*865

**PHASE I AND PHARMACOKINETIC (PK) STUDY OF THE GLYCINAMIDE RIBONUCLEOTIDE FORMYLTRANSFERASE (GARFT) INHIBITOR LY309887 AS A BOLUS EVERY 3 WEEKS WITH FOLIC ACID (FA).** *C. Aylesworth, S.D. Baker, J. Stephenson, P. Monroe, I. Sanchez, J. Walling, R. Johnson, D. Von Hoff and E. Rowinsky. Brooke Army Medical Center and Cancer Therapy and Research Center, San Antonio, TX; Eli Lilly Pharmaceuticals.*

LY309887 is a potent inhibitor of GARFT that catalyzes the first two folate-dependent steps of *de novo* purine biosynthesis. Compared to Lometrexol, a "first generation" GARFT inhibitor that induced delayed and cumulative clinical toxicity, LY309887 is less extensively polyglutaminated and 9-fold more potent at inhibiting GARFT. Also, LY309887 showed greater affinity for folate receptor isoforms in malignant compared to liver tissue. Co-administration of LY309887 and FA resulted in an increased therapeutic index in mice. The objectives of this study were to assess the feasibility of administering LY309887 as an iv bolus every 21 days with FA 5 mg/day for 5 days starting 2 days before LY309887 in patients (pts) with advanced solid cancers and to determine the maximum tolerated dose (MTD) and both toxicity and PK profiles. To date, 14 pts have received drug at the following levels (mg/m$^2$): 1 (3 pts/ 8 courses (Cs)), 2 (1 pt/ 2Cs), 4 (1 pt/ 4Cs), 8 (4 pts/ 7Cs), 12 (2 pts/ 2Cs) and 6 (3 pts/ 6Cs). At 12 mg/m$^2$, no toxicity occurred during C1, but C2 was associated with grade 4 neutropenia and grade 3 thrombocytopenia with recovery at day 64. Subsequent experience at 8 mg/m$^2$ resulted in grade 4 neutropenia (C1) and grade 4 thrombocytopenia (C2). Modest neurosensory toxicity has also been noted in 4 pts across all dose levels. During C1, both $C_{max}$ and $AUC_{0-24h}$ values increased linearly with dose. Approximately 63 % of drug was excreted unchanged in urine. The $t_{1/2}$ and Cl were dose-independent with mean values of 4.3 hours and 92.7 ml/min, respectively. Increasing levels of drug exposure were associated with greater platelet toxicity. Interpatient variability in FA exposure was observed with $C_{max}$ and $AUC_{0-24h}$ values ranging from 500–2330 ug/ml and 77–220 ug*hr/ml, respectively, which may have contributed to large interpatient variability in toxicity. To date, 3 pts have received 6 Cs at the 6 mg/m$^2$ without grade 3/4 hematologic toxicity. This dose level will be further evaluated to determine the MTD that permits repetitive dosing with acceptable toxicity and describe the relationship between PK and toxicity.

*866

**A PHASE I AND PHARMACOKINETIC (PK) STUDY OF THE MULTITARGETED ANTIFOL (MTA) LY231514 WITH FOLIC ACID.** *L. Hammond, M. Villalona-Calero, S.G. Eckhardt, R. Drengler, C. Aylesworth, T. Johnson, M. Hidalgo, G. Rodriguez, S. Diab, P. Monroe, D. Thornton, D. Von Hoff, and E. Rowinsky. Cancer Therapy and Research Center and Brooke Army Med Center, San Antonio, TX, and Eli Lilly Company, Indianapolis, IN.*

MTA (LY 231514) is a new antifol that inhibits multiple folate-dependent enzymes, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. Initial phase I trials demonstrated major antitumor responses when MTA was given as a 10 min i.v. infusion, however, myelosuppression precluded dose escalation above 500–600 mg/m$^2$. Since preclinical studies indicated that folic acid supplementation increases the therapeutic index of MTA, the feasibility of administering folic acid 5 mg daily for 5 days starting 2 days before MTA in minimally- and heavily-pretreated pts was evaluated to determine if folic acid supplementation ameliorates the toxic effects of MTA, permitting significant dose-escalation above the recommended phase II dose of MTA alone. Thus far, 21 pts with solid cancers have received 55 courses at the following dose levels: 600, 700, and 800 mg/m$^2$. Drug-related toxicities have included neutropenia, anemia, and thrombocytopenia, which have been more severe in heavily-pretreated pts. Other toxicities (grade 1–2) include rash, somnolence, fatigue, leg edema, and diminished renal function manifested by a decrease in creatinine clearance. One pt taking a non-steroidal anti-inflammatory agent experienced severe toxicities at the 800 mg/m$^2$ dose, which resolved after administration of leucovorin and thymidine. One partial response in a pt with metastatic colon cancer has been observed. PK and vitamin (folic acid) metabolite profiles were done during cycles 1 and 3 at 600 and 800 mg/m$^2$. To date, serum folic acid levels do not appear to be related to toxicity, but homocysteine was significantly elevated in the pt with severe toxicities at the 800 mg/m$^2$ dose. Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m$^2$ and accrual continues at 700 and 900 mg/m$^2$, respectively. These results indicate that folic acid supplementation appears to permit MTA dose escalation.

*867

**A PHASE I AND PHARMACOKINETIC (PK) STUDY OF TRIMETREXATE (TMTX) IN CANCER PATIENTS (PTS) WITH RENAL (RI) OR HEPATIC IMPAIRMENT (HI).** *M.L. Gillison, S. O'Reilly, R.C. Donehower, D.A. Noe, M. Duerr, L.B. Grochow. Johns Hopkins Oncology Center, Baltimore, MD.*

The antifolate TMTX is undergoing phase III evaluation with 5FU in colon cancer pts. In phase I studies significant interpt variability in toxicity was observed and was related to hepatic function. A phase I and pk study was performed in pts without and with RI or HI. Cohorts included: controls (creatinine clearance (CrCl) >70mL/min total bilirubin (TB) <1.6mg/dL); pts with mild RI (CrCl 40–60 mL/min); pts with moderate RI (CrCl 20–40mL/min); pts with severe RI (CrCl < 20mL/min); and pts with HI (TB > 2.0 mg/dL, albumin < 3.6mg/dL). TMTX was given iv over 30 min every 21 days. Doses were escalated from 140 mg/m$^2$ in controls and pts with mild RI; from 105 mg/m$^2$ in pts with moderate RI; and from 70 mg/m$^2$ in pts with severe RI or HI. Dose limiting toxicities (DLT) were grade IV neutropenia, thrombocytopenia, mucositis and rash. Ten DLT occurred in 3/17 controls who received 62 cycles of TMTX (range 105–275 mg/m$^2$); 27 DLT occurred in 9/13 RI pts over 61 cycles (range 35–175 mg/m$^2$); and 10 DLT occurred in 4/11 HI pts over 26 cycles (range 35–105mg/m$^2$). Dose was reduced to 35mg/m$^2$ in HI pts, after the first 2 pts had severe DLT. Prior pelvic irradiation or nitrosourea therapy increased the risk of DLT ($p = 0.06$). Single clinical measures of RI or HI did not correlate with TMTX pk ($r < 0.5$). However, mean TMTX clearance was lower in HI pts compared to controls (36.5 vs. 64.3 mL/min; $p = 0.016$). Increasing hematologic toxicity was observed with increasing TMTX AUC in controls and RI pts but not in HI pts, suggesting variable metabolism of TMTX. TMTX pk is altered in HI pts, for whom a starting dose of 35 mg/m$^2$ is recommended. A dose of 105mg/m$^2$ is recommended for pts with CrCl of 20–60mL/min. Subsequent dose escalations may be considered for pts without DLT. Supported by grants no. NO1 CM 07302 and CA 01709-03 (NIH)

*868

**INTERIM RESULTS OF A PHASE I TRIAL SUGGEST THAT TOMUDEX® (RALTITREXED) MAY ACT SYNERGISTICALLY WITH 5-FLUOROURACIL (5-FU) IN PATIENTS WITH ADVANCED COLORECTAL CANCER (ACC).** *K.H. Dragnev, G.K. Schwartz, J. Bertino, N. Kemeny, L. Saltz, A. Sugarman, D.K. Kelsen, W. Tong, C. Lowery. Memorial Sloan-Kettering Cancer Center, New York, NY and Zeneca Pharmaceuticals, Wilmington, DE.*

'Tomudex' is a direct inhibitor of thymidylate synthase with activity in ACC. Synergy has been demonstrated in cell lines when 'Tomudex' is followed by 5-FU. 21 patients were given 'Tomudex' followed 24 hours later by 5-FU every 21 days. All but five had failed prior modulated 5-FU therapy:

| Dose, mg/m$^2$ 'Tomudex'/ 5-FU | OR (duration months) | SD (duration months) | PD | Mean 5-FU Cmax (μM) | Mean 5-FU AUC (μM/min) |
|---|---|---|---|---|---|
| 0.5/900 | 1PR(5.9)* | 1 (3.7) | 1 | 306 ± 32 | 10498 ± 1119 |
| 1.0/900 | 0 | 2 (3.8, 13–1) | 1 | 278 ± 52 | 9176 ± 611 |
| 1.5/900 | 0 | 2 (6.0, 9.6) | 1 | 166 ± 86 | 5362 ± 2591 |
| 2.0/900 | 1PR(5.2)* | 1 (6.6) | 1 | 216 ± 27 | 6794 ± 1167 |
| 2.5/900 | 0 | 3 (5.5, 6.5, 3.0) | 0 | 648 ± 74 | 19593 ± 6074 |
| 3.0/900 | 1CR(9.5+) ** | 0 | 2 | 528 ± 136 | 16360 ± 1452 |
| 3.0/1050 | 0 | 1 (3.0+) | 2 | 667 ± 116 | 20979 ± 6046 |
| Total | 3 | 10 | 8 | | |

*received prior 5-FU based therapy, **received no prior therapy

Therapy was well tolerated. There was no grade 3 or 4 mucositis; the most common toxicity was neutropenia. Eighteen patients are alive. Clinical activity, including disease stabilization, was seen in patients previously treated with 5-FU. Pharmacokinetic data suggest synergy between 'Tomudex' and 5-FU. At 'Tomudex' doses above 2.0 mg/m$^2$ DLT has not yet been reached. Dose escalation continues. Tomudex is a trademark and property of Zeneca Ltd.