously once every 3 weeks is generally well tolerated up to the 210 mg/m^2 dose level. The PK parameters show large interpatient variation; the MTD has not been reached.

104 ORAL

Pharmacokinetic (PK) and Pharmacodynamic Analysis of Aspirin Administered with Multi-targeted Antifolate (ALIMTA)

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Purpose: ALIMTA (pemetrexed disodium, LY231514) is an antimetabolite, which inhibits three folate dependent enzymes. ALIMTA has a similar structure to methotrexate and both are excreted unchanged in the urine. Salicylates have been shown to impair the renal clearance and enhance the toxicity of methotrexate and thus patients (pts) taking non-steroidal anti-inflammatory drugs have been excluded from ALIMTA trials. Myelosuppression with ALIMTA is most pronounced in pts with folic acid or B12 deficiency.

Methods: Pts with normal renal function (as determined by glomerular filtration rate) were randomized to receive asplrin (ASA) either with the first cycle of ALIMTA (Group 1) or with the second cycle (Group 2). After the first cycle the pt was crossed-over to the alternate treatment. ALIMTA was dosed at 500 mg/m2 day 1 of a 3 week cycle. Vitamin supplementation was mandated: Folic acid, at least 350 µg per day, beginning at least one week prior to the first dose of ALIMTA;1000 µg of intramuscular vitamin B12 one to two weeks prior to first day of treatment then every 9 to 12 weeks. ASA 325 mg was given orally every 6 hours starting 2 days prior to ALIMTA with the 9th dose taken 1 hour prior to infusion. Samples for PK analysis were obtained with the first and second cycles.

Results: 24 pts (15 men and 9 women) with solid tumors, a median number of 2 prior therapies and a median age of 52 years (range: 34 - 71) received at least two cycles. ASA was administered to 12 pts in their first cycle and 12 pts took ASA with their second cycle. Preliminary PK analysis was performed on the first 7 pts in each group and showed that ASA ingestion did not appear to alter the clearance, mean steady state volume of distribution (Vss - L/m2), or area under the curve (AUC - µg/mL*hr). The median nadir neutrophil count for Group 1 after the 1st and 2nd cycles were 2.0 and 1.44 respectively and were 2.85 and 1.81 respectively for Group 2. A paired analysis of each individual pt's nadir neutrophil count from cycles 1 and 2 demonstrates that ASA did not augment the myelosuppression of ALIMTA (p=0.199). There were 3 episodes of grade 3/4 granulocytopenia and all occurred in cycles without ASA. There were no episodes of febrile neutropenia.

Conclusions: ALIMTA administered with folic acid has minimal myelosuppression and is well tolerated even when administered with ASA. Preliminary PK analysis suggest that ASA ingestion does not alter the disposition profile of ALIMTA

105 ORAL

Extended temozolomide (TMZ) dosing schedules permit the administration of higher TMZ dose intensities and inhibit the DNA repair enzyme O6-alkylguanine DNA alkyltransferase (AGAT)

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Purpose: AGAT has been implicated in the development of resistance to alkylating agents such as TMZ. Preclinical studies of prolonged exposure to TMZ have shown progressive depletion of AGAT. Extended TMZ dosing schedules may therefore decrease resistance and enhance cytotoxicity. We have conducted two dose-escalation studies to evaluate extended TMZ dosing.

Methods: Two TMZ dosing schedules were studied: 7-days on/7-days off (7/7) and 21-days on/7-days off (21/7). All patients received escalating doses of TMZ from 50 mg/m2 up to 150 mg/m2 per day; patients on the 7/7 schedule were titrated to a maximum dose of 175 mg/m2 per day.

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.

106 ORAL

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.

107 ORAL

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

108 ORAL

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