greater tail moments than was observed for cells exposed to 5-FU. The results are consistent with FdUMP[10] displaying enhanced DNA-directed effects relative to 5-FU.

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The antitumor activity of OSI-7836 (GS7836, 4'-thio-araC), a nucleoside analog, in combination with cisplatin in human NSCLC xenografts in mice

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OSI-7836 (GS7836, 4'-thio-araC) is a nucleoside analog currently in Phase I trials for the treatment of solid tumors. OSI-7836 has been shown to have antitumor efficacy in a range of xenograft models, including non-small cell lung carcinoma (NSCLC). Cisplatin, a standard agent used in combination in the treatment of NSCLC, was selected for combination studies with OSI-7836 in three NSCLC xenograft models (Calu-6, H460, HOP-92). Each drug was administered alone at its predetermined optimal dose on a day 1,8 schedule (OSI-7836, 1000 mg/kg; cisplatin, 9 mg/kg) and at 60% of optimal dose of each drug for the combination (OSI-7836, 600 mg/kg; cisplatin, 5.4 mg/kg). In the H460 xenograft model, the combination of OSI-7836 and cisplatin demonstrated increased efficacy with a Log Cell Kill (LCK)= 2.4, compared to OSI-7836 alone (LCK=1.4) or cisplatin alone (LCK= 0.6). In addition, the combination produced cures in 2 of 8 animals compared to 0 of 8 animals for either single agent. In the HOP-92 xenograft model, LCK could not be determined for either group dosed with OSI-7836 due to the large number of cures, but the OSI-7836 plus cisplatin combination demonstrated improved efficacy (6 of 8 animals cured) compared to OSI-7836 alone (4 of 8 cures) and cisplatin alone (1 of 8 cures). Similarly, in the Calu-6 xenograft model, the combination of OSI-7836 and cisplatin demonstrated improved efficacy (7 of 8 cures) compared to OSI-7836 alone (2 of 8 cures) and cisplatin alone (1 of 8 cures). Further preclinical OSI-7836 and cisplatin combination studies are ongoing. These data demonstrate that OSI-7836 can be combined effectively with cisplatin to improve the antitumor efficacy in lung xenograft models, supporting the investigation of this combination in the clinic for NSCLC.

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Phase II trial of edatrexate in adult patients with metastatic soft tissue sarcomas, an Eastern Cooperative Oncology Group (ECOG) final report

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Edatrexate (EDX) is a water soluble anti-folate, formed by modification of the N10 position of 4-amino-folate. Based on promising preclinical and clinical data for soft tissue sarcoma (STS) (Casper et al. Cancer 1993;72:766-770), ECOG performed a phase II study of EDX as first line chemotherapy in metastatic STS. Wasserheit, C. et al (ASCO, 1998) reported preliminary data. All types of adult STS were allowed, with the exception of synovial cell sarcoma (competing trial). EDX was given as an intravenous infusion of 80 mg/m^2 weekly for 5 weeks, followed by dosing every other week. Starting week 7, doses were escalated every other week by 10 mg/m^2 unless toxicity occurred. Of the 46 patients entered, two were ineligible. Patients' histologies included 16 leiomyosarcomas, 7 MFH, 5 spindle cell tumors, 4 liposarcomas, and the remainder with various other histologies. For the 44 eligible patients, based on an intent to treat analysis, the response rate was 14% (95% confidence interval 5-27%), including 5 partial responses 11% (95% confidence interval 4-27%), and 1 complete response 2%. The duration of partial responses ranged from 54 to 598 days with the complete response continuing at last follow up. At a median follow-up period of 18.2 months, the median survival was 14.5 months. For the 45 patients with toxicity data, two toxic deaths occurred, which may have been EDX related: hemorrhage; pneumonia. Grade 3 or 4 toxicity occurred in 29% of patients. Most common toxicities were liver (11%), stomatitis (9%), anemia (9%), nausea (7%), arthralgias (7%), and less than 5% included leukopenia, thrombocytopenia, vomiting, diarrhea, and fatigue. In conclusion, response rates and durations, survival and toxicity are comparable with that achieved by chemotherapy considered "standard of care." This study population had a high proportion of patients with unfavorable risk factors for response to chemotherapy, including 36% leiomyosarcoma, 42% older than 60 years and 45% with liver metastases. Further EDX study is justified given these results and the limited efficacy of currently available therapy.

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A pharmacokinetic (PK) phase I (PI) study of ZD9331 and carboplatin in relapsed ovarian cancer (ROC) with a pharmacodynamic (PD) endpoint

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ZD9331 is a rationally designed, specific non-polyglutamatable thymidylate synthase (TS) inhibitor that is active against ROC in phase I/II trials (Plummer et al, Proc. Am. Soc. Clin. Onc., 1999: Rader et al, Annals Oncol, 11: 83; 2000). In light of broad sensitivity of human ovarian tumour cell lines to ZD9331 and non cross resistance to platinum based drugs (Jackman et al, Biochem Biophys Acta, in press) we studied the combination ZD9331/carboplatin in a PI PK & PD study in ROC. Eligible patients were 18 yrs or over, with a histological diagnosis and radiological evidence of ROC, and a platinum treatment - free interval of at least 6 months. Up to 3 prior lines of chemotherapy were permitted. Carboplatin was administered on day 1 of each 21day cycle (60-min IV infusion) at a fixed dose of AUC5. ZD9331 was given on day 1 (2 hrs after carboplatin, 30-min IV infusion) and day 8 of each 21day cycle. Thirteen patients have been enrolled to date (median age of 57), treated with ZD9331 at 4 dose levels, 40 mg/m^2(1), 65 mg/m^2(2), 85 mg/m^2(3)and 100 mg/m^2(4). No grade 3 or 4 toxicities were seen at dose level 1. One patient had grade 3 neutropaenia at level 2, and 1 patient had grade 3 neutropaenia at level 3. Dose limiting toxicities were seen in 2 patients at 100 mg/m^2 (grade 4 neutropaenia $>$ 7 days, and grade 4 fatigue $>$ 7 days). Plasma deoxyuridine (measured by HPLC in 6 patients in dose levels 1 and 2) was elevated indicating TS inhibition to at least day 12. Plasma ZD9331 was measured by ELISA, using a specific ZD9331 rabbit polyclonal antibody. Carboplatin was assayed by atomic absorption spectrometry. There was no PK interaction between the 2 drugs as ZD9331 PK data were similar to previous monotherapy studies, and measured AUC of carboplatin corresponded with that administered (WinNonlin professional, compartmental analysis). Antitumour activity was observed in 4/13 patients. The likely recommended phase II dose (carboplatin AUC5, ZD9331 85mg m^2) is being expanded to 6 patients with further PK and PD evaluation at this dose level. We conclude that this combination is well tolerated, TS inhibition is achieved at doses below the maximum tolerated dose, and antitumour activity is observed.

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Phase I and pharmacokinetic study (PK) of the combination of multitargeted antifolate pemetrexed (ALIMTA) with irinotecan (CPT-11) in patients with advanced malignancies

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Inhibition of key enzymes involved in folate metabolism remains an attractive therapeutic strategy. Pemetrexed, pyrrolopyridimine based antifolate is a potent inhibitor of multiple folate-dependent enzymes including thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase and has broad-spectrum antitumor activity. Preclinical evidence of synergy and minimally overlapping toxicity profiles served as the rationale for this clinical evaluation of the combination of pemetrexed and CPT-11. The feasibility of administering this combination is being evaluated in a phase I trial. Pemetrexed is given IV over 10 min followed by CPT-11 as a 90-min IV infusion every 3 weeks. 23 patients received 75 courses at the following pemetrexed/CPT-11 doses (mg/m^2) (patients/courses): 300/175 (3/13), 300/250 (6/22), 400/250 (9/21), 500/250 (5/19). Myelosuppression was the principal toxicity in this group of patients. Febrile neutropenia was seen at 300/250 (1 patient) and grade 4 vomiting at 400/250 (1 patient)(DLT). Other non-dose-limiting toxicities were diarrhea and skin rash. The protocol was then amended to include 'nutritional' quantities of folic acid (FA) (400 mcg/d) and vitamin B12 (1mg/9 weeks) supplements so as to reduce pemetrexed-induced toxicity and allow further dose-escalation. Doses explored with FA and B12 are 450/250 (4/41), 500/250 (9/61) and 500/300 (4/21). Demographics: median age- 58 (30-77); 30 M/10 F; PS 0-1(36) and PS 2(4). Primary tumors: Colorectal (10), Mesothelioma (10), Lung (6), Pancreas (3), Hepatobiliary (3) and others (8). One febrile neutropenia (DLT) was seen at 500/300 and accrual continues at this dose. One partial response in a patient with a 5-FU-refractory metastatic rectal cancer and 3 minor responses in patients with ampullary,

colorectal and carcinoid tumors have been observed. Disease stabilization has been seen in 7 /10 mesothelioma and 3/6 NSCLC patients with mean times to progression of 5.5+ and 4.5 months respectively. The PK behavior of the combination of pemetrexed and CPT 11 is presently being analyzed and will be available for presentation at the meeting. This data denotes that administering clinically relevant single-agent doses of pemetrexed and CPT-11 in combination is feasible with FA and B12, with minimal toxicity. Coupled with the preclinical data, these results provide the rationale for continued disease-directed evaluation of this combination.

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NCIC CTG IND.147: A first in man dose escalation and pharmacokinetic study of the novel nucleoside analog OSI-7836 given in a day 1 and 8 schedule

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Background: OSI-7836 (previously GS-7836, 4-thio-araC) is a nucleoside analog with a number of favorable characteristics. It is a weak substrate for both deoxycytidine kinase and deaminase resulting in reduced inactivation and prolonged intracellular activity. In several xenograft models antitumour effects were greater than gemcitabine at equitoxic doses. Toxicity in non-clinical models is consistent with that expected for this class of compounds.
Methods: An accelerated phase I design was used; starting dose was 100mg/m^2 and 1-2 patients (pts) were entered at each dose level (DL) until > grade 1 clinically relevant toxicity was encountered, after which 3-6 pts were entered. Dose limiting toxicity (DLT) and recommended phase II dose followed standard criteria. All patients underwent full clinical, laboratory and pharmacokinetic testing.
Results: Nine pts have been entered to four DLs to date (100, 200, 400 and 600mg/m^2). Median age was 55 years; 7 pts had a performance status of 1 or 2; 5 pts were female; all pts had had prior chemotherapy; 3 pts had colorectal cancer, 2 pts NSCLC, and 4 pts had other primaries. Grade 1 or 2 emesis necessitated the introduction of prophylactic 5-HT3 antiemetics at DL 3. Toxicities included mild transaminase increases and diarrhea, rash, lymphopenia, nausea and vomiting, herpes simplex reactivation and fatigue. No hematologic toxicity has been seen to date other than lymphopenia seen in all dose levels. At the 4th DL (600mg/m^2) both patients entered experienced protocol defined DLTs. These included grade 3 rash, fever, seizure, and grade 3 fatigue (both patients had lymphopenia and herpes simplex). The 5th dose level has opened at 500mg/m^2. One pt with lymphoepithelioma of the thymus showed evidence of tumour shrinkage in pulmonary lesions. Pharmacokinetic analyses are ongoing.
Conclusions: OSI-7836 is a promising nucleoside analog with excellent activity in nonclinical solid tumour models. Early evidence of antitumour activity has been seen in this clinical study.

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Pemetrexed translational research in patients with previously untreated breast cancer

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Pemetrexed (ALIMTA) is a novel antifolate with demonstrated activity in locally advanced and metastatic breast cancer. Molecular targets include folate dependent enzymes involved in both pyrimidine and purine neosynthesis. The primary objective of this Phase II trial was to determine whether a correlation exists between expression of targeted molecular markers and clinical response. We administered single agent pemetrexed in the neoadjuvant setting to patients (pts) with advanced disease. Pts could have either positive or negative ER/PR receptor status, or any menopausal status. Tumor biopsies were taken prior to drug exposure, 24 hrs after the initial dose, and following [up to] three 21-day cycles of pemetrexed. Pemetrexed was dosed at 500 mg/m^2 IV over 10 minutes. Low-dose folic acid, vitamin B12, and dexamethasone were given to all pts. Sixty-one pts enrolled and were treated on the trial. Nineteen pts achieved partial response, for an overall response rate of 31%. Tissue analysis is ongoing. Tumor tissue analyses have been completed for mRNA expression of thymidylate synthase (TS). Analyses of dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), p53, and erbB2 by RT-PCR; for immunohistochemical staining (IHC) of TS, DHFR, and GARFT; for p53 mutations with single-stranded conformation polymorphism (SSCP); and for c-erbB2 expression with fluorescent in-situ hybridization (FISH), are all ongoing. Preliminary results on TS expession levels over time are displayed in Table 1:

Table 1: Mean TS level by study best response over time

Best Study Response	Mean TS Baseline	Mean TS Within 24hr of Dose 1	Cycle 3
Responders	44.0 (SE=8.3; n=17)	101.1 (SE=22.5; n=15)	40.1 (SE=9.5; n=15)
Stable Disease	110.1 (SE=32.4; n=31)	168.5 (SE=49.1;n=26)	113.8 (SE=31.5; n=20)
Progressive Disease	169.6 (SE=49.0; n=6)	220.0 (SE=125.7; n=5)	286.0 (SE=61.3; n=4)

These early results indicate that -TS expression at baseline may correlate with clinical response and that after 3 cycles of therapy, pemetrexed does not appear to upregulate TS in those patients who benefit from therapy. Analyses of biopsies obtained at baseline and subsequent to drug exposure are anticipated to provide information on the modulation at both the gene and functional levels. Transcript profiling is planned to expand on these observations, and will likely yield further correlations. The complete correlative analysis of the relevant biomarkers and their relationships to response is in progress and will be reported.

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A phase 1 and pharmacokinetic study of TAS-106 administered weekly for 3 consecutive weeks every 28 days in patients with solid tumors

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Many chemotherapeutic agents target the S phase of the cell cycle and are therefore theoretically more effective against rapidly proliferating tumors than slowly growing tumors. Most solid tumors are slow-growing and therefore S-phase specific anti-tumor drugs have limited efficacy. A chemotherapeutic agent that affects mechanisms other than DNA synthesis would be beneficial. The antitumor nucleoside 3'-C-ethynylcytidine (ECyd, TAS-106) was designed to specifically inhibit RNA synthesis. TAS-106 inhibits RNA synthesis in a dose-dependant manner by blocking RNA polymerases I, II, and III. TAS-106 is phosphorylated by cytidine/uridine kinase, which is preferentially distributed in malignant cells rather than normal cells. Cellular metabolism of TAS-106 leads to the production of one active metabolite, ECTP, which has a prolonged intracellular half-life, even after short-term exposure to TAS-106.Therefore intermittant (weekly) treatment with TAS-106 may be preferred. In vitro, TAS-106 has demonstrated cytotoxicity 300 times greater than that of 5-FU against human lung, colorectal, gastric, pancreas and breast cancer cells. The objectives of this study were: (1) to determine the recommended Phase II dose and the dose-limiting toxicity (DLT) of TAS-106 administered weekly for 3 consecutive weeks;(2)determine toxicity and reversibility of toxicity of TAS-106 administered on this schedule;(3)to investigate the clinical pharmacokinetics (PK)and pharmacodynamics(PD)of TAS-106,and(4)document any antitumor activity observed. The starting dose was 0.22 mg/m^2 per dose; dose escalation has continued to 3.96 mg/m^2/dose. The study utilized a "3 + 3" dose escalation design, and escalation was in 100% increments unless grade 2 or higher toxicity was observed. To date, 21 patients (pts) have been enrolled, 17 are evaluable for response and toxicity, 1 inevaluable, and 3 too early. The median age was 51 (12 male, 9 female, median Zubrod PS 1, primary tumor:colorectal 13,other 8.Two pts demonstrated stable disease (SD) for 2 full courses, and fifteen pts showed PD.One pt treated at the 3.96 mg/m^2/week experienced Grade 3 peripheral neuropathy after course 2, that was considered a DLT. Grade 1-2 toxic effects during course 1 included palmar skin peeling(5 pts, 29%), peripheral neuropathy (5 pts, 29%),fatigue(2 pts, 12%),and anemia 1 pt(<10%).Skin peeling was mild (grade 1) and generally occurred over the distal digits, and the entire palmar surface in 1 pt. Blood and urine samples for PK/PD analyses were collected on Day 1 for all consenting pts, and on Day 15 for pts after the first occurrence of a DLT.A recommended Phase II dose has not been identified and updated PK analysis,response and toxicity data will be presented.