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A PHASE I AND PHARMACOKINETIC (PK) STUDY OF THE MULTITARGETED ANTIFOL (MTA) LY231514 WITH FOLIC ACID (Meeting abstract).

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Sub-category: [Other](#)

Category: Developmental Therapeutics - Clinical Pharmacology and Immunotherapy

Meeting: [1998 ASCO Annual Meeting](#)

Abstract No: 866

Author(s): L Hammond, M Villalona-Calero, SG Eckhardt, R Drengler, C Aylesworth, T Johnson, M Hidalgo, G Rodriguez, S Diab, P Monroe, D Thornton, Hoff D Vo, E Rowinsky

Abstract:

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/m². 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/m². 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/m² 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 to 800 mg/m². 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/m² dose. Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m² and accrual continues at 700 and 900

mg/m2, respectively. These results indicate that folic acid supplementation appears to permit MTA dose escalation.

► Associated Presentation(s):

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Meeting: [1998 ASCO Annual Meeting](#) Abstract No: 715 First Author: [Stewart C](#)
Category: Developmental Therapeutics - Clinical Pharmacology and Immunotherapy - [Other](#)

2. [POPULATION PHARMACOKINETIC \(PK\) MODEL FOR TOPOTECAN \(TPT\) \(Meeting abstract\).](#)

Meeting: [1998 ASCO Annual Meeting](#) Abstract No: 716 First Author: [PB Laub](#)
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3. [CYCLOSPORIN A \(CsA\) STRONGLY ENHANCES ORAL BIOAVAILABILITY OF PACLITAXEL \(pac\) IN CANCER PATIENTS \(Meeting abstract\).](#)

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1. [ILX651 administered daily for five days every 3 weeks \(qdx5dq3w\) in patients \(pts\) with inoperable locally advanced or metastatic melanoma;phase II experience](#)

Meeting: [2005 ASCO Annual Meeting](#) Abstract No: 7556 First Author: [D. F. McDermott](#)
Category: Melanoma/Skin Cancers - [Melanoma](#)

2. [A phase I pharmacokinetic \(PK\) trial of XAA296A \(Discodermolide\) administered every 3 wks to adult patients with advanced solid malignancies.](#)

Meeting: [2004 ASCO Annual Meeting](#) Abstract No: 2025 First Author: [A. Mita](#)
Category: Developmental Therapeutics - Clinical Pharmacology and Immunotherapy - [Pharmacology/Pharmacokinetics](#)

3. [A pharmacologic and metabolic study of docetaxel \(D\) administered on a continuous weekly schedule in patients with advanced solid tumors.](#)

Meeting: [2003 ASCO Annual Meeting](#) Abstract No: 651 First Author: [J. D. Rizzo](#)
Category: Developmental Therapeutics - Clinical Pharmacology and Immunotherapy - [Pharmacology/Pharmacokinetics](#)
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► Presentations by L Hammond:

1. Phase (Ph) I evaluation of the dolastatin analogue synthadotin (SYN-D; ILX651): Pooled data analysis of three alternate schedules in patients (pts) with advanced solid tumors.

Meeting: [2004 ASCO Annual Meeting](#)
Presenter: [Lisa A. Hammond, MD](#)
Session: [Developmental Therapeutics: Molecular Therapeutics](#) (General Poster Session)

2. Phase I study of pemetrexed (LY231514) with vitamin supplementation in patients with locally advanced or metastatic cancer

Meeting: [2003 ASCO Annual Meeting](#)
Presenter: [Lisa A Hammond, MD](#)
Session: [Developmental Therapeutics - Cytotoxic Chemotherapy](#) (General Poster Session)

3. Phase I and pharmacokinetic (PK) trial of sequences of the rebeccamycin analog, NSC 655649, and cisplatin (CDDP)

Meeting: [2002 ASCO Annual Meeting](#)
Presenter: [Lisa A. Hammond, MD](#)
Session: [Pharmacology](#) (General Poster Session)
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