were not attempted. Intra-patient escalation was permitted in 18 studies. Definitions of dose limiting toxicity (DLT) varied widely, with no clear pattern over time or between SA and CS; only 3 studies incorporated prophylactic use of colony-stimulating factors.

Trial Results: Sixty-seven studies are completed with data available from 63, which recruited 1939 patients (pts). The median (M) number of dose levels (DL) was 4 (range 2-14); significantly more DL were explored for SA than CS (M 6.5 vs 3; P<0.001), and for conventional compared to more aggressive dose escalation regimens (4 vs 7; P=0.01). Fewer pts per study were treated below the RD in combination than in SA trials (7 vs 16 patients, P=0.13), and in trials using more aggressive dose escalation strategies (12 vs 15; P= 0.15). The first dose level at which DLT ocurred was close to the final MTD (M ratio 1.0). There were 16 toxic deaths (8 in SA and 8 in CS). Although patients appeared at greater risk in CS and more aggressive SA studies, this mirrors the greater proportion of pts treated at or above the RD.

Conclusion: The number of Phase I trials of anti-cancer drugs, in particular combination trials, has increased. More aggressive study designs can reduce the size of Phase I trials, limit the number of patients treated at doses below the RD and appear to have an appropriate safety profile.

247 POSTER

Phase I study of intermittent (weekly) topotecan in non small cell lung cancer (NSCLC)

T. Nogami[1], S. Negoro[2], N. Masuda[3], S. Kudoh[4], K. Nakagawa[1], M. Fukuoka[1]. [1] *Kinki University School of Medicine, 4th Department of Internal Medicine, Osaka, Japan;* [2] *Osaka City General Hospital, Respiratory Medicine and Oncology, Osaka, Japan;* [3] *Osaka Prefectural Habikino Hospital, Department of Internal Medicine, Osaka, Japan;* [4] *Osaka City University School of Medicine, 1st Department of Internal Medicine, Osaka, Japan*

Introduction: Topotecan (T) is a water soluble, semisynthetic analog of the alkaloid camptothecin, which is a specific inhibitor of topoisomerase I. Clinically, it has antitumor efficacy in small cell lung cancer and ovarian cancer when administered as a 30-minute intravenous infusion given daily for 5 consecutive days, repeated every 3 weeks. In preclinical studies, the tumor growth inhibition rates were similar between 5 consecutive days and intermittent administration at the same total dose.

A Phase I study was undertaken to determine the MTD and recommended dose of T when administered intermittently to patients (pts) with NSCLC, previously treated and untreated, and to study the pharmacokinetics.

Method: T was administered once a week (Days 1, 8 and 15), by 30-minute intravenous infusion; the cycle was repeated every 4 weeks. The dose was escalated from the starting dose of 4 mg/m2 in 2 mg/m2 increments. At least three pts were treated at each escalated dose level.

Results: 12 pts were given 20 cycles of treatment (median 2, range 1-2). No dose limiting toxicities (DLTs) were observed at 4 mg/m2 in previously treated pts. At 6 mg/m2, DLTs were observed in all three previously treated pts (1 patient with of Grade 4 febrile neutropenia, and 2 pts with Grade 3 infection without neutropenia). Therefore, the MTD and recommended dose for the intermittent dose schedule in previously treated pts were 6 and 4 mg/m2, respectively.

In previously untreated pts, no DLT was observed at 6 mg/m2, and only one patient showed DLT (Grade 4 neutropenia persisting for at least 3 days) at 8 mg/m2. However, 2 pts including the one with DLT could not receive the treatment on day 15 because their hematological parameters failed to show recovery to the predetermined level. On the basis of these results, MTD was estimated at 8 mg/m2 and the recommended dose at 6 mg/m2 in previously untreated pts.

No differences were noted in pharmacokinetic parameters between previously treated and untreated pts at 6 mg/m2. Urinary excretions of T (lactone plus carboxylate form) were similar at two dose levels in both subgroups of pts, and no altered elimination was observed.

Regression of the primary lung tumor and/or lymph node metastases was observed in some of the previously treated and untreated pts, but none of them achieved PR or CR.

Conclusions: Further investigation is necessary to determine the efficacy and dosing schedule of T for NSCLC.

248 POSTER

Phase I-II and pharmacokinetic study combining gemcitabine (GEM) with oxaliplatin (OX) in patients (pts) with advanced non-small-cell lung (NSCLC) and ovarian carcinoma (OC)

S. Faivre[1], E. Raymond[1], F. Lokiec[2], C. Monnerat[1], S. Novello[1], P. Pautier[1], C. Lhommé[1], L. Kayitalire[3], J.P. Armand[1], T. Le Chevalier[1]. [1] *I. Gustave-Roussy, Médecine, Villejuif, France;* [2] *I. René Huguenin, Pharmacology, St. Cloud, France;* [3] *Eli Lilly, France*

Background: GEM and OX combinations have in vitro synergy, with a schedule dependency favoring GEM given prior OX (Faivre, 1999).

Aim: considering the non-overlapping toxicity for both drugs, and activity of GEM and OX as single agent in NSCLC and OC, we designed a phase I-II outpatient combination schedule to establish the maximal tolerated dose (MTD), the dose limiting toxicity (DLT), the recommended dose (RD), the pharmacokinetics profile, and to evaluate the antitumor activity of GEMOX in pts with potentially sensitive tumor i.e. advanced NSCLC and OC.

Methods: GEM was administered as a 30-minutes infusion followed by OX infused over 2 hours on D1 and D15 every 4 week (wk)-cycle (cy). Doses of GEM/OX were 800-1500/70-100 mg/m*, respectively. Results: 44 pts (M/F: 26/18, median age 55, 61% PS 0) received a total of 180 cycles. There were 35 NSCLC (5 platinum-pretreated, 2 resistant) and 9 OC pts (all platinum-pretreated, 2 resistant).

Toxicity: 44 pts were evaluable for acute and 32 pts for chronic toxicity. No acute DLT occurred at cy 1. Hematologic toxicity was < Gr3 except for 9 episodes of Gr3-4 non febrile neutropenia in 7 pts, and 3 episodes of Gr3-4 thrombocytopenia in 2 pts. Other toxicities were mild to moderate. Transient Gr3 asthenia occurred in 2% of cy. Eight pts (3 pretreated, 5 chemonaive) experienced cumulative Gr3 OX-related neurotoxicity requiring treatment discontinuation for 4 pts at cy 5.

Activity: Among 37 evaluable pts, 13/28 NSCLC and 3/9 OC pts showed an objective responses (1 CR, 15 PR including 3 PR in platinum-resistant pts). Pharmacokinetics suggested no drug interaction.

Conclusion: GEM/OX combination could be safely administered on a D1 and D15 schedule without acute toxicity, at the RD of 1500/85 mg/m2 q2 weeks. Promising antitumor activity is reported in pts with NSCLC and platinum-pretreated OC, deserving further evaluation of GEMOX.

249 POSTER

A phase IB study evaluating the scheduling and pharmacokinetic interaction between alimta and gemcitabine in patients with advanced cancer

A. Adjei[1], C. Erlichman[1], R. Johnson[2], S. Alberts[1], J. Sloan[1], R. Goldberg[1], H. Pitot[1], J. Reid[1], P. Burch[1], J. Rubin[1]. [1] *Mayo Clinic, Rochester, MN, USA;* [2] *Eli Lilly and Company, Indianapolis, IN, USA*

ALIMTA (pemetrexed disodium) is a novel multi-targeted antifolate agent, which inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR) and the purine biosynthetic enzyme, glycinamide ribonucleotide formyl transferase (GARFT). ALIMTA is active in breast, lung, bladder and GI malignancies in early clinical trials. We have completed a phase I study in which ALIMTA was administered 90 minutes after gemcitabine (GEM), based on a demonstration of sequence-dependent in vitro cytotoxic synergy. In the present trial, we have investigated the simultaneous administration of ALIMTA and GEM. 14 patients with solid tumors (9 male, 5 female; median age 60 (36-74); median ECOG PS 1) have received 70 courses of treatment at the MTD of our initial phase I study (GEM 1250 mg/m2 days 1 and 8 and ALIMTA 500 mg/m2 on d8). Cycles are repeated every 3 weeks. ALIMTA alone was given in cycle 1 to allow for pharmacokinetics (PK) sampling to evaluate the effect of GEM on the disposition of ALIMTA and vice versa. Folic acid/vitamin B12 supplementation was not included in this study. Neutropenia was the most common toxicity (grades 3 and 4 in 28 and 15% of patients in cycle 1, respectively). Non-hematologic toxicities were mild to moderate and included anorexia, nausea, fatigue, fever, rash, and pulmonary toxicity. 1 PR was noted in a patient with NSCLC. 8 patients had disease stabilization for 5 or more cycles (4 patients with 8 or more cycles). The change in schedule of drug administration does not appear to have any significant effect on the toxicity or efficacy of this combination. Results of PK studies will be discussed. Supported by grants from NCI (CA77112) and Eli Lilly and Company.