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.

66

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

G. Goss[1], L. Siu[1], J. Powers[1], L. Adams[2], K. Trader[2], L. Seymour[1].
[1]NCIC CTG, IND Program, Kingston, Canada; [2]OSI Pharmaceuticals, Boulder, Colorado, USA

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.

67

Pemetrexed translational research in patients with previously untreated breast cancer

A.-R. Hanauske[1], P. Paoletti[2], C.H. Robb[2], R.D. Hockett[2], C. Niyikiza[2].
[1]St. Georg Hospital, Leiter der Sektion Onkologie, Hamburg, Germany; [2]Eli Lilly and Company, Indianapolis, United States

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.

67A

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

M. Thomas[1], A. Mita [2], L. Hammond [3], M. Iwasaki[1], Y. Lassere[1], G. Bland[1], J. Norris[3], M. Beeram[3], E. Rowinsky[3], J. Abbruzzese[1]. [1] *University of Texas M.D. Anderson Cancer Center, Department of Gastrointestinal Medical Oncology, Houston, USA; [2] Taiho Pharmaceutical Co., Ltd, Clinical Oncology Department, Tokyo, Japan; [3] Cancer Therapy and Research Center, Department of Clinical Research, San Antonio, USA*

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.