Lilly

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A Division of Eli Lilly and Company

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July 29, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncologic Drug Products, HFD-150
1451 Rockville Pike
Rockville, MD 20852-1448

**Subject: IND 40,061, MTA (LY231514) -- Serial no. 126**
**Briefing document for End-of-Phase II Meeting (mesothelioma, non-small cell lung cancer and head/neck cancer)**

Reference is made to our July 13, 1998 (Serial no. 125) request for an end of Phase II meeting for MTA (LY231514). As stated in that request, please find enclosed 10 copies of the briefing document to facilitate discussion on the development of MTA for patients with mesothelioma, non-small cell lung cancer and head/neck cancer.

Included in this briefing document is an overview of the development of MTA as well as sections on the clinical program, non-clinical pharmacology including toxicology and ADME, human pharmacology, clinical statistics with analysis, and the risk to benefit ratio. It is not our intent to discuss the nonclinical issues of MTA at this requested meeting. Section 3 of the briefing document contains a summary of issues and questions; this summary was provided as an attachment to the July 13, 1998 submission.

Appendices to the briefing document are also included. These appendices include more extensive data on pharmacokinetics, adverse events, draft clinical study protocols for the registration trials of MTA, a list of completed, ongoing and planned clinical studies, and bibliography.

Our issues for the requested meeting focus on these areas:

- The dose and dosing schedule to proceed with initial registration trials in patients with mesothelioma, patients with NSCLC who have failed prior platin- and taxane-based therapy and patients with head or neck cancer who have failed an initial chemotherapy regimen for locally recurrent and/or metastatic disease.

- Our specific strategy for clinical and non-clinical development and NDA submission for treatment of these patients. Specific advice will be requested on the appropriateness of the overall study designs (i.e., selection of the MTA regimen for phase III, selected efficacy endpoints, active control, overall study size, analysis plan and confirmation that the overall patient exposure is sufficient for an integrated summary of safety). It is our understanding that there is no effective therapy for these patients and thus the studies proposed will satisfy the requirements for accelerated approval.

- Identification and resolution of any issues that could alter the timing/quality of the NDA or the review of that application

Since MTA has broad clinical activity in multiple tumor types, our clinical efforts will continue to evaluate its safety and efficacy in patients with various tumors, either alone or in rational combination with drugs already active in patients with those tumor types. It is our understanding that the briefing document and subsequent discussion will focus on an overview of the development of MTA with specific focus on issues associated with adequate and well-controlled studies to support NDAs for treating patients with mesothelioma, NSCLC and head/neck cancer. We have undertaken parallel clinical development for other patient populations (breast cancer, colo-rectal cancer, first-line NSCLC), and propose that further discussions focus on the adequate and well-controlled studies to support supplemental NDAs for those patient populations.

We request that the FDA provide Eli Lilly and Company with a list of the FDA invitees to this meeting. In addition, it would be extremely helpful and lead to a more productive discussion if the FDA could provide their responses to our questions and any questions or issues that the FDA may have prior to the requested meeting.

Please contact Dr. Steven A. Hamburger at (317) 277-8900 concerning proposed meeting times. If you require any additional information or clarifications, please contact either Dr. Hamburger or me at (317) 277-3799.

Sincerely,
ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure

dmm

6731.3

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date:* December 31, 1999
*See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
ELI LILLY AND COMPANY

2. DATE OF SUBMISSION
July 29, 1998

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, IN 46285

4. TELEPHONE NUMBER *(Include Area Code)*
(317) 276-2000

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Compound LY231514 Disodium (MTA)

6. IND NUMBER *(If previously assigned*
IND 40,061

7. INDICATION(S) *(Covered by this submission)*
Cancer

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER NA *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.
NA

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submission should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
126

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ■ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

**CHECK ONLY IF APPLICABLE**

**JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.**

☐ **TREATMENT IND 21 CFR 312.36(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)**

**FOR FDA USE ONLY**

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | IND NUMBER ASSIGNED: |
|---|---|---|
| | | DIVISION ASSIGNMENT: |

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 [21 CFR 312.23(a)(1)]
- ☐ 2. Table of Contents [21 CFR 312.23(a)(2)]
- ☐ 3. Introductory statement [21 CFR 312.23(a)(3)]
- ☐ 4. General Investigational plan [21 CFR 312.23(a)(3)]
- ☐ 5. Investigator's brochure [21 CFR 312.23(a)(5)]
- ☐ 6. Protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ a. Study protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ b. Investigator data [21CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)]
- ☐ ☐ Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
- ☐ 8. Pharmacology and toxicology data ]21 CFR 312.23(a)(8)]
- ☐ 9. Previous human experience [21 CFR 312.23(a)(9)]
- ☐ 10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

NA

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Steven J. Nicol, M.D.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Same as #14 Above

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

| 16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | 17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | |
|---|---|---|
| Gregory T. Brophy, Ph.D., Director<br>U.S. Regulatory Affairs | Gregory T Brophy | |
| 18. ADDRESS *(Number, Street, City, State and Zip Code)* | 19. TELEPHONE NUMBER *(Include Area Code)* | 20. DATE |
| Eli Lilly and Company<br>Lilly Corporate Center<br>Indianapolis, IN 46285 | (317) 277-3799 | 7/26/98 |

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**Washington, DC 20201**

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# 28 July 1998
# MTA (LY231514)
# FDA Briefing Document

Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46285

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# Section 1: Overview of End of Phase 2 Briefing Document

## 1.1. Scientific Rationale

Background information is provided below on the preclinical profile, clinical pharmacology, clinical data to date (Phase 1 and 2 studies), and the safety profile of MTA (LY231514). MTA inhibits multiple enzymes in the folate pathway including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT) (Shih et al 1997). Initial clinical studies have shown that, as a single agent given once every 21 days at either 500 or 600 mg/m$^2$, MTA appears to have broad spectrum antitumor activity. Responses have been observed in patients treated in Phase 2 clinical trials of non-small cell lung cancer, colorectal cancer, pancreas cancer, locally advanced/metastatic breast cancer, head and neck cancer, renal cell cancer, bladder cancer, and cervical cancer. A Phase 1 trial (JMAP) has shown that MTA can be successfully combined with cisplatin, and that full doses of both compounds may be given. In this trial, partial responses were noted in 5 of 13 mesothelioma patients treated with MTA plus cisplatin.

## 1.2. Summary of Development Program to Date and Integrated Timeline for Future Activities

This document focuses on the efficacy of MTA in the tumor types in which we are seeking initial registration, ie, mesothelioma, second-line non-small cell lung cancer, and second-line head and neck cancer. Validated safety data (cutoff date of 11 December 1997) from Phase 2 trials in NSCLC (JMAL and JMAN), colorectal cancer (JMAC and JMAO), pancreatic cancer (JMAD), esophageal cancer (JMAH), and locally advanced or metastatic breast cancer (JMAG) are presented. The safety profile in these 250 patients (with 1,020 cycles of treatment) appears typical of an antifolate; this is discussed in greater detail in Section 6.2.

Phase 2 studies have shown that MTA has broad activity (see Tables 1.1 and 1.2). This presents a challenge in drug development, ie, to define the appropriate role for MTA in the treatment of cancer patients. Our overall clinical development strategy has two components. The first involves initial registration in "refractory" tumor types or settings, such as mesothelioma, second line NSCLC, and second line head and neck cancer. The second component involves the continued clinical development in a parallel fashion in breast cancer and front line NSCLC.

**Table 1.1. Activity of MTA in the Phase 2 Setting (Colorectal Cancer and NSCLC)**

| | JMAC | JMAO | JMBB | JMBM | JMAN | JMAL | JMBR | JMAY |
|---|---|---|---|---|---|---|---|---|
| Location | US | Canada | US | US | Canada | Australia/S Africa | Europe | Germany |
| MTA | 600 | 500 | 500 | 500 | 500 | 600 | 500 | 500 |
| Cisplatin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 75 |
| Tumor type | Colorectal | Colorectal | Colorectal | Colorectal | NSCLC | NSCLC | NSCLC A/B* | NSCLC |
| Evaluable Patients | 41 | 29 | 31 | 31 | 30 | 42 | 10/9 | 11 |
| CR | 1 | 0 | 0 | 0 | 0 | 0 | 0/0 | 0 |
| PR | 5 | 5 | 0 | 1 | 7 | 7 | 3/0 | 4 |
| Overall RR | 15 | 17 | 0 | 3 | 23 | 17 | – | – |
| Median survival (mo) | 16.2 + | 15 | – | – | 9.6 + | 9.7 + | – | – |
| Percent Censoring | 54 | – | – | – | 33 | 61 | – | – |
| Median Time to PD | 4.6 | 3.3 | – | – | 3.8 | 4.4 | – | – |
| Percent Censoring | 15 | – | – | – | – | 18 | – | – |

* "A" Treatment group consists of those patients who received a prior platinum containing regimen.

"B" Treatment group consists of those patients who received a prior chemotherapeutic regimen which did not contain platinum.

– Indicates that this information is not available.

**Table 1.2.** **Activity of MTA in the Phase 2 Setting (Pancreas, Breast, Head and Neck, Bladder, and Cervical Cancers)**

| | JMAD | JMAG | JMBP | JMAJ | JMAK | JMAM |
|---|---|---|---|---|---|---|
| Location | US | UK | Europe | France | Spain | S Africa |
| MTA | 600 | 600 | 500 | 500 | 600 | 600 |
| *Tumor type* | Pancreas | Breast | Breast A/B* | Head and Neck | Bladder | Cervix |
| Evaluable Patients | 35 | 36 | 12/16 | 15 | 20 | 24 |
| CR | 1 | 1 | 0/2 | 1 | 0 | 0 |
| PR | 1 | 10 | 2/4 | 6 | 7 | 5 (+6[a]) |
| Overall RR | 6 | 31 | – | 47 | 35 | 21 |
| Median survival (mo) | 6.5 | 13 | – | – | – | – |
| Percent Censoring | 34 | 39 | – | – | – | – |
| Median Time to PD | 3.9 | 4.0 | – | – | – | – |
| Percent Censoring | 11 | 16 | – | – | – | – |

* "A" Treatment group consists of those patients who are defined as refractory to prior anthracycline therapy.

"B" Treatment group consists of those patients who are defined as having failed prior anthracycline therapy.

a These were 6 additional investigator determined partial responders which could not be confirmed for a variety of reasons.

– Indicates that this information is not available.

### 1.2.1. Development Program to Date

A total of 748 patients have received MTA worldwide as of 21 April 1998. Table 1.3 shows the number of patients treated in Phase 1 and Phase 2 studies.

**Table 1.3. Patients Treated with MTA in Phase 1 and 2 Studies**

| | Number of Patients |
|---|---|
| Phase 1 Single Agent | 100 |
| Phase 1 Combination | 109 |
| Phase 2 Single Agent | 504 |
| Phase 2 Combination | 35 |

During the course of clinical development of MTA we decided to perform a multivariate analysis to test the hypothesis that patients at risk of developing serious toxicity could be predicted from a knowledge of potential prognostic factors. Early pre-clinical and clinical studies of other antifolates had suggested that a patient's folate status might play a role in the likelihood of experiencing severe toxicity. A key part of this multivariate analysis was to examine the role of a patient's functional folate status as assessed by homocysteine, cystathionine, methyl citrate I and II, and methylmalonic acid levels in determining the risk for developing toxicity. The rationale for looking at these vitamin metabolites as potential indicators is described in more detail in Appendix 5. Thus, vitamin metabolite data were prospectively obtained from patients in studies JMAC, JMAD, JMAG, and JMAH. Results from the multivariate analysis are based on a total of 139 patients. However, this is a dynamic process and additional analyses will be undertaken as data becomes available from studies (including NSCLC) which will start shortly. Toxicities resulting from therapy with MTA appear to be predictable from pretherapy homocysteine levels. Elevated baseline homocysteine levels ($\geq$10$\mu$M) highly correlate with severe hematologic and nonhematologic toxicities following therapy with MTA. The results of this multivariate analysis are discussed in Section 6.3.3.

In summary, MTA has shown broad activity in multiple tumor types including mesothelioma, NSCLC, and head and neck cancer, and the toxicity profile is consistent with that of other antifolates. Work is underway to identify patients at risk of developing serious toxicity. A knowledge of potential risk factors may allow better management of individual patients, the use of appropriate prophylactic measures, or potentially the identification of those patients for whom MTA might be an appropriate therapy. The efficacy data (response and survival) from the completed Phase 2 MTA studies in NSCLC compares favorably with historical data on other single agents in chemotherapy naive patients. In addition, the emerging data from the ongoing Phase 2 study in head and neck cancer and the responses observed in mesothelioma in the Phase 1 study of MTA and cisplatin are encouraging. We therefore believe that registration efforts in these tumor types are warranted.

# Section 2: Clinical Program to Date

## 2.1. Phase 1 Experience

### *2.1.1. Phase 1 Monotherapy Studies*

Three monotherapy dosing schedules have been investigated in Phase 1 studies.

- In Study JMAA: 37 patients were treated on a schedule of once every 21 days.
- Study JMAB: 24 patients received drug once weekly for 4 weeks every 6 weeks.
- Study BP-001: 38 patients were treated using a schedule of daily times five every 21 days.

The once every 21 day schedule has been carried forward into Phase 2 trials. In the Phase 1 trial investigating this dose, 37 patients were administered drug at doses ranging from 50 to 700 mg/m$^2$. Dose escalation proceeded by the Modified Continual Reassessment Method in this study limiting the number of patients exposed to lower, potentially less effective doses of drug (Rinaldi et al 1996). Toxicity experienced in this study is described in Section 6.2.2.1.

The weekly times four, every 6 weeks schedule is not currently being pursued in Phase 2 trials. Dose-limiting toxicity (DLT) on this schedule was myelosuppression, particularly leukopenia and granulocytopenia. Inability to maintain the weekly treatment schedule due to neutropenia limited dose escalation on this schedule.

The daily times five every 3 weeks schedule resulted in an MTD of 4 mg/m$^2$/day. DLTs on this schedule were reversible neutropenia and elevated liver enzymes. Nonhematologic toxicities were mild and included mucositis, diarrhea, rash, fatigue, and elevated transaminases. Minor responses were observed using this schedule in 1 patient with colorectal cancer and 1 patient with NSCLC. This schedule is being evaluated in a single Phase 2 trial in colorectal cancer in order to further assess its feasibility.

The Phase 1 experience is summarized in Table 2.1.

**Table 2.1. Phase 1 Experience**

| | JMAA | JMAB | BP-001 |
|---|---|---|---|
| Schedule* | Once every 21 days | Weekly × 4, every 6 weeks | Daily × 5, every 21 days |
| No. of patients treated | 37 | 24 | 38 |
| Dose range | 50 to 700 mg/m$^2$ | 10 to 40 mg/m$^2$ | 0.2 to 5.2 mg/m$^2$ |
| Recommended Phase 2 dose | 600 mg/m$^2$ | 30 mg/m$^2$ | 4 mg/m$^2$ |
| DLT | Neutropenia, mucositis, fatigue | Myelosuppression, particularly granulocytopenia | Neutropenia |
| Responses | Partial responses in pancreas (2), and colorectal (2) | Minor responses in colorectal (2) | Minor responses in colorectal (1) and NSCLC (1) |

* all doses administered as a 10-minute infusion

Details of the pharmacokinetic determinations from Study JMAA are given in Section 5.1.

A more complete description of the JMAB (weekly times four every 6 weeks) and BP-001 (daily times five every 21 days) studies can be found in Appendix 2 (McDonald et al 1998; Rinaldi et al 1995).

### *2.1.2. Phase 1 Combination Study JMAP (MTA plus cisplatin)*

In a Phase 1 trial of MTA in combination with cisplatin, patients with solid tumors were enrolled into one of two cohorts. The first cohort received MTA followed 30 minutes later by cisplatin on Day 1 of a 21-day cycle, and the second cohort received MTA on Day 1 and cisplatin on Day 2 of a 21-day cycle. Forty patients were enrolled into the first cohort; the MTD was reached at 600 mg/m$^2$ MTA and 100 mg/m$^2$ cisplatin, with dose-limiting toxicities of thrombocytopenia and febrile neutropenia. Eleven patients were enrolled into the second cohort. The degree of toxicity seen using this split schedule, which has included two therapy-related deaths, has led to the conclusion that the second schedule is clinically inferior. Partial responses were seen in 1 of 6 patients with non-small cell lung cancer, 2 of 4 patients with colorectal cancer (one of these on the split schedule), 3 of 9 patients with head and neck cancer, 1 of 2 patients with melanoma, 1 patient with cancer of unknown primary, and in particular, 5 of 13 patients with mesothelioma (12 of the 13 had pleural mesothelioma). All responses with the exception of one response in colorectal cancer and one response in mesothelioma were seen in the first cohort (MTA and cisplatin on Day 1). Table 2.2 includes information regarding

these responses with corresponding dose level and tumor type. The toxicity seen in this study is discussed in greater detail in Section 6.2.2.2.

**Table 2.2. Tumor Responses from Study JMAP**

| Dose Level (MTA/cis) | Tumor Type | Response | Duration (months) |
|---|---|---|---|
| | Day 1/Day 1 administration | | |
| 300/60 | non-small cell lung | PR | 2 |
| 300/60 | colorectal | PR | 7 |
| 400/75 | cancer of unknown primary | PR | 7 |
| 400/75 | head and neck | PR | 4+ |
| 600/75 | mesothelioma | PR | 8+ |
| 600/75 | melanoma | PR | 2 |
| 600/75 | head and neck | CR | 4 |
| 600/75 | head and neck | PR | 3+ |
| 600/75 | mesothelioma | PR | 5 |
| 600/100 | mesothelioma | PR | 3+ |
| 600/100 | mesothelioma | PR | 2+ |
| | Day 1/Day 2 administration | | |
| 500/75 | mesothelioma | PR | 2+ |
| 600/75 | colorectal | PR | 2+ |
| 600/75 | adenocarcinoma of the submandibular gland | MR | 1 |

A listing of other ongoing combination Phase 1 trials involving MTA is provided in Appendix 8.

## 2.2. Phase 2 Experience

### *2.2.1. Non-Small Cell Lung Cancer*

We have performed two multi-institutional studies in chemo-naive NSCLC patients. One study (JMAN) has been completed in Canada (Rusthoven et al. 1997) and an additional study (JMAL) is closed to accrual with several patients still on study in Australia and South Africa (Clarke et al. 1997).

The majority of patients on the Canadian study used a dose of 500 mg/m$^2$, which was reduced from 600 mg/m$^2$ during the course of the study after 1 of the first 3 patients experienced CTC Grade 3 mucositis and Grade 4 vomiting and myalgia. Seven partial responses have been observed in 30 evaluable patients for an overall response rate of 23.3% (95% CI 9.9-42.3%). All responding patients were treated at the 500 mg/m$^2$ dose level. As of 7 May 1998, median survival was 9.6 months (range 3.3 to 16.8+ months) and median time to progression was 3.8 months (range 0.5 to 15.8+ months).

The second NSCLC study, which was carried out in Australia and South Africa, has entered 61 patients, with 42 evaluable for response. All patients received a starting dose

of 600 mg/m$^2$ every 3 weeks in this study. Seven partial responses have been noted for an overall response rate of 17%. The median survival on this study to date is 9.7 months with a 42% 1-year survival rate (61% censoring). The median time to progressive disease has been 4.4 months, with a 23% 6-month progression free interval (18% censoring).

### 2.2.2. Head and Neck Cancer

A Phase 2 study of MTA in locally advanced or metastatic squamous cell carcinoma of the head and neck is ongoing in France (Pivot unpublished data 1998). To date, 19 patients have been enrolled, and 15 of these are evaluable for response. One patient has experienced a complete response, and 6 patients have achieved partial responses, for an overall response rate of 47%. These responses have not yet been independently reviewed; however, all but two have been confirmed by follow-up radiology. Three of the 7 responders had received prior 5-FU and cisplatin in combination. CTC Grade 3 or 4 neutropenia has been seen in 48% of cycles, Grade 3 or 4 anemia in 17% of cycles, moderate or severe mucositis in 14% of cycles, rash in 5% of cycles, and severe nausea in 12% of cycles. Febrile neutropenia has been seen in 19% of cycles, and one death due to treatment-related neutropenic sepsis occurred.

### 2.2.3. Summary of Other Clinical Experience

Clinical activity of MTA in metastatic colorectal carcinoma has been demonstrated in two multicenter trials performed in Canada (Cripps et al. 1997) and the US (John et al. 1997). Prior adjuvant chemotherapy was allowed if completed at least 1 year prior to study entry.

In the Canadian study, the starting dose of 600 mg/m$^2$ was reduced to 500 mg/m$^2$ after dose reductions were required in 5 of the first 8 patients. Toxicities leading to these reductions included rash, mucositis, neutropenia, and febrile neutropenia. Responses were seen at this reduced dose in 5 patients for an overall response rate of 17% (95% CI: 6-36%). All responses in this study have been validated by an independent radiologic review. As of 7 May 1998, median survival was 15 months (range 0.5 to 20+ months) and median time to progression was 3.3 months (range 0.5 to 16.1+ months). In the US colorectal study, objective tumor responses were seen in 6 of 40 patients for an overall response rate of 15% (95% CI: 6 - 31%). The median survival on this study has been 16.2 months (range 1.3 months to 23.7+ months), with a 65% 1-year survival (54% censoring). The median time to progressive disease has been 4.6 months (range 1.0 month to 16.3 months), with a 31% 6-month progression free interval (15% censoring). Few responses were noted in two monotherapy Phase 2 studies in patients with refractory colorectal cancer (see Table 1.1).

Two responses, one complete and one partial, were observed in 35 evaluable patients in the pancreatic cancer Phase 2 study for an overall response rate of 6% (Miller et al. 1997). Importantly, there were 13 additional patients with stable disease lasting for over 6 months of treatment, suggesting a clinical benefit not immediately apparent from

objective tumor measurements. The median survival was estimated to be 6.5 months (95% CI of 4.5 to 10.5 months), with a 31% 1-year survival (34% censoring). The median time to progressive disease was 3.9 months (95% CI of 1.2 to 19.5 months).

A Phase 2 study in patients with locally advanced and/or metastatic breast cancer is ongoing and includes patients who have received prior adjuvant chemotherapy as well as one prior therapy for metastatic disease (Lind et al 1998). Thirty-eight patients have been enrolled into the study. Thirty-three patients had received prior chemotherapy, 16 as adjuvant treatment, 12 for metastatic disease, and 5 patients who received chemotherapy in both the adjuvant and metastatic setting. Of the 36 patients evaluable for response, one complete and ten partial responses have been documented for an overall response rate of 31% (95% confidence intervals of 16 to 46%). Responses have been seen in pulmonary and hepatic metastases. Six of the 11 responders had received prior chemotherapy for metastatic disease. Prior therapy included paclitaxel, docetaxel, or an anthracycline. As of April 30, 1998, the median survival on this study has been 13.0 months (range 0.5 months to 25.7 months) with a 34% 1-year survival (39% censoring). The median time to disease progression has been 4.0 months (range 0.2 months to 16.7 months with) with a 38% 6-month progression free interval (16% censoring).

A table including this information as well as preliminary results from other ongoing studies was previously presented in Section 1.2.

A listing of other ongoing Phase 2 trials is provided in Appendix 8.

# Section 3: Summary of Issues and Questions

## Issue 1. Dose and schedule

The once every 21 day dosing schedule was selected for further clinical evaluation on the basis of results from the Phase 1 study, JMAA. This study showed that a dose of 600 mg/m$^2$ was tolerable and could be repeatedly administered. Although evaluation of efficacy is not a primary endpoint in Phase 1 clinical trials, four partial responses were observed, three of which were in patients who had received prior therapy with a thymidylate synthase inhibitor. The projected Phase 2 dose was studied in 20 patients in the course of study JMAA. Further clinical experience with this dose and schedule in Phase 2 studies has revealed a toxicity profile characterized predominantly by myelosuppression, thrombocytopenia, mucositis, self-limiting rises in transaminases, and a skin rash which can be ameliorated or prevented by dexamethasone. Further details are provided in the safety summary.

During the course of Phase 2 evaluation, it became apparent that in some patients MTA at 600 mg/m$^2$ was not well tolerated. This prompted a reduction in the starting dose to 500 mg/m$^2$ in selected studies. A comparison of toxicity seen at 500 mg/m$^2$ versus that seen at 600 mg/m$^2$ in the initial Phase 2 experience is provided in Section 6. The dataset at 600 mg/m$^2$ includes patients with colorectal, pancreas, esophageal, breast, and non-small cell lung cancers, while the 53 patients treated at 500 mg/m$^2$ had either colorectal or non-small cell lung cancer. These data show that the incidence of combined CTC Grade 3 and 4 neutropenia is essentially the same, ie, 48% at a starting dose of 600 mg/m$^2$ (n = 197) versus 41% at a starting dose of 500 mg/m$^2$ (n = 53). While Grade 3 myelosuppression is probably not of clinical significance, an infection in the setting of Grade 4 myelosuppression is life threatening, and there have been thirteen deaths of septic complications of myelosuppression in 748 patients who have been exposed to MTA. In a further 3 patients, neutropenia is thought to have contributed to the patient's death and an additional two patients died of both GI and myelosuppresive toxicities. The remaining death occurred in a patient with a prior history of cardiac failure, including 3 prior infarcts. He had severe MTA-related anemia which was thought to have contributed to his fatal cardiac failure while on therapy. These deaths are described in Appendix 3 and commented on in Section 7. A multivariate analysis was conducted in an attempt to identify those patients who might be at risk of developing serious toxicity. This analysis (which is discussed in more detail in Section 6.3), has shown that both elevated homocysteine (a marker of folate deficiency), and low albumin levels at baseline are independent predictive markers of the risk of developing serious toxicity. While both of these markers reflect poor nutritional status, homocysteine was found to be better than albumin at predicting serious toxicity. In addition, homocysteine levels did not change during the course of MTA therapy, making it an ideal marker for use in screening patients at risk of serious toxicities.

These observations raise the possibility that supplementing patients with folic acid (and other associated vitamins such as $B_6$ and $B_{12}$) may ameliorate toxicity. It is important that this hypothesis is tested clinically, and a number of studies have therefore been designed to address this issue in the clinical development plan of MTA.

As part of this multivariate analysis, the relationship between AUC and neutropenia also has been examined (this data is presented and discussed in Section 6.2.3.2). The data suggest that those patients who develop CTC Grade 4 neutropenia do not have significantly greater AUCs than those who develop Grade 0 to 3 neutropenia. The relationship of efficacy to dose intensity is clearly an important concept in cancer chemotherapy. In many cases this relationship may not be fully defined until many years after a drug has been in widespread clinical practice. Therefore, in selecting an appropriate dose for MTA, a number of factors need to be balanced. These include the potential need for dose intensity to achieve efficacy, the need for tolerability, and the variation in sensitivity of patients with different nutritional status. We propose therefore to use a dose of 600 mg/m$^2$ in single agent studies.

**Question 1:** Do you agree with the proposed dosing schedule for single agent MTA studies - specifically the registration studies involving NSCLC and head and neck cancer patients?

## Issue 2. MTA in Mesothelioma

The indication being pursued is: "MTA injection is indicated for treatment of pleural mesothelioma."

Mesothelioma is an uncommon and usually fatal primary neoplasm of the pleura. Currently there are no chemotherapeutic agents specifically approved or effective for the treatment of mesothelioma. However, cisplatin is commonly used as a single agent in this tumor type. In a Phase 1 study of MTA and cisplatin (JMAP), a total of 13 patients with mesothelioma were recruited. Of these, 5 had partial responses. Four of these have been independently confirmed, and the fifth will be submitted for review shortly. Four of these patients had received no prior chemotherapy, and the fifth had received an experimental agent. The Phase 1 study defined doses of 500 mg/m$^2$ MTA and 75 mg/m$^2$ cisplatin when given on Day 1 of a 21-day cycle as appropriate for Phase 2 evaluation. Further details of Study JMAP can be found in Section 2.1.1.

We intend to conduct a single randomized study (JMCH) in which the activity of MTA (500 mg/m$^2$) combined with cisplatin (75 mg/m$^2$) will be compared to that of cisplatin alone. Seventy-five patients with pleural disease will be treated in each arm of the study. Patients will be balanced between the two arms with respect to baseline homocysteine levels, histologic subtype, white blood cell count, gender, and performance status. The primary endpoint will be response rate (to be followed by CT scanning). Because bidimensional measurements in this disease are very difficult if not impossible to make, unidimensionally measurable target lesions will be followed and their response assessed

using SWOG criteria. A justification will be presented addressing the validity of unidimensional measurements in this tumor type (see Section 8). Unidimensional versus bidimensional measurable disease will also therefore be used as a balancing factor. This study is powered to detect a 15% difference in response rate between the arms of the study. Secondary endpoints will include time to progression, survival, clinical benefit (as measured by changes in pain, analgesic use, dyspnea, and weight loss), and toxicity. A copy of the draft protocol may be found in Appendix 7.

It is anticipated that at the time of submission, the summary of safety would include information on 240 patients who have received MTA plus cisplatin in the Phase 2 setting, approximately 1300 patients who have received MTA as a single agent, and approximately 750 patients who have received MTA in combination with other oncolytics not including cisplatin.

Included in these patient numbers are the following studies:

JMAP: Completed Phase 1 study of MTA and cisplatin in patients with a range of malignancies.

JMAY and JMBZ: Two separate ongoing multicenter Phase 2 studies of MTA and cisplatin. Each of these will recruit 35 patients with NSCLC who have not previously received chemotherapy. The dosing schedule for these studies is identical to that of the MTA plus cisplatin arm for Study JMCH.

**Question 2a:** Do you agree this is an acceptable registration strategy (ie, patient population, patient numbers, endpoints) for accelerated approval in this indication?

**Question 2b:** Is the design of the study described above (JMCH) adequate and well controlled?

**Question 2c:** Do you agree that the choice of primary and secondary endpoints, and the analysis plan in study JMCH is acceptable?

**Question 2d:** Do you agree that allowing the measurement of unidimensional disease will provide sufficient information for determining response rate?

**Question 2e:** Do you agree that there will be sufficient safety data to support registration, ie, the studies of MTA and cisplatin in NSCLC may be used to support the safety profile obtained in mesothelioma?

## Issue 3. NSCLC

The indication being pursued is: "MTA Injection is indicated for treatment of patients with advanced non-small cell lung cancer (NSCLC) whose disease has recurred or progressed following platin- and taxane-based therapy." Briefly, our clinical plan for this indication is:

(a) Study JMBQ is a randomized study in which the primary endpoint is time to disease progression in patients with either Stage IIIb or IV NSCLC, who have failed one prior regimen containing platinum and a taxane. This study will compare a selected MTA regimen with vinorelbine using a Phase II/III design (Thall et al 1988).

The protocol for Study JMBQ is included as Appendix 6.

In this study, patient randomization to treatment arms will be balanced for the following baseline prognostic factors: performance status, response to prior chemotherapy, homocysteine levels, time since last chemotherapy, and type of platinum regimen. All patients will be initially randomized to one of the following three treatment arms:

Arm A: MTA (600 mg/m$^2$ once every 21 days),

Arm B: MTA (600 mg/m$^2$ once every 21 days), plus daily vitamin supplementation. The vitamin supplementation will be as follows: daily $B_6$ 12.5 mg, $B_{12}$ 1 mg, folic acid 0.5 mg. Patients will take these starting 7 days prior to starting MTA and will continue to take them for as long as they remain on the study. For the first 7 days only, the dose of vitamins will be doubled. The choice of a combination of vitamins was made on the basis of data showing that a combination may be slightly more effective than folic acid alone in reducing homocysteine levels.

Arm C: Vinorelbine (30 mg/m$^2$ weekly)

Once 55 patients are randomized to each of the MTA arms (Arms A and B), an independent data monitoring board will review the response and toxicity data on these two treatment arms. The objective of the review will be to determine if MTA has enough activity to warrant further study in this patient population, and to select the best MTA regimen to take forward into the comparative Phase 3 portion of the study against the vinorelbine treatment arm. If the combined response rate in the two MTA arms is less than 10%, the study will stop. Otherwise, the MTA regimen for Phase 3 will be selected based on a 50% difference of the incidence of CTC Grade 3 or Grade 4 neutropenia in the first two cycles of treatment.

In the Phase 3 portion, patients will be randomized to receive the selected MTA regimen or vinorelbine. The primary objective will be to compare time to progression between MTA and vinorelbine-treated patients. The inclusion criteria will allow patients with measurable or evaluable disease. An additional total of 165 patients will be randomized to each treatment arm, for a total of 220 evaluable patients per arm in this portion of the study. Additional endpoints will include objective tumor response, time to event variables including survival, duration of response for responding patients, time to objective tumor response, and time to treatment failure, clinical benefit, toxicity, and QOL.

Quality of life data will be collected using the EORTC QLQ-C30 and LC-13 questionnaire. For each cohort, we will perform a comparison from baseline of each subscale after each cycle. In addition, we will focus on the following disease related symptoms: dyspnea, cough, lack of energy, insomnia, worrying, lack of appetite, chest pain, constipation, and despondency. These items will be obtained from the QLQ-C30 and LC13 data and will constitute a symptom index. Changes from baseline in the symptom index will be measured after each cycle, with the primary focus on changes after two cycles of therapy.

(b) In addition the following studies will be completed or ongoing at the time of a potential submission and may be useful as supportive information for the target patient population:

JMAN: Phase 2 study in 33 chemonaive NSCLC patients

JMAL: Phase 2 study in 53 chemonaive NSCLC patients

JMAP: Phase 1 study combining MTA and cisplatin in 35 chemonaive patients

JMBZ: Phase 2 study (MTA in combination with cisplatin) in 35 chemonaive NSCLC patients

JMAY: Phase 2 study (MTA in combination with cisplatin) in 35 chemonaive NSCLC patients

JMBR: Phase 2 study of MTA in 70 NSCLC patients who have failed either a platinum based regimen or a nonplatinum based regimen

**Question 3a:** Do you agree that this is an acceptable registration strategy (ie, patient population, patient numbers, endpoints) for this indication?

**Question 3b:** Is the design of study JMBQ as described above adequate and well controlled?

**Question 3c:** Do you agree that the Thall-Simon-Ellenberg design is adequate to select the best MTA regimen in the Phase 2 portion of JMBQ (Thall et al. 1988)?

**Question 3d:** Do you agree with the choice of the primary and secondary endpoints as well as the statistical analysis plan and methods for the Phase 2 and Phase 3 portions of study JMBQ?

**Question 3e:** Do you agree with our choice of quality of life instrument, symptoms, and analysis plan?

## Issue 4. MTA and NSAIDS

Currently, the Phase 2 studies and all registration directed studies have excluded those patients who have a need for chronic administration of NSAIDs or aspirin. This was based in part on MTA's structural similarity to methotrexate and also on data from a single patient in the Phase 1 studies, in whom the terminal half life of MTA appeared to be prolonged when aspirin was administered concomitantly, compared to another course of MTA treatment given without concurrent aspirin administration.

In Study JMAA, Patient 4407 took aspirin at the time of MTA administration during Cycle 11. Pharmacokinetic assessments were conducted during Cycles 1 and 11. It appears that the total plasma clearance of MTA was prolonged in Cycle 11 relative to that in Cycle 1. The observed differences in MTA pharmacokinetics were attributed to potential drug-drug interaction between MTA and aspirin due to structural similarities between MTA and methotrexate. After careful review of the case report form, serum creatinine levels in this patient were observed to increase steadily from 1.4 mg/dL at the time of the first MTA dose to 1.9 mg/dL on the day prior to the MTA dose in Cycle 11. On the day of the MTA dose, the serum creatinine level dropped to 1.4 mg/dL, suggesting that the patient had been prehydrated. Further details of this patient can be found in Section 5.1.4.2. It appears that this patient was experiencing a steady decline in renal function during the study. Since MTA is cleared from the general circulation primarily by renal excretion, the observed alteration in MTA pharmacokinetics cannot necessarily be attributed to a drug-drug interaction with aspirin since the administration of the concomitant medication in confounded by a apparent decline in renal function. However, we have had additional clinical experience, described in Section 5.1.4.2 which suggests that a possible interaction with NSAIDs or aspirin cannot be excluded.

Studies designed to assess the pharmacokinetics and toxicity of MTA in the presence and absence of ibuprofen and in the presence and absence of aspirin have been completed in dogs. The data suggests there is no evidence for a pharmacokinetic interaction (see Section 4.3.1).

This will also be studied clinically in an ongoing Phase 1 study (JMAW). This is a study in renally impaired patients; however, for the purpose of studying any potential pharmacokinetic interaction, the protocol will be modified to additionally study up to an additional 24 patients. Because aspirin is not widely prescribed for cancer patients, the study will be limited to ibuprofen. In this part of the study, patients will receive vitamin supplementation (the dosing regimen will be identical to that used in study JMBQ).

Detailed pharmacokinetic sampling will be done for each patient. Six "good risk" patients, ie, those with a GFR >80 mL/min, homocysteine levels less than 10 μM and no prior pelvic radiotherapy, will be treated with MTA at 500 mg/m$^2$. The sequence of administration of the MTA plus ibuprofen combination will be alternated with each successive patient entered. For example, the first patient enrolled will receive MTA plus ibuprofen during Cycle 1 and MTA alone during Cycle 2, the second patient will receive MTA alone during Cycle 1 and MTA plus ibuprofen during Cycle 2, etc. In this way, each patient will act as his or her own control for this portion of the study. The next cohort of six patients will be enrolled and treated similarly, but will have a minimum GFR of 60 mL/min. If there is no evidence for a pharmacokinetic interaction at the completion of these two cohorts, then the conclusion will be drawn that it is appropriate to remove the exclusion criterion from both ongoing and planned studies, and it will not be part of the label.

**Question 4:** Do you agree that if this study shows no pharmacokinetic interaction that this will be sufficient evidence to take the course of action outlined, ie, remove the exclusion criterion, and to prevent this exclusion from being part of the label?

## Issue 5. Population Pharmacokinetics

The pharmacokinetic analysis of MTA has been completed in all Phase 1 and many Phase 2 patients. The pharmacokinetics of MTA determined from an interim analysis of approximately 100 patients after three cycles was highly predictable between and within patients. This data is discussed in Section 5.1.4.3. The clinical study reports (CSRs) for the Phase 1 studies will contain complete pharmacokinetic assessments while the CSRs from Phase 2 studies will contain analyses appropriate for the amount of available data. Our intent is to provide in the NDA a discussion of population pharmacokinetics in a stand-alone summary using information obtained from the Phase 2 monotherapy studies in which appropriate pharmacokinetic assessments were obtained. Population pharmacokinetics will also be carried out in Study JMBQ. In Study JMCH (MTA plus cisplatin in mesothelioma) population pharmacokinetics for both MTA and cisplatin will be done. The parameters selected and types of analyses will be determined when more data is available.

**Question 5:** Do you agree with this strategy?

## Issue 6. Renal Impairment Study

In Study JMAA a mean of approximately 78% of an MTA dose was excreted unchanged in urine. The clearance of MTA was correlated with renal function as assessed by calculated creatinine clearance (see Section 5.1.4.1).

It is our intent to perform a pharmacokinetics study in cancer patients with renal impairment (study JMAW; described previously in Issue 4). This study started in May 1998 and it is anticipated to be ongoing at the time of submission. Recruitment will be slow due to the scarcity of patients with severe renal impairment. Our strategy is to

include all information available from this study when the registration studies in the target patient populations are completed. We anticipate that the NDA will contain information from the cohorts with mild renal impairment (creatinine clearance >45 mL/min), as well as from patients who have received concomitant ibuprofen or concomitant aspirin (see Issue 4), but not in patients with severe renal impairment. We have designed the trial based upon our knowledge of MTA and in accordance with the FDA Draft Guidance for Industry entitled "Pharmacokinetics and Pharmacodynamics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" which was released for comment on May 30, 1997.

**Question 6:** Do you agree that information from the mild renal impairment cohort from the JMAW study will not be sufficient as to delay the review and approval of the NDA?

## Issue 7. Hepatic Impairment Study

In vitro studies suggest that MTA would not cause a clinically significant inhibition of the metabolic clearance of drugs metabolized by the major P450 isozymes CYP3A, CYP2D6, CYP2C9 and CYP1A2. Since approximately 78% of an MTA dose was excreted unchanged in urine and the clearance of MTA correlated with renal function as assessed by creatinine clearance, these data indicate that the elimination of MTA in humans is not dependent on hepatic metabolism or biliary excretion to any great extent and that the compound at physiological concentrations would not inhibit the major P450 isozymes. Therefore, a separate study in patients with hepatic dysfunction does not appear to be warranted. Markers of hepatic dysfunction such as bilirubin and liver enzymes will be evaluated as covariates in the population pharmacokinetic analyses as well as in the multivariate analysis.

**Question 7:** Do you agree that a separate study in patients with hepatic dysfunction does not appear to be warranted?

## Issue 8. Nonclinical Information

The toxicology, ADME and nonclinical pharmacology plans for the MTA NDA are provided in Section 4.

**Question 8:** Do you agree that these plans are sufficient?

## Issue 9. MTA in Head and Neck Cancer

The label claim being pursued is: "MTA injection is indicated in patients with locally advanced/metastatic head and neck cancer who have progressed following prior therapy".

A Phase 2 study of MTA in head and neck cancer (JMAJ) is ongoing. Patients may have received chemotherapy in the adjuvant setting, and the minimum chemotherapy free interval is 6 months. To date, there have been 7 responses to MTA in 15 patients treated. Although data is preliminary, this is an encouraging level of activity. However, some serious toxicity had been observed. This patient population is likely to be nutritionally

deprived, and might be expected to be functionally folate deficient. We know from a multivariate analysis that such patients are at risk of developing serious toxicity (see Section 6). The development plan involves a randomized study in the same patient population as study JMAJ, in which patients with receive either MTA or MTA plus vitamins ($B_6$, $B_{12}$ and folic acid). One objective of this study is to determine the effect of vitamins on both efficacy and toxicity. The primary endpoint of this study will be response rate. Secondary endpoints will include toxicity and survival time. This is study JMDG, which is due to start in September 1998.

At the same time, it is intended to start an extended Phase 2 trial (JMLI) in the second-line setting in patients with either locally recurrent or metastatic head and neck cancer who have failed prior cisplatin or 5-FU. Patients in this study will receive vitamin supplementation. The primary endpoint will be response rate. The first 45 patients will be enrolled and data from these patients will be used to assess efficacy, with an additional 115 patients enrolled into the second part of the trial in order to further assess the efficacy and safety profile of MTA plus vitamins in this patient population. Statistical aspects of the study are that of a standard Phase 2 study and are described as follows:

Twenty qualified patients will be enrolled into the first stage of the study. If fewer than two patients respond to MTA therapy, the accrual into the study will be stopped. If at least two patients respond to MTA therapy, another 25 qualified patients will be enrolled into the second stage of the study. If fewer than 9 patients exhibit a response to MTA therapy by the end of the second accrual stage, by which time 45 qualified patients will have been enrolled in the study, the conclusion may be drawn that this regimen is not worthy of further study in this indication. If at least 9 patients respond after the second accrual stage, the conclusion will be drawn that the treatment is promising.

The procedure described above tests the null hypothesis ($H_0$) that the true response rate is less than or equal to 10% versus the alternative hypothesis ($H_A$) that the true response rate is at least 25%. The significance level (ie, the probability of rejecting the $H_0$ when it is true) is 0.04. The power (ie, the probability of rejecting $H_0$ when the alternative hypothesis is true) is 83%. The expected sample size under both the null hypothesis ($H_0$) and the alternative hypothesis ($H_A$) is 35 patients.

**Question 9a:** Do you agree this is an acceptable registration strategy (ie, patient population, patient numbers, endpoints) for this indication?

**Question 9b:** Do you agree with the primary endpoint, the statistical analysis plan and methods in study JMLI?

**Question 9c:** Do you agree that Study JMDG described above could be considered a supportive study for the purpose of registration?

# Section 4: Pharmacology, Toxicology, and ADME

## 4.1. Summary of Nonclinical Mechanism of Action Studies

N-[4-[2-(2-amino-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid, MTA, is a novel pyrrolo[2,3-d]pyrimidine based antifolate currently undergoing extensive Phase 2 clinical trials. MTA is one of the best substrates for the enzyme folylpolyglutamate synthetase (FPGS, Km = 1.6 μM and Vmax/Km = 621). It is believed that polyglutamation and the polyglutamated metabolites of MTA play profound roles in determining both the selectivity and the antitumor activity of this novel agent. Studies now have demonstrated that the polyglutamates of MTA potently inhibit several key folate-requiring enzymes of folate metabolism. This includes thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT), with Ki values of 1.3, 7.2 and 65 nM for the pentaglutamate of MTA against these enzymes, respectively. The polyglutamates of MTA also inhibit other folate-requiring enzymes such as aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT), C-1 tetrahydrofolate synthase and C-1 tetrahydrofolate dehydrogenase but with higher Ki values ( Ki = 0.26, 1.6 and 5.0 μM, respectively for the pentaglutamate of MTA).

This multiple folate-enzyme inhibition mechanism of MTA was also reflected in cell-based reversal studies. It was found that the antiproliferative effect of MTA in various human cell lines (CCRF-CEM, GC3/C1 and HCT-8) can only be partially reversed by the addition of thymidine (5 μM). However, the combination of thymidine and hypoxanthine (100 μM) can completely reverse the cytotoxicity exerted by MTA in all cell lines. This reversal pattern suggests that although TS may be a major site of action for MTA at concentrations near the $IC_{50}$, higher concentrations can lead to inhibition of DHFR and/or other folate enzymes along the purine *de novo* pathway. MTA also demonstrates much less cross-resistance to cells (MCFTDX and H630TDX) that are resistant to the specific TS inhibitor raltitrexed through over expression of TS, again suggesting TS is not the only target for this agent.

The effect of MTA on intracellular folate and nucleotide pools also suggests that MTA is an agent with a unique metabolic effect. The metabolic signature of MTA was found to be quite different from other antifolates such as methotrexate, raltitrexed (primarily inhibits TS) and LY309887 (primarily inhibits GARFT).

Overall, MTA is a classical antifolate, the antitumor activity of this novel agent may derive from simultaneous and multiple inhibition of several key folate-requiring enzymes via its polyglutamated metabolites. The combined effects of the multiple enzyme inhibition exerted by MTA at each target gives rise to an unusual end product reversal pattern and signature of metabolic folate and nucleotide pools, which are different from other antifolates that have been studied so far.

# 4.2. Toxicology

## *4.2.1. Overview*

In dogs and mice, the toxicologic profile of MTA is consistent with the known antiproliferative activities of folate-antimetabolites. The major pathologic effects associated with MTA disodium administration occurred in the intestinal tract and lymphoid tissues; the bone marrow was only minimally affected in dogs and mice given repeated doses. Clinical manifestations of toxicity were delayed approximately 1 week from the time of dose administration, with individual animal variability in response to the compound. In dogs, modest signs of toxicity were generally reversible with supportive care and interruption of MTA treatment. Prominent toxicity was generally more evident in the daily dose schedule even though the weekly dose was a much larger total dose of MTA. Based on the clinical presentation, mortality, and microscopic and clinicopathological alterations, the dog appears to be a more sensitive indicator than the mouse for systemic toxicity of MTA.

Minimally toxic doses for the dog, based on the intensity of morphologic and clinicopathologic alterations, were considered to be 0.11 mg/kg/day (2.2 mg/m$^2$/day) and 26.24 mg/kg/week (524.8 mg/m$^2$/week). A minimally toxic dose was not established for the twice weekly schedule. Minimally toxic doses for mice based on the intensity of morphologic and clinicopathologic alterations were considered to be 10.6 mg/kg/day (31.8 mg/m$^2$/day), 105 mg/kg twice weekly (315 mg/m$^2$ twice weekly), and 314.8 mg/kg/week (944.4 mg/m$^2$/week).

MTA yielded negative results in the Ames assay, the in vitro chromosome aberration test, and the mammalian HGPRT$^+$ locus forward mutation assay. However, MTA induced micronuclei in the bone marrow polychromatic erythrocytes of ICR mice. Thus the compound may be a clastogenic hazard for man.

Two studies were conducted to evaluate potential rescue agents (leucovorin and thymidine) for treatment of severe toxicity due to MTA administration. Two intravenous doses of 50 mg MTA/kg, 3 days apart, were used to produce toxicity. In the leucovorin rescue study, both clinical signs of toxicity and hematological alterations were reversed by co-administration of leucovorin, a reduced form of folate. In the thymidine, rescue study, subsequent (24 hr after last MTA dose) administration of thymidine, the end product of thymidylate synthase, as a continuous infusion for 3 days was successful in rescuing dogs from life-threatening toxicity associated with MTA.

**Table 4.1. Completed Studies with MTA disodium**

| Study Type | Duration of Treatment | Strain Species or Cell Type | Route of Administration | Treatment Intervals |
|---|---|---|---|---|
| **Dose Ranging/Pilot** (non-GLP studies) | 2 weeks | CD-1 mouse | i.p. | 1/day |
| | Single dose | Beagle dog | i.v. | NA |
| | 5 days | Beagle dog | i.v. | 1/day |
| | 2 weeks | Beagle dog | i.v. | 1/day, 2/week |
| **Acute Toxicology** | | | | |
| | Single dose | CD-1 mouse | i.v. | NA |
| | Single dose | Fischer 344 rat | i.v. | NA |
| **Subchronic Toxicology** | | | | |
| | 6 weeks | CD-1 mouse | i.p. | 1/day, 2/week, or 1/week |
| | 6 weeks | Beagle dog | i.v. | 1/day, 2/week, or 1/week |
| **Genetic Toxicology** | | | | |
| Bacterial mutation assay | | *S. typhimurium* strains: TA1535, TA1537, TA98, and TA100 *E. coli* strain: WP2uvrA- | In vitro | NA |
| Forward mutation assay | | HGPRT+ Chinese hamster ovary cells | In vitro | NA |
| Chromosome aberration assay | | Chinese hamster ovary cells | In vitro | NA |
| Micronucleus assay | 2 days | ICR mouse | i.v. | 1/day |
| **Leucovorin Rescue** | | | | |
| | 2 doses | Beagle dog | i.v. | 3 days |
| Leucovorin: First dose given 5 hrs after second LY231514 dose, then daily for 7 days. | | | | |
| **Thymidine Rescue** | | | | |
| | 2 doses | Beagle dogs | i.v | 3 days |
| Thymidine: administered as a continuous i.v infusion for 3 days starting 24 hours after last LY231514 dose | | | | |

Abbreviations: i.v. = intravenous; i.p.= intraperitoneal; NA = Not applicable; *S.* = *Salmonella; E.* = *Escherichia.*

### *4.2.2 Other Completed Studies*

The following studies were conducted to qualify a related substance, the gamma monoethyl ester of MTA, that is anticipated to occur in commercial lots for use in humans.

- 2-week subchronic study in mice

- Ames assay
- Chromosome aberration assay

### 4.2.3. Ongoing Studies

None.

### 4.2.4. Future Studies

**Table 6.2. Future Studies with MTA**

| Study Type | Strain Species or Cell Type | Route of Treatment | Treatment Intervals | Start Date |
|---|---|---|---|---|
| **Reproduction/Developmental** | | | | |
| Seg. II | CD-1 mouse | i.v. | 1/day | January 1999 |
| Seg. II | NZW rabbit | i.v. | 1/day | January 1999 |

## 4.3. ADME

### 4.3.1. Overall Summary

MTA has been administered intravenously in the majority of the toxicokinetic and ADME work. In mice, however, intraperitoneal dosing has been used for most of the nonclinical studies. The half-life of MTA in dogs was short and ranged from about 2 hours to 4 hours, whereas in mice the half-life was longer ranging from 7 hours to 10 hours. In dogs the AUC appeared to increase proportionately with increasing doses over the dose range 0.11 mg/kg to approximately 100 mg/kg. Very little metabolism has been observed in mice and dogs, as only two minor metabolites have been identified in urine. In dogs and mice, parent accounted for 68% to 80% of the urinary radioactivity after intravenous administration of $^{14}$C-LY231514. Urinary excretion has been the predominant route of elimination in humans as well. Quantitative whole-body autoradiography studies in CD-1 mice indicated that radiocarbon associated with $^{14}$C-MTA or its metabolites was rapidly distributed into tissues, and was eliminated via both renal and biliary routes. Radiocarbon did not accumulate in tissues and was detected only in kidney and liver at times beyond 3 hours postdose. The results from in vitro studies indicated that MTA would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. The percent of $^{14}$C-LY231514 bound to plasma proteins in vitro was found to be approximately 53% to 58% in mouse plasma, 46% to 47% in dog plasma and approximately 81% in human plasma at concentrations of 500 and 5000 ng/mL. Single and repeated oral doses of either 5 mg/kg/day of ibuprofen or 10 mg/kg/day of aspirin administered approximately 30 minutes before a single intravenous bolus dose of MTA did not appear to cause a consistent alteration in the pharmacokinetics of MTA in female dogs.

### 4.3.2. Completed Studies

**Table 4.4. ADME Report List for LY231514**

| ADME Report | Title of Report |
|---|---|
| 1 | Relative Bioavailability of IP Administration and Plasma Pharmacokinetics of LY231514 in Male CD-1 Mice after IV Administration of 20 mg/kg or IP Administration of 20 or 200 mg/kg (BE) LY231514 $Na_2$ |
| 2 | Plasma Pharmacokinetics of LY231514 in Beagle Dogs after IV Administration of 7.5 or 100 mg/kg (BE) LY231514 $Na_2$ (from Toxicology Study D05091) |
| 3 | Summary of the Whole-Body Autoradiographic Distribution of [$^{14}$C]-LY231514 Disodium in Male CD-1 Mice After a Single Intravenous 20 mg/kg Dose |
| 4 | Synthesis of N-[4-[[2-(2-Amino-4,7-dihydro-4-oxo-3H-pyrrolo-[2,3-d]-pyrimidin-5-yl)ethyl]benzoyl-[carbonyl-$^{14}$C]]-L-glutamic Acid Disodium Salt, LY231514-[$^{14}$C] $Na_2$ |
| 5 | Excretion and Metabolism of [$^{14}$C]-LY231514 $Na_2$ in Male CD-1 Mice After a Single Intravenous 20 mg/kg Dose; Comparison to a Single Oral 20 mg/kg Dose |
| 6 | Excretion and Metabolism of [$^{14}$C]-LY231514 $Na_2$ in Female Beagle Dogs After a Single Intravenous 7.5 mg/kg Dose |
| 7 | Protein Binding of [$^{14}$C]-LY231514 in Mouse, Dog, and Human Plasma |
| 8 | Urinary Metabolites of [$^{14}$C]LY231514 $Na_2$ in Mice and Dogs |
| 9 | Quantitative Whole-Body Autoradiographic Disposition of $^{14}$C-LY231514 Disodium in Male CD-1 Mice After a Single Intravenous 20 mg/kg Dose (Free Acid) |
| 10 | Identification of a Urinary Metabolite of [$^{14}$C]LY231514 $Na_2$ in Mice and Dogs |
| 11 | In Vitro Interaction of LY231514 with Human Cytochromes P450 CYP3A, CYP2D6, CYP2C9, and CYP1A2 |
| 12 | Pharmacokinetic Interaction Study of LY231514 and Aspirin in Beagle Dogs Following a Single Intravenous Bolus Dose of 25 mg/kg LY231514 as the Disodium Salt |
| 13 | Pharmacokinetic Interaction Study of LY231514 and Ibuprofen in Beagle Dogs Following a Single Intravenous Bolus Dose of 25 mg/kg LY231514 as the Disodium Salt |

### 4.3.3. Future Studies

Urine samples from patients enrolled in Study H3E-MC-JMAW (A Phase 1 pharmacokinetic trial of MTA administered intravenously every 3 weeks in advanced cancer patients with varying degrees of renal function) will be collected for determination of possible metabolites of MTA.

## 4.4. Pharmacology

General Pharmacology Overview

The secondary pharmacology of MTA included mild effects on renal and cardiovascular function and alterations in pain sensitivity. All observed effects were produced at doses well above the anticipated clinical doses.

Administration of MTA disodium to mice at doses of ≤600 mg/kg did not alter gastrointestinal function or CNS activity except for acetic acid writhing. Acetic acid writhing, a measure of pain perception, was reduced at intravenous doses ≥200 mg/kg and a mild increase in the excretion of sodium and potassium was seen at doses ≥200 mg/kg. Intravenous administration of MTA to beagle dogs at a dose of 105 mg/kg produced a mild decrease in peripheral vascular resistance and an increase in stroke volume.

**Table 4.3. General Pharmacology Studies with LY231514**

| Study Type | Species (Strain) or Cell Type | Route of Administration |
|---|---|---|
| **General Pharmacology** | | |
| Smooth muscle Effects | Various rat and guinea pig smooth muscles | In vitro |
| Cardiovascular Effects | Dog (Beagle) | i.v. |
| Behavior and CNS Effects | Mouse (CD-1) | i.v. |
| Gastrointestinal Effects | Mouse (CD-1) | i.v. |
| Renal Effects | Rat (Fischer 344) | i.v. |

Publications of nonclinical pharmacology/ADME studies of MTA (Jan. 1997- ):

C. Shih, V. J. Chen, L. S. Gossett, S. B. Gates, W. C. MacKellar, L. L. Habeck, K. A. Shackelford, L. G. Mendelsohn, D. J. Soose, V. F. Patel, S. L. Andis, J. R. Bewley, E. A. Rayl, B. A. Morrison, G. P. Beardsley, W. Kohler, M. Ratnam and R. M. Schultz, (1997) LY231514, A Pyrrolo[2,3-d]pyrimidine Based Antifolate That Inhibits Multiple Folate Requiring Enzymes. Cancer Research, 57, 1116-1123.

J. L Tonkinson, P. Marder, S. L. Andis, R. M. Schultz, L. S. Gossett, C. Shih and L. G. Mendelsohn, (1997) Cell Cycle Effects of Antifolate Antimetabolites: Implications for Cytotoxiocity and Cytostasis. Cancer Chemotherapy and Pharmacology, 39, 521-540.

J. M. Woodland, C. J. Barnett, D. E. Dorman, J. M. Gruber, C. Shih, L. A. Spangle, T. Wilson and W. J. Ehlhardt, (1997) The Metabolism and Disposition of he Antifolate LY231514 (MTA) in Mice and Dogs. Drug Metabolism and Disposition, 25, 693-700.

J. Chen, J. R. Bewley, S. L. Andis, R. M. Schultz, P. W. Iverson, C. Shih, L. G. Mendelsohn, D. E. Seitz and J. L. Tonkinson, (1997) Preclinical Cellular Pharmacology of LY231514: A Comparison with Methotrexate, LY309887 and Ralitrexed for Their Effects on Intracellular Folate and Nucleotide Triphosphate Pools and CCRF-CEM Cells. British Journal of Cancer (submitted)

Shih, G. P. Beardsley, V. J. Chen, W. J. Ehlhardt, W. C. Mackellar, L. G. Mendlesohn, M. Ratnam, R. M. Schultz, E. C. Taylor and J. F. Worzalla, (1997) Biochemical

Pharmacology Studies of Multitargeted Antifolate: LY231514. Chemistry and Biology of Pteridine (submitted)

# Section 5: Human Pharmacokinetics and Bioavailability

## 5.1. Clinical Pharmacology

### *5.1.1. Introduction*

The pharmacokinetics of MTA in man were evaluated in three dose escalating Phase 1 studies designed to determine the maximal tolerated dose using different anticipated therapeutic dosing regimens. A summary of MTA administration in these studies was previously presented in Table 2.1.

Additional pharmacokinetic assessments were performed on plasma concentration time data collected by a sparse sampling regimen in four Phase 2 studies (Studies JMAC, JMAD, JMAG, and JMAH) in which MTA was administered once every 21 days at a dose of 600 mg/m$^2$.

### *5.1.2. Pharmacokinetic Methods*

#### 5.1.2.1. Phase 1 Studies

Blood and urine samples were collected at regular intervals over 48 hours for the determination of MTA concentrations. Plasma and urine MTA concentrations were quantified by UV detection (250 nm) using a high pressure liquid chromatographic (HPLC) assay. The assay was specific for MTA with minimum quantitation limits (MQL) of 5 ng/mL in plasma and 1 μg/mL in urine. MTA pharmacokinetic parameters were calculated by noncompartmental methods.

#### 5.1.2.2. Phase 2 Studies

Four blood samples were collected from each patient over a 36-hour time period for three consecutive cycles. The 36-hour sampling period was divided into four intervals as summarized in Table 5.1.

**Table 5.1. Sampling Intervals Used in Phase 2 Studies**

| Blood Sample Interval | Time Range (hours) |
|---|---|
| 1 | 0 - 2 |
| 2 | 2 - 6 |
| 3 | 6 - 12 |
| 4 | 12 - 36 |

Blood samples were collected randomly at specified times within each interval. Population pharmacokinetic parameters were estimated by nonlinear mixed-effect modeling (NONMEM) using an open two-compartment model parametized in terms of clearances and volumes of distribution. Following an initial screening of all potentially relevant covariates using a general additive modeling analysis (GAM), the affect of the

remaining covariates from the GAM analysis on the pharmacokinetic parameters was assessed by stepwise regression methods using the NONMEM program (Mandema et al 1992).

### 5.1.3. Pharmacodynamic Methods

Neutrophil and platelet counts were measured as markers of hematologic toxicity of MTA. Nadirs of absolute neutrophil counts (cells/$mm^3$) and platelet counts (platelets/$mm^3$) obtained during Cycle 1 and the maximum nadir observed over all cycles (total therapy) were correlated with representative indices of drug exposure ($AUC_{0-\infty}$ and $C_{max}$) obtained during Cycle 1 in two Phase 1 studies (JMAA and JMAB). Regression analysis was performed assuming a log-linear relationship between between pharmacokinetic parameters ($C_{max}$ and $AUC_{0-\infty}$) and blood counts (neutrophil count nadirs and platelet count nadirs).

### 5.1.4. Summary of Human Pharmacokinetics

#### 5.1.4.1. Phase 1 Studies

Mean plasma concentration-time plots over a 0.2 to 700 mg/$m^2$ dose range are illustrated in Figure 1, Appendix 1. After termination of the 10 minute infusion, plasma MTA concentrations decline steadily and generally fall below the MQL within 48 hours at the higher doses (JMAA) and within 12 hours at the lower doses (BP-001). The terminal slopes of the plasma concentration-time profiles were nearly parallel in each respective study suggesting that MTA elimination was consistent within the dose ranges evaluated in each study.

Mean (%CV) pharmacokinetic parameters for the three studies are presented in Tables 1 and 2, Appendix 1. MTA has a small steady-state volume of distribution ($V_{ss}$ ~ 15 L) suggesting that the compound has limited tissue distribution. The $V_{ss}$ value of MTA is consistent with drugs which distribute into extracellular fluid. MTA is approximately 81% bound to human plasma proteins and exhibits linear binding over a concentration range of 500 to 5000 ng/mL (ADME Report 7, 1995).

MTA is eliminated rapidly from plasma with a mean terminal elimination half-life value of about 2 to 3 hours at the higher end of the dose range (525 to 700 mg/$m^2$). Mean $t_{1/2}$ values appeared to decline with decreasing dose; however, the smaller $t_{1/2}$ values observed at the lower doses are probably due to plasma concentrations falling below the MQL prior to reaching the terminal elimination phase.

Relationships between maximum plasma concentration ($C_{max}$), and total systemic drug exposure ($AUC_{0-\infty}$) with dose were assessed by linear regression analysis in each study and after combining the data from the three studies (Figures 2 and 3, Appendix 1). Both $C_{max}$ and $AUC_{0-\infty}$ values increased linearly with dose. Good correlations ($r^2 \geq 0.8$) were

obtained when the data from all three studies were pooled. These results also suggest that the pharmacokinetics of MTA are linear over a 0.2 to 700 mg/m$^2$ dose range.

Urinary excretion data for MTA was available only in 18 patients (7 females and 11 males) of the 35 evaluated in Study JMAA. Urinary excretion of MTA was rapid and nearly complete within 24 hours of infusion. Recovery of MTA in urine generally ranged from 70 to 90% of the administered dose. Therefore, relationships between plasma MTA clearance and renal function as assessed by the calculated creatinine clearance were explored (Figure 4, Appendix 1). In general, decreases in renal function resulted in decreases in total plasma MTA clearance as expected for drugs which are eliminated primarily by renal excretion.

### 5.1.4.2. Special Populations (Gender, Renal, and NSAID Effects)

Since the pharmacokinetics of MTA were shown to be linear over a wide range of doses, an analysis of gender effects was restricted to $CL_p$, $V_{ss}$, and cumulative urinary excretion (Figure 5, Appendix 1). Based upon the small sample size (7 females and 11 males) of patients from which urinary excretion data was available, female patients excreted a higher percentage of MTA unchanged in urine than male patients (90% versus 70%; p=0.01). Due to the small number of patients evaluated in this comparison as well as the logistical difficulty associated with complete urine collection, the clinical relevance of this finding is currently unknown. Urinary excretion of MTA is being further evaluated in a study designed to assess the effects of renal insufficiency on the safety and pharmacokinetics of MTA (Study JMAW). The results of this study will assess whether there are any gender-specific differences in cumulative urinary excretion of MTA. Additional analyses may then be performed to determine the clinical relevance of the observed findings.

In Study JMAA, Patient 4407 had renal cell carcinoma and had undergone a nephrectomy prior to receiving MTA. The patient's baseline serum creatinine was 1.4 mg/dL prior to the first cycle of treatment. Over 7 months of therapy, the patient's serum creatinine increased to a maximum value of 1.9 mg/dL on the day immediately prior to Cycle 11. On the day of treatment in Cycle 11, the patient's serum creatinine was 1.4 mg/dL, suggesting that the patient had been hydrated. The patient took one dose of aspirin (650 mg) and 2 hours later, received MTA at a dose of 225 mg/m$^2$. Pharmacokinetic assessments conducted on this patient suggest that the total plasma clearance of MTA was prolonged in Cycle 11 relative to that in Cycle 1. However, because the patient's serum creatinine was back up to 1.9 mg/dL 1 week after administration of MTA, it is very likely that the 60% decrease in MTA clearance and 60% increase in MTA AUC seen in Cycle 11 was a result of declining renal function over the 11 cycles. Since MTA is cleared from the general circulation primarily by renal excretion, the observed alteration in MTA pharmacokinetics cannot necessarily be attributed to a drug-drug interaction with aspirin since the administration of the concomitant medication is confounded by a apparent decline in renal function.

Two patients experienced severe toxicity during Cycle 1 in Study JMAS, which is an MTA plus folic acid Phase 1 study. One of these patients was on stable doses of naproxen (500 mg twice per day) concurrent with MTA at 800 mg/m$^2$. The other patient was on stable doses of a long acting NSAID concurrent with MTA at 900 mg/m$^2$. It is anticipated that a 3- to 4-fold higher MTA concentration would be achieved at these doses in relation to the dose received by Patient 4407 in study JMAA. At these higher concentrations, it is more likely that MTA may compete with aspirin or other NSAIDs for renal tubular secretion. Until the pharmacokinetic parameters have been calculated for these 2 patients, the possibility that concurrent NSAID therapy decreased MTA clearance (predisposing these patients to severe toxicity) cannot be ruled out. Additional considerations include the potential renal toxicity of chronic NSAID therapy and the nutritional and folate status of these patients.

### 5.1.4.3. Phase 2 Studies

Results from the population pharmaco-statistical analysis **using PK data from (list studies** identified the following relationships between covariates and pharmacokinetic parameters.

**Clearance: dependent upon calculated creatinine clearance (Clcr), body weight (WGT), serum alanine transaminase concentrations (ALT), and functional folate status (FOL)**

$$Cl_p = \left(2.81 + 0.029 \bullet Cl_{cr} + 0.048 \bullet (WGT - 70) + 0.004 \bullet (ALT - 30.5)\right) \bullet (1 - 0.34 \bullet FOL)$$

Interpatient Variability on Clearance: reduced from 24.1% in the base model to 19.6% using the above relationship.

**Volume of Distribution (Central Compartment): dependent upon WGT and GENDER**

$$V_1 = \left(11.3 + 0.105 \bullet (WGT - 70)\right) \bullet (1 - 0.324 * GENDER)$$

Interpatient Variability on $V_1$: reduced from 21.9% in the base model to 15.6% using the above relationship.

**Volume of Distribution (Peripheral Compartment): dependent upon body surface area (BSA) and serum albumin concentrations (ALB)**

$$V_2 = 5.20 + 4.28 \bullet (BSA - 1.8) - 1.25 \bullet (ALB - 3.67)$$

Interpatient Variability on $V_2$: reduced from 36.7% in the base model to 21.6% using the above relationship

A comparison between the predicted plasma concentration-time profile for the population and observed plasma concentrations is illustrated in Figure 6, Appendix 1. Predicted plasma MTA concentrations for individual patients (from post hoc analysis) agreed well with observed plasma concentrations (Figure 7, Appendix 1). A linear relationship between total clearance and calculated creatinine clearance was observed which is consistent with Phase 1 results. Functional folate status, based upon serum homocysteine, cystathionine, and methylmalonic acid concentrations (homocysteine >13.5 μM; cystathionine >342 nM; 271 <methylmalonic acid <73 nM), identified 2 patients with folate deficiency. This definition of functional folate deficiency predates current work on the multivariate analysis. Slightly different cutoff values for homocysteine, cystathionine, and methylmalonic acid have been used to define folate deficiency in this analysis than are currently being used for the multivariate analysis (Section 6.3). Future population pharmacokinetic analysis will use the most current definition of folate deficiency. Taking into consideration that only 2 patients from this patient population were folate deficient (ie, homocysteine ≥13.5 μM), results from this analysis suggests that the typical value of $Cl_p$ for patients with this level of folate deficiency was 34% less than in patients without folate deficiency. The central compartment volume of distribution was 32% higher in males than females.

### 5.1.5. Summary of Pharmacodynamic Assessments

Despite the variability observed between patients, nadirs of both platelet and neutrophil counts (Figures 8 and 9, Appendix 1) appear to decrease with increasing systemic drug exposure. A log-linear relationship between the nadirs of neutrophil and platelet counts during Cycle 1 (first cycle hematologic toxicity) and the overall nadirs after multiple cycles (worst hematologic toxicity) versus total drug exposure ($AUC_{0-\infty}$) was established. Inspection of the regression results showed that the slope values observed for the worst toxicity increased slightly from the slope values observed for the first cycle toxicity for nadir values of both neutrophils and platelets.

### 5.1.6. Conclusions

- MTA is cleared fairly rapidly from plasma with a terminal elimination half-life of approximately 2 to 3 hours.
- The pharmacokinetics of MTA appear to be linear up to 700 mg/m$^2$ dose level.
- MTA is eliminated predominantly by urinary excretion.
- Pharmacokinetics of MTA are highly predictable.
- With the exception of the fraction of drug excreted unchanged in urine, MTA pharmacokinetics were independent of gender.

- On the basis of data obtained in Cycles 1 and 3, it would appear that increasing systemic drug exposure increases worst hematological toxicity (overall nadir over all cycles)

The pharmacokinetics of MTA in Phase 2 studies were consistent with results from Phase 1 studies.

# Section 6: Clinical/Statistical

## 6.1. Table of Studies

The following table lists in summary form the number of ongoing, completed or planned studies; a more detailed list including information on each study is provided in Appendix 8.

**Table 6.1. Ongoing, Completed, and Planned Studies**

| | Completed | Ongoing | Planned |
|---|---|---|---|
| Phase I monotherapy | 3 | 1 | 1 |
| Phase I combination therapy | 1 | 8 | 13 |
| Phase II | 7 | 12 | 35 |
| PhaseII/III or III | 0 | 0 | 6 |

## 6.2. Safety Overview

### *6.2.1. Studies Included*

This safety summary focuses on data on patients from nine studies; seven completed studies carried out by Eli Lilly and Company (Lilly) [one using the CRO, Theradex, and two completed studies carried out by the National Cancer Institute of Canada (NCIC)]. This data will be presented as four data sets:

- 37 patients from one single agent Phase 1 single agent study (JMAA)
- 51 patients from one combination Phase 1 combination study of MTA and cisplatin (JMAP) which used Theradex for clinical monitoring
- 185 patients from five single agent Phase 2 studies (JMAC, JMAD, JMAG, JMAH, JMAL
- 65 patients from the two single agent NCIC Phase 2 studies.

The NCIC studies utilized the NCIC modified toxicity scale, while the other studies used the NCI modified CTC toxicity scale.

A complete safety dataset is not available for eight ongoing combination Phase 1 studies, or for ten ongoing single agent Phase 2 studies, but serious adverse events and deaths will be reported from these ongoing studies as well as the two NCIC studies.

### *6.2.2. Phase 1 Studies*

Three dosing schedules have been investigated in Phase 1 studies.

- JMAA, 37 patients were treated on a schedule of once every 21 days.

- JMAB, 24 patients received drug once weekly for 4 weeks every 6 weeks.
- BP-001, 38 patients were treated using a schedule of daily times five every 21 days.

The weekly times four every 6 weeks schedule is not currently being pursued in Phase 2 trials. Inability to maintain the weekly treatment schedule due to neutropenia limited dose escalation on this schedule. The daily times five every 3 weeks schedule resulted in an maximum tolerated dose (MTD) of 4 mg/m$^2$/day. This schedule is currently being carried forward in a single Phase 2 trial in colorectal cancer in order to further assess its feasibility.

In addition, in the ongoing JMAP trial we are investigating the MTD and DLT for MTA in combination with cisplatin.

### 6.2.2.1. JMAA

The once every 21 day schedule is being carried forward into Phase 2 trials. In the Phase 1 trial investigating this dose, 37 patients were administered drug at doses ranging from 50 to 700 mg/m$^2$. Dose escalation proceeded by the Modified Continual Reassessment in this study limiting the number of patients exposed to lower doses of drug. Twenty patients were treated at the recommended Phase 2 dose of 600 mg/m$^2$.

#### *Demographics*

A total of 37 patients were treated with a total of 132 courses over 9 dose levels in the Phase 1 study (JMAA) of MTA on the every 21 day schedule. Table 6.2 summarizes the demographics of this study.

**Table 6.2. Patient Demographics from Study JMAA**

| | | |
|---|---|---|
| Patients | | 37 |
| Male/Female | | 27/10 |
| Median age (range) | | 59 (30-74) |
| Performance Status (KPS) | 100 | 16 |
| | 90 | 4 |
| | 80 | 14 |
| | 60 | 3 |
| Prior Regimens of chemotherapy | 0 | 4 |
| | 1 | 8 |
| | 2 | 12 |
| | 3+ | 13 |
| Prior pelvic XRT | | 8 |

***Toxicity***

In the Phase 1 study JMAA, a total of 132 courses of MTA were administered in 37 patients at doses from 50 to 700 mg/m$^2$, with a range of 1 to 12 courses per patient.

There were no instances of CTC Grade III or IV toxicities during the initial courses of therapy in patients treated at the 350 mg/m$^2$ or lower dose levels. At the 525 mg/m$^2$ dose level, a total of 4 patients were treated with 1 patient developing CTC Grade III thrombocytopenia. No other CTC Grade III or IV toxicity was observed. A total of 6 patients were treated at the 700 mg/m$^2$ dose level with 3 developing CTC Grade IV neutropenia. CTC Grade III or IV thrombocytopenia also occurred in these 3 patients. Non-hematologic toxicity was also substantial, with CTC Grade III side effects in 4 patients (mucositis in 2 patients, fatigue, diarrhea, rash, and anorexia in 1 patient each). This was not considered a tolerable dose level.

Since toxicity was significant at 700 mg/m$^2$, but relatively mild at 525 mg/m$^2$, an intermediate dose level of 600 mg/m$^2$ was added. A total of 20 patients were treated at this dose level. Five patients developed CTC Grade IV neutropenia, with one of these patients requiring hospitalization for infection. One of these patients also developed CTC Grade IV thrombocytopenia. Mild to moderate non-hematologic toxicity also occurred in most patients at this dose level. No patient developed CTC Grade III-IV non-hematologic toxicity during their first course. The most common moderate (CTC Grade II) non-hematologic toxicity was a pruritic rash occuring in 10 patients, which was ameliorated with the use of a prophylactic 3-day course of steroids (dexamethasone 4 mg orally twice per day for 3 days starting day -1) around future doses. Six of the 20 patients developed moderate non-dermal toxicity at this dose level. The 600 mg/m$^2$ dose was felt to be the MTD and recommended dose for Phase 2 clinical trials using this schedule of MTA.

Mild reversible renal dysfunction was observed in multiple patients treated at the highest dose levels, and drug toxicity appeared to correlate with renal function. Serum creatinine levels were obtained weekly. Five of 20 patients treated at the 600 mg/m$^2$ dose level and 2 of 6 patients treated at the 700 mg/m$^2$ dose level exhibited a maximal serum creatinine that was greater than 50% over baseline. The highest measured serum creatine level was greater than 2 mg/dL in 5 patients (2.5. 2.6, 2.6, 3.1 and 3.4 mg/dL respectively). This nephrotoxicity appeared to be reversible and nonprogressive despite continued treatment in the majority of these patients. Effects on renal function are still being evaluated in the Phase 2 setting. In addition, the Phase 1 study JMAW has been designed to evaluate the relationship between renal function and the safety profile of MTA in patients with varying degrees of renal impairment.

Of the 37 patients enrolled on the trial, 23 were withdrawn due to disease progression. Seven patients were withdrawn due to toxicity, without evidence of disease progression. This was due to fatigue in 6 patients and thrombocytopenia in 1 patient. Three patients died during the study related to drug toxicity, 2 from neutropenic sepsis and one from

acute respiratory distress syndrome. These deaths occurred after 3, 4, and 8 treatment courses respectively.

#### 6.2.2.2. JMAP

A Phase 1 trial of MTA in combination with cisplatin has recently completed patient accrual. In this study, patients with solid tumors were enrolled into one of two cohorts. The first cohort received both MTA and cisplatin on Day 1 of a 21-day cycle, and the second cohort received MTA on Day 1 and cisplatin on Day 2 of a 21-day cycle. Forty patients were enrolled into the first cohort; the MTD was reached at 600 mg/m$^2$ MTA and 100 mg/m$^2$ cisplatin, with dose-limiting toxicities of thrombocytopenia and febrile neutropenia. Eleven patients were enrolled into the second cohort. The toxicity seen using this split schedule, which has included two therapy-related deaths, has led to the conclusion that the split schedule is clinically inferior.

##### *Demographics*

Table 6.3 summarizes the patient demographics of this study.

**Table 6.3. Patient Demographics from Study JMAP**

| | Cohort 1 | Cohort 2 |
|---|---|---|
| Patients Entered/Evaluable | 42/40 | 12/11 |
| Male/Female | 35/7 | 9/3 |
| Median age (range) | 57 (42 - 73) | 55 (29 - 73) |
| Median WHO Performance Status (range) | 1 (0 - 2) | 1 (0 - 2) |
| Tumor types | | |
| Mesothelioma | 10 | 3 |
| Head and Neck | 9 | 1 |
| Non-small cell lung | 6 | 1 |
| Other | 17 | 7 |

##### *Toxicity*

In the combination Phase 1 study JMAP, 53 patients were treated with MTA plus cisplatin at dose levels from 300 mg/m$^2$ MTA and 60 mg/m$^2$ cisplatin to 600 mg/m$^2$ MTA and 100 mg/m$^2$ cisplatin. In Cohort 1, patients were treated with both drugs on Day 1, and in Cohort 2, patients were treated with MTA on Day 1 and cisplatin on Day 2. The number of patients entered at each dose level in shown in Table 6.4.

**Table 6.4. JMAP Dose Levels**

| Dose Level | MTA (mg/m²) | Cisplatin (mg/m²) | Patients Entered Cohort 1 | Patients Entered Cohort 2 |
|---|---|---|---|---|
| 1 | 300 | 60 | 6 | ---- |
| 2 | 300 | 75 | 7 | ---- |
| 3 | 400 | 75 | 6 | ---- |
| 4 | 500 | 75 | 3 | 7 |
| 5 | 600 | 75 | 12 | 4 |
| 6 | 600 | 100 | 6 | ---- |

The toxicities experienced in Study JMAP are shown in Tables 6.5 through 6.7.

**Table 6.5. Hematological Toxicities in Study JMAP**

| MTA/Cisplatin (m/m2) | # Pts | WBC | | ANC | | HB | | PLT | |
|---|---|---|---|---|---|---|---|---|---|
| | | 3 | 4 | 3 | 4 | 3 | 4 | 3 | 4 |
| Cohort 1 | | | | | | | | | |
| 300/60 | 6 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 0 |
| 300/75 | 7 | 3 | 0 | 3 | 1 | 1 | 0 | 0 | 0 |
| 400/75 | 6 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| 500/75 | 3 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| 600/75 | 12 | 7 | 0 | 5 | 2 | 6 | 2 | 0 | 0 |
| 600/100 | 6 | 3 | 3 | 1 | 3 | 1 | 1 | 0 | 0 |
| Cohort 2 | | | | | | | | | |
| 500/75 | 7 | 3 | 1 | 1 | 1 | 1 | 0 | 0 | 0 |
| 600/75 | 4 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |

**Table 6.6. Nonhematologic Toxicities in Study JMAP (Cohort 1)**

| | 300/60 | | | 300/75 | | | 400/75 | | | 500/75 | | | 600/75 | | | 600/100 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 3 | 4 |
| Anorexia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Nausea | 1 | 0 | 0 | 3 | 1 | 0 | 5 | 1 | 0 | 2 | 0 | 0 | 9 | 2 | 0 | 4 | 1 | 0 |
| Vomiting | 0 | 1 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 4 | 4 | 0 | 3 | 1 | 0 |
| Diarrhea | 1 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Fatigue | 1 | 0 | 0 | 2 | 2 | 0 | 2 | 1 | 0 | 1 | 0 | 0 | 4 | 1 | 0 | 3 | 2 | 0 |
| Infection | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 0 |
| Mucositis | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 0 |
| Skin | 1 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |

This data shows that MTA and cisplatin can be combined at full doses. The toxicity profile appears to be similar to that of MTA alone apart from some cisplatin specific toxicities of tinnitus and peripheral neuropathy. The toxicity profile seen in the subgroup of mesothelioma patients in this study is similar to that of the entire study population.

Two patients receiving the split schedule died of treatment related toxicity. One patient died of septic complications of myelosuppression and the other died of metabolic shock secondary to diarrhea and mucositis. These deaths were the primary reason that the same day schedule was selected for further clinical development rather than the split schedule. Further details on these deaths may be found in Appendix 3.

**Table 6.7. Nonhematologic Toxicities in Study JMAP (Cohort 2)**

| | 500/75 | | | 600/75 | | |
|---|---|---|---|---|---|---|
| | 2 | 3 | 4 | 2 | 3 | 4 |
| Anorexia | 1 | 0 | 0 | 0 | 0 | 0 |
| Nausea | 6 | 1 | 0 | 2 | 0 | 0 |
| Vomiting | 4 | 1 | 0 | 1 | 0 | 0 |
| Diarrhea | 0 | 0 | 1 | 0 | 0 | 0 |
| Fatigue | 3 | 0 | 0 | 0 | 0 | 0 |
| Infection | 0 | 0 | 1 | 0 | 0 | 1 |
| Mucositis | 1 | 0 | 0 | 0 | 0 | 1 |
| Skin | 2 | 1 | 0 | 0 | 1 | 0 |

## *6.2.3. Phase 2 Studies*

### 6.2.3.1. Lilly Studies JMAC, JMAD, JMAG, JMAH, JMAL

Five single agent Phase 2 studies have been completed under the sponsorship of Lilly. Single studies have been completed in patients with colorectal cancer (JMAC), pancreatic cancer (JMAD), breast cancer (JMAG), esophageal cancer (JMAH), and non-small cell lung cancer (JMAL). JMAC and JMAD were multi-institutional studies performed in the United States at six academic institutions. All of these studies used a starting dose of 600 mg/m$^2$ administered every 21 days. The patient population in JMAC included patients who had no prior therapy for metastatic colorectal cancer but may have had adjuvant therapy if completed greater than 1 year prior to study entry. JMAD included patients with advanced pancreatic cancer without previous chemotherapy. JMAG was a multi-institutional study conducted at four referral centers in the UK. Patients with locally advanced or metastatic breast cancer were included in the patient population. Eligible patients may have received prior chemotherapy in either the adjuvant or metastatic setting but may not have received more than one prior regimen for metastatic disease. Prior therapy with a thymidylate synthase inhibitor was not allowed if used within 1 year of study entry. JMAH was conducted at four centers in the UK and South Africa and

included patients with advanced esophageal carcinoma without prior chemotherapy. JMAL was conducted at five centers in South Africa and Australia, and included patients with Stage III and IV non-small cell lung cancer who had not received prior chemotherapy.

### *Demographics*

A total of 185 patients have been treated representing 755 total doses with MTA on Studies JMAC, JMAD, JMAG, JMAH, and JMAL at the 600 mg/m$^2$ dose level on the 21 day schedule. Table 6.8 summarizes the demographics of this patient population.

**Table 6.8. Summary of Patient Demographics in Studies JMAC, JMAD, JMAG, JMAH, and JMAL**

| | |
|---|---|
| Patient Number | 185 |
| Male / Female | 92 / 93 |
| Median Age (range) | 58 yrs (33 - 79 yrs) |
| Performance Status (ECOG) | |
| 0 | 57 |
| 1 | 93 |
| 2 | 33 |
| missing data | 2 |
| Tumor Type | |
| Colorectal | 40 |
| Pancreatic | 42 |
| Esophageal | 20 |
| Breast | 38 |
| Non-small Cell Lung | 45 |

Fifteen (38%) patients in JMAC had prior adjuvant chemotherapy. Thirty-three (87%) patients in JMAG had prior chemotherapy either in the adjuvant setting and or up to one regimen given for metastatic disease. Patients in JMAD, JMAH, and JMAL were not permitted to have had prior chemotherapy. One patient in JMAH had prior radiotherapy.

### *Toxicity*

A total of 185 patients in five initial Phase 2 (Lilly) studies have been treated on the once every 21 days schedule in the Phase 2 setting at a starting dose of 600 mg/m$^2$ for which we have clean data and are therefore evaluable for safety analysis. Dose adjustments in the second and subsequent cycles were based on nadir blood counts and presence of mucositis. Toxicity was reported according to the modified Common Toxicity Criteria (CTC) of the National Cancer Institute. Complete blood counts were required on a weekly basis throughout the course of therapy. As demonstrated in the Phase 1

experience, the most frequent toxicity has been hematologic in nature. Hematologic toxicity has been manageable and noncumulative in the Phase 2 experience.

Severe neutropenia was the most common hematologic toxicity but was reversible and infrequently led to serious outcomes. CTC Grade 4 neutropenia was experienced by 24% of patients and associated with 76 (10%) cycles of treatment. Overall, the reported frequency of serious infection has been low (Grade 4 infection 2%). Nevertheless, there have been 13 of 748 patients who died of septic complications of myelosuppresion, and in an additional 3 patients, neutropenia is thought to have contributed to the patients' deaths (see Appendix 3).

Thrombocytopenia and anemia were frequently experienced by patients but severe episodes were less frequent than severe neutropenia. CTC Grade 3 and 4 thrombocytopenia was experienced by 6% and 9% of patients and associated with 12 (1.6%) and 16 (2%) of cycles. Serious episodes of bleeding have been rare (CTC Grade 4 hemorrhage <1%). Platelet transfusions were administered in 16 (2%) cycles. CTC Grade 3 and Grade 4 anemia was reported for 12% and 2% of patients and associated with 28 (4%) and 5 (<1%) cycles. Red cell transfusions were administered in 61 (8%) cycles. Severe anemia was felt to have contributed to the death of a patient who had cardiac failure while on study (see Appendix 3 for further details). This patient had a prior history of cardiac events including three prior myocardial infarcts.

The common nonhematological toxicity experienced by patients in the Phase 2 setting has been similar to that reported in the Phase 1 study JMAA and includes skin rash, transient elevation of the liver transaminases, and gastrointestinal toxicity. Skin rash has been reported in 77% of patients (Grade 1: 37 patients, 20%; Grade 2: 71 patients, 38.4%; Grade 3: 22 patients, 12%; Grade 4: 12 patients, 6.5%). Two patients (in the Lilly monitored Phase 2 studies) discontinued treatment because of rash. Dexamethasone 4 mg orally twice per day given 1 day for 3 days beginning 1 day prior to therapy was noted to prevent or ameliorate rash in the Phase 1 setting. This dose and schedule was used in the Phase 2 setting as prophylaxis once the patient had experienced rash, and has been successful in reducing the frequency and severity of rash in subsequent cycles. Transient Grade 3 and 4 elevation of liver transaminases are common but have not been dose-limiting. There have been no cases of persistent transaminase elevation within this integrated data set. While fatigue has been an important reported toxicity in both the Phase 1 and Phase 2 experience, no patients have discontinued therapy because of fatigue in the Phase 2 setting (in the Lilly monitored studies). Reported gastrointestinal toxicity as demonstrated by nausea, vomiting, diarrhea and stomatitis have been common but less frequently severe. Prophylactic anti-emetic regimens were determined by the individual treating physician and not required in the Phase 2 protocols. Gastrointestinal toxicity did not appear to be cumulative in nature, however of the 22 of 748 patients who died secondary to MTA treatment (see Section 7 and Appendix 3), five patients died of complications of diarrhea. Three of these five developed renal failure, one developed hypotensive shock and one developed metabolic shock. In a further two patients,

gastrointestinal toxicity contributed to the patients' deaths. In one of these cases, the patient had a gastrointestinal hemorrhage secondary to stomach cancer. The death was not thought to be study drug related by the investigator, but it occurred in the setting of myelosuppression secondary to MTA. In the remaining case, a patient who experienced intractable nausea, vomiting, dehydration, mucositis and hematologic toxicities. This patient recovered, but subsequently developed acute respiratory distress syndrome. The investigator's opinion was that the prior toxicities had predisposed this patient to developing ARDS. The incidence of Grade 3 and 4 diarrhea is 7%. Based on this data, all new protocols contain language stating that in the event of CTC Grade 3 or 4 diarrhea, patients should receive hydration and antidiarrheals. If diarrhea is severe (requiring intravenous rehydration), or associated with fever or severe neutropenia (Grade 3 or 4), the administration of broad spectrum antibiotics is recommended. Patients with severe diarrhea (requiring intravenous rehydration) with severe nausea or vomiting must be hospitalized for intravenous hydration and correction of electrolyte imbalances.

Tables 6.9 and 6.10 summarize the laboratory and nonlaboratory toxicity data from the Lilly Phase 2 studies conducted at a starting dose of 600 mg/m$^2$.

**Table 6.9. Laboratory Toxicity (n=185) in Studies JMAC, JMAD, JMAH, JMAG, and JMAL**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| ANC | 9 | 21 | 24 | 24 |
| Leukocytes | 14 | 28 | 35 | 10 |
| Platelets | 31 | 6 | 6 | 9 |
| Hb | 34 | 43 | 12 | 2 |
| ALT | 33 | 26 | 22 | 0 |
| AST | 42 | 30 | 10 | 0 |
| Bilirubin | 0 | 18 | 7 | 2 |
| Creatinine | 13 | 5 | 0 | 0 |

**Table 6.10. Nonlaboratory Toxicity (n=185) in Studies JMAC, JMAD, JMAH, JMAG, and JMAL**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Cutaneous | 19 | 39 | 11 | 5 |
| Diarrhea | 17 | 11 | 4 | 3 |
| Infection | 13 | 8 | 2 | 2 |
| Nausea | 33 | 30 | 9 | 1 |
| Fatigue | 13 | 11 | 6 | 0 |
| Pulmonary | 0.5 | 7 | 2 | 2 |
| Stomatitis | 23 | 16 | 6 | 1 |
| Vomiting | 13 | 30 | 2 | 3 |

### 6.2.3.2. NCIC Studies JMAN and JMAO

Two Phase 2 studies were conducted by the NCIC-CTG in patients with colorectal cancer (JMAO) and NSCLC (JMAN). These studies included 65 patients and involved 265 total doses. Table 6.11 summarizes the patient demographics in these two studies. The initial starting dose of 600 mg/m$^2$ was reduced to 500 mg/m$^2$ after 7 of the first 9 patients experienced adverse events requiring dose reductions. Toxicities leading to these reductions included rash, mucositis, neutropenia, and febrile neutropenia. Toxicities on these trials were reported as the NCI-Canada modified toxicity criteria and are presented in Tables 6.12 through 6.17. This data is consistent with the data presented above. There were no deaths secondary to MTA therapy in these studies.

### *Demographics*

**Table 6.11. Summary of Patient Demographics in Studies JMAN and JMAO**

| | |
|---|---|
| Patient Number | 65 |
| Male / Female | 41 / 24 |
| Median Age (range) | 65 yrs (42 - 77 yrs) |
| Performance Status (ECOG) | |
| 0 | 25 |
| 1 | 37 |
| 2 | 3 |
| Tumor Type | |
| Colorectal | 32 |
| Non-small cell lung | 33 |

**Table 6.12. Laboratory Toxicity in Study JMAO (n = 32)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| ANC | 6 | 28 | 28 | 22 |
| WBC | 19 | 44 | 22 | 13 |
| Platelets | 50 | 0 | 3 | 9 |
| Hb | 44 | 38 | 13 | 0 |
| Alk Phos | 34 | 3 | 0 | 0 |
| Bilirubin | 0 | 13 | 13 | 0 |
| Creatinine | 19 | 6 | 0 | 0 |
| AST | 53 | 16 | 3 | 0 |

**Table 6.13. Nonlaboratory Toxicity in Study JMAO (n = 32)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Rash/Itch | 13 | 38 | 41 | 0 |
| Diarrhea | 22 | 16 | 3 | 6 |
| Infection | 3 | 22 | 9 | 0 |
| Nausea | 25 | 34 | 16 | 0 |
| Fatigue | 25 | 41 | 16 | 3 |
| Pulmonary | 9 | 13 | 6 | 3 |
| Stomatitis | 28 | 16 | 3 | 0 |
| Vomiting | 6 | 31 | 3 | 9 |

**Table 6.14. Laboratory Toxicity in Study JMAN (n = 33)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| ANC | 9 | 30 | 27 | 12 |
| WBC | 15 | 27 | 33 | 6 |
| Platelets | 42 | 3 | 0 | 3 |
| Hb | 42 | 30 | 9 | 0 |
| Alk Phos | 42 | 3 | 0 | 0 |
| Bilirubin | 0 | 9 | 0 | 0 |
| Creatinine | 3 | 0 | 0 | 0 |
| AST | 48 | 21 | 6 | 0 |

**Table 6.15. Nonlaboratory Toxicity in Study JMAN (n = 33)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Rash/Itch | 9 | 30 | 39 | 0 |
| Diarrhea | 18 | 6 | 9 | 0 |
| Infection | 0 | 3 | 3 | 0 |
| Nausea | 39 | 24 | 12 | 0 |
| Fatigue | 9 | 45 | 21 | 0 |
| Pulmonary | 3 | 9 | 6 | 0 |
| Stomatitis | 15 | 12 | 6 | 0 |
| Vomiting | 21 | 15 | 9 | 0 |

Tables 6.16 through 6.19 show toxicities for those patients in all seven Phase 2 studies discussed in this section treated with a starting dose of 600 mg/m$^2$ and toxicities for those patients treated with a starting dose of 500 mg/m$^2$.

**Table 6.16. Laboratory Toxicity (n=197) in Studies JMAC, JMAD, JMAH, JMAG, JMAL, JMAO, and JMAN (600 mg/m$^2$)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| ANC | 9 | 22 | 24 | 24 |
| Leukocytes | 14 | 28 | 35 | 10 |
| Platelets | 31 | 6 | 6 | 10 |
| Hb | 33 | 45 | 12 | 2 |
| AST | 43 | 30 | 9 | 0 |
| Bilirubin | 0 | 18 | 7 | 2 |
| Creatinine | 13 | 5 | 0 | 0 |

**Table 6.17. Nonlaboratory Toxicity (n=197) in Studies JMAC, JMAD, JMAH, JMAG, JMAL, JMAN, and JMAO (600 mg/m$^2$)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Cutaneous | 18 | 39 | 13 | 5 |
| Diarrhea | 17 | 11 | 4 | 4 |
| Infection | 12 | 9 | 3 | 2 |
| Nausea | 34 | 29 | 9 | 1 |
| Fatigue | 14 | 14 | 6 | 0 |
| Pulmonary | 5 | 7 | 3 | 2 |
| Stomatitis | 24 | 16 | 6 | 1 |
| Vomiting | 13 | 30 | 2 | 3 |

**Table 6.18. Laboratory Toxicity in Studies JMAO and JMAN Patients Treated at 500 mg/m$^2$ (n = 53)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| ANC | 9 | 30 | 26 | 15 |
| WBC | 17 | 36 | 26 | 8 |
| Platelets | 49 | 2 | 0 | 4 |
| Hb | 43 | 32 | 9 | 0 |
| Alk Phos | 42 | 4 | 0 | 0 |
| Bilirubin | 0 | 11 | 8 | 0 |
| Creatinine | 13 | 6 | 0 | 0 |
| AST | 55 | 17 | 6 | 0 |

**Table 6.19. Nonlaboratory Toxicity in Studies JMAO and JMAN Patients Treated at 500 mg/m$^2$ (n = 53)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Rash/Itch | 13 | 32 | 40 | 0 |
| Diarrhea | 25 | 11 | 8 | 2 |
| Infection | 8 | 21 | 11 | 0 |
| Nausea | 30 | 32 | 15 | 0 |
| Fatigue | 17 | 40 | 25 | 2 |
| Pulmonary | 9 | 28 | 8 | 4 |
| Stomatitis | 19 | 15 | 4 | 0 |
| Vomiting | 17 | 15 | 8 | 4 |

The incidence of combined Grade 3 and 4 toxicity and of Grade 4 toxicity alone was compared in a data set of 197 patients treated at 600 mg/m$^2$ (colorectal, pancreas,

esophagus, breast, and lung cancer) and 53 patients with either colorectal or lung cancer treated at 500 mg/m2. Fishers exact test was used to test for significance. Data is shown in Tables 6.20 and 6.21. It can be seen that there is no significant difference with respect to the laboratory parameters between the two groups, for either combined Grade 3 and 4 toxicity or for Grade 4 alone. However, for symptomatic parameters, there does appear to be a statistically significant difference in favor of the 600 mg/m2 dose level with respect to combined Grade 3 and 4 cutaneous toxicity, fatigue, and stomatitis. Data is shown in Tables 6.22 and 6.23. This difference is unlikely to be due to the 600 mg/m2 dose level and is more likely to reflect a change in the administration of dexamethasone or other supportive measures. The difference was not apparent apart from a comparison of Grade 4 toxicity.

**Table 6.20. Incidence of Laboratory Toxicities 600 mg vs. 500 mg, Grade 3 or 4**

| | 600 mg (n=197) | 500 mg (n=53) | Fisher's Exact Test P-Value |
|---|---|---|---|
| ANC | 95 (48%) | 22 (41%) | 0.439 |
| Leukocytes | 89 (45%) | 18 (34%) | 0.161 |
| Platelets | 32 (16%) | 3 (4%) | 0.072 |
| Hb | 28 (14%) | 5 (9%) | 0.494 |
| AST | 18 (9%) | 6 (8%) | 0.605 |
| Bilirubin | 18 (9%) | 3 (6%) | 0.580 |
| Creatinine | 0 (0%) | 0 (0%) | 1.000 |
| Alk Phos | --- | 0 (0%) | --- |

**Table 6.21. Incidence of Laboratory Toxicities 600 mg vs. 500 mg, Grade 4**

| | 600 mg (n=197) | 500 mg (n=53) | Fisher's Exact Test P-Value |
|---|---|---|---|
| ANC | 47 (24%) | 8 (15%) | 0.195 |
| Leukocytes | 20 (10%) | 4 (8%) | 0.793 |
| Platelets | 20 (10%) | 2 (4%) | 0.180 |
| Hb | 4 (2%) | 0 (0%) | 0.581 |
| AST | 0 (0%) | 0 (0%) | 1.000 |
| Bilirubin | 4 (0%) | 0 (0%) | 0.581 |
| Creatinine | 0 (0%) | 0 (0%) | 1.000 |
| Alk Phos | --- | 0 (0%) | --- |

**Table 6.22. Incidence of Nonlaboratory Toxicities 600 mg vs. 500 mg, Grade 3 or 4**

| | 600 mg (n=197) | 500 mg (n=53) | Fisher's Exact Test P-Value |
|---|---|---|---|
| cutaneous | 35 (18%) | 21 (40%) | 0.001 |
| diarrhea | 16 (8%) | 5 (10%) | 0.781 |
| infection | 10 (5%) | 6 (11%) | 0.115 |
| nausea | 20 (10%) | 8 (15%) | 0.329 |
| fatigue | 12 (6%) | 14 (27%) | 0.001 |
| pulmonary | 10 (5%) | 6 (12%) | 0.115 |
| stomatitis | 3 (7%) | 14 (27%) | 0.001 |
| vomiting | 12 (5%) | 6 (11%) | |

**Table 6.23. Incidence of Nonlaboratory Toxicities 600 mg vs. 500 mg, Grade 4**

| | 600 mg (n=197) | 500 mg (n=53) | Fisher's Exact Test P-Value |
|---|---|---|---|
| cutaneous | 10 (5%) | 0 (0%) | 0.126 |
| diarrhea | 8 (4%) | 1 (2%) | 0.689 |
| infection | 4 (2%) | 0 (0%) | 0.581 |
| nausea | 2 (1%) | 0 (0%) | 1.000 |
| fatigue | 0 (0%) | 1 (2%) | 0.212 |
| pulmonary | 4 (2%) | 2 (4%) | 0.610 |
| stomatitis | 2 (1%) | 0 (0%) | 1.000 |
| vomiting | 6 (3%) | 2 (4%) | 0.678 |

The relationship of AUC to neutropenia has also been studied and is presented in the table below (Table 6.24). These data suggest a lack of dependency of CTC Grade 4 neutropenia to AUC in Phase 2 studies.

**Table 6.24. CTC Grade 4 Neutropenia as a Function of MTA AUC**

| | CTC Grade 0 - 3 Neutropenia | CTC Grade 4 Neutropenia |
|---|---|---|
| JMAA (Phase 1) | **(50 to 600 mg/m$^2$)** | **(patients treated at 600 mg/m$^2$)** |
| Mean AUC | 215 | 267 |
| (range) | (14 - 423) | (208 - 362) |
| # patients | (n = 28) | (n = 5) |
| Phase 2 Studies | **(500 or 600 mg/m$^2$)** | **(500 or 600 mg/m$^2$)** |
| Mean AUC | 214 | 236 |
| (range) | (151 - 315) | (191 - 373) |
| # patients | (n = 109) | (n = 18) |

Taken together, this data suggests that there is no evidence currently to favor a 500 mg/m2 dose level over 600 mg/m2. Therefore, all new protocols where MTA is evaluated as a single agent will study the 600 mg/m2 dose level.

## 6.3. Multivariate Analysis

### *6.3.1. Introduction*

A variety of folic acid analogues are potent chemotherapeutic agents against a number of human malignancies. The most common toxic side effects include hematologic abnormalities such as neutropenia, thrombocytopenia, and anemia as well as mucositis. These abnormalities resemble those seen in patients with folic acid deficiency who often develop neutropenia, thrombocytopenia and anemia. They sometimes also develop mucosal abnormalities such as glositis, although severe mucositis is very unusual. It has been postulated that folate status, both before and during therapy with folic acid analogues, might be inversely correlated with the occurrence and severity of toxic side effects.

Recent studies have demonstrated that levels of serum homocysteine, a metabolite that is a substrate for one of the folate dependent enzymes methionine synthase, is inversely proportional to folate status and is a more sensitive indicator or folate status than are measurements of serum or red cell folate (Vu et al, 1991; Joosten et al, 1993). When we began Phase 2 studies, we determined that it was important to understand the relationship between folate status and toxicity; thus, in many Phase 2 studies we measured vitamin metabolites. Our goal was to determine if levels of vitamin metabolites correlated with and/or were predictive of various toxic side effects, as well as tumor response.

Cobalamin (vitamin $B_{12}$) is a required cofactor for methionine synthase and vitamin $B_6$ is a required cofactor for cystathionine synthase which converts homocysteine to cystathionine. Cobalamin and vitamin $B_6$ deficiencies also result in elevated serum homocysteine levels. Serum methylmalonic acid levels are elevated in cobalamin deficiency, but not in folate deficiency, and are useful in distinguishing between cobalamin and folate deficiency. Cystathionine levels are markedly elevated in vitamin $B_6$ deficiency and are elevated to a lesser extent in both cobalamin and folate deficiency. Therefore, we also decided to measure methylmalonic acid and cystathionine in an attempt to elucidate the relative importance of folate, cobalamin and vitamin $B_6$ status in determining homocysteine levels and the incidence and severity of toxicity seen with MTA. We also hoped to determine if pre and/or post chemotherapy treatment with folic acid, cobalamin or vitamin $B_6$ would be useful in decreasing the incidence and severity of various toxic side effects and whether such therapy would have an impact on therapeutic efficacy.

### *6.3.2. Analysis*

The objectives of this multivariate analysis were to:

1. assess the relationship of vitamin metabolites, drug exposure and other prespecified patient characteristics to toxicity following single or multiple courses of therapy with MTA, and
2. determine to what extent several clinical factors known about a patient beforehand can help predict whether the patient is likely to experience severe toxicity following MTA therapy.

This analysis used information from 139 Phase 2 patients with tumors of the colon, breast, pancreas, and esophagus since homocysteine (Hcys), cystathionine, and methylmalonic acid were measured at baseline and once each cycle thereafter. Stepwise regression modeling was used to help trim out models to predict the toxicity, with a careful review of correlation between various prognostic to avoid issues of colinearity. Prognostic factors retained (p-value<0.15) were then used in a standard least square regression model fitting to confirm their correlation with the toxicity. Threshold values were tested using chi-square test. A multivariate fitting using MANOVA with the identity matrix as the response design matrix was implemented with the final selected predictors. These selected predictor variables were used in a multivariate discriminant analysis to predict patients who will develop toxicity. Prognostic factors considered were age, gender, baseline performance status, baseline albumin, liver enzymes, creatinine clearance, prior treatment with a myelosuppressive agent, ANC, platelets, vitamin metabolites (ie, homocysteine, cystathionine, and methylmalonic acid), and AUC.

For a detailed discussion of the methodology used in this analysis, see Appendix 5.

### 6.3.3. Results

Following one course of therapy with MTA, statistically significant predictors of Grade 4 neutropenia (n=21 pts) were baseline albumin (p<0.0001) and baseline Hcys (p=0.002), while Grade 4 thrombocytopenia (n=8) was predicted by baseline Hcys (p<0.0001) and baseline albumin (p=0.0237). Baseline Hcys was also found to be the only statistically significant (p=0.0014) prognostic factor for Grade 3/4 mucositis, diarrhea, rash, or fatigue after one cycle of treatment. A threshold baseline homocysteine value of 10 μmol/L for Grade 4 neutropenia after Cycle 1 was identified ($\chi^2$=6.2, p=0.01). Hcys levels did not change from baseline (p=0.77) during MTA therapy. Hcys ≥10μM predicted Grade 4 neutropenia in cycle one 75% of the time. Grade 4 neutropenia was predicted by Hcys alone in 71% of cases. Hcys ≥10μM predicted Grade 4 thrombocytopenia in Cycle 1 87.5% of the time.

Statistically significant predictors of Grade 4 neutropenia at any time during MTA therapy (n=32 patients) were again found to be albumin (p=0.0021) and Hcys (p=0.0065), while Grade 4 thrombocytopenia at any time during MTA therapy (n=16 patients) was predicted by Hcys (p=0.0014). Hcys ≥10μM predicted Grade 4 neutropenia at any time during MTA therapy 66% of the time. Grade 4 thrombocytopenia at any time during MTA therapy was predicted by Hcys alone in 81% of cases. Homocysteine was identified as the only statistically significant (p=0.0014) prognostic factor for Grade 3/4

mucositis, diarrhea, rash, or fatigue following one course of MTA therapy. While AUC was not found to be a predictor of toxicity, little variability was observed in AUC. Maximum values were still below AUC values related to hematologic toxicity in Phase 1 studies.

### 6.3.4. Conclusion

Toxicities resulting from therapy with MTA appear to be predictable from pretherapy homocysteine levels. Elevated baseline homocysteine levels (≥10μM) highly correlate with severe hematologic and nonhematologic toxicities following therapy with MTA. Homocysteine was found to be better than albumin at predicting hematologic toxicity. Homocysteine levels were not altered by MTA therapy, making it an ideal marker for use in screening patients at risk of hematologic and nonhematologic toxicities prior to therapy with MTA. These results apply to the tumor types studied. Further studies are underway in patients with renal impairment or patients who received prior cisplatin.

# Section 7: Risk to Benefit Ratio

MTA has very broad antitumor activity , as evidenced by its response rate in a variety of unrandomized multi-institutional Phase 2 studies (see Tables 1.1 and 1.2). Of particular note is the 20% response rate in chemotherapy naïve NSCLC patients, the 47% response rate in an ongoing study in head and neck cancer, and the 31% response rate in advanced/metastatic breast cancer. Some of the emerging time to event variables are also intriguing, such as the median duration of survival in frontline colorectal and pancreas cancer, (16.2 months in study JMAC and 6.5 months in study JMAD respectively). It should be remembered that this data is subject to the important caveat that it is derived from unrandomized Phase 2 studies, where the patient population is selected

This activity needs to be balanced against the toxicity profile to determine the risk to benefit ratio of MTA.

The dose limiting toxicity of MTA is myelosuppression, with a 48% combined incidence of Grade III and IV toxicity (Table 6.20). Common nonhematologic toxicities include elevations of transaminases, fatigue, a skin rash. and gastrointestinal toxicity (stomatitis and diarrhea). This profile is typical of an antifolate, and as such toxicities are routinely managed by the oncology physician. In 748 patients treated with MTA to date, there have been 22 deaths which are clearly treatment related (2.9%). These are reviewed in Appendix 3. Thirteen of these 22 patients died of septic complications of myelosuppression, and in an additional 3 patients, neutropenia is thought to have contributed to the patients' deaths. Five of the 22 patients died due to events secondary to diarrhea (3 with renal failure, 1 with hypotensive shock, 1 with metabolic shock). Two patients had both gastrointestinal toxicity and neutropenia; one of these expired of acute respiratory distress syndrome. The remaining death occurred in a patient with a prior history of cardiac failure, including 3 prior infarcts. He had severe MTA-related anemia which was thought to have contributed to his fatal cardiac failure while on therapy. Seven of these 22 treatment-related deaths occurred in Phase 1 studies, of which 2 occurred secondary to treatment with the combination of MTA and cisplatin. To date, there have been no treatment-related deaths in Phase 2 MTA combination studies, or in other Phase 1 combination studies.

The finding of a strong correlation between baseline homocysteine and various toxicities (including neutropenia and diarrhea) in the multivariate analysis provide the opportunity for improved individual patient management and for reduction in toxicity by vitamin supplementation. These hypotheses need to be tested prospectively in clinical trials, but the ability to dose intensify to 1250 mg/m$^2$ in the folate supplementation Phase 1 study (JMAS) supports the notion that supplementation reduces toxicity.

Taken together this data suggests that MTA has good activity for this stage of its clinical development, and an acceptable toxicity profile. The current clinical development strategy therefore includes registration directed clinical trials, while at the same time

incorporates measures directed toward improving our understanding of the risk factors for toxicity, and how to improve tolerance. These same registration directed trials will clearly help to better define the risk to benefit ratio for MTA.

# Section 8: Measurement of Unidimensional Disease is Appropriate in Mesothelioma

Study JMCH is a randomized clinical trial designed to evaluate the efficacy of MTA plus cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. There currently exists no standard chemotherapeutic treatment regimen for patients with this rare and lethal tumor, and no agent has been able to demonstrate better than modest response rates. For these reasons, we have designed a protocol which will allow us to accrue a sufficient number of patients to demonstrate differences in response rate between the two treatment arms.

The accuracy with which a mesothelioma lesion may be measured is potentially hampered by factors which include the existence of pleural fluid and possible fibrotic changes. Because the tumor encases and surrounds the hemithorax, forming a rind rather than producing a nodule, it is inherently difficult to obtain two dimensional measurements, and in fact those two dimensional measurements that are provided for in the protocol stem from lesions secondary to the primary tumor. We are therefore proposing that this study will include patients who have either unidimensionally measurable or bidimensionally measurable disease, and this degree of measurability has been included as a stratification factor.

Many have argued that unidimensional tumor measurements provide sufficient information for determining tumor response in clinical trials and in fact, that they are as useful as bidimensional measurements in all tumor types (Gurland 1966). This is especially true in mesothelioma where bidimensional measurement is not appropriate. Spears has demonstrated that unidimensional measurements are valid in estimating tumor size except in cases where the length of the tumor mass is more than twice its width (Spears 1984). In a retrospective study carried out by the NCIC, NCI (US), NCI (Italy), and EORTC, there was a 95% agreement in designation of partial responders when unidimensional measurements were compared to bidimensional measurements (James et al 1997).

Because of the general growth pattern of the mesothelioma lesion, we are proposing that as the thickness of the rind approaches zero, a decrease in tumor thickness will result in a reduction in tumor size. We have imposed strict guidelines on the radiologic imaging of the tumor. Within 4 weeks of study enrollment each patient will have been assessed by computerized tomography of the chest and upper abdomen. Contrast medium will be used consistently throughout the study unless clinically contraindicated. The thickness of sections will be 10 mm and the spacing will be 10 mm. Scans will include the apex through the base of the lung. This method will be used consistently for tumor assessment and will be repeated every 6 weeks (prior to every other cycle). For each patient, every CT image will be compared to the corresponding image from the previous examination. To ensure identical localization of CT images, anatomical landmarks in vertebrae, ribs, or the central bronchial tree will be used during the CT scanning procedure. The thickness

of the tumorous parietal, visceral, diaphragmatic, and mediastinal pleura will be measured together with any enlarged lymph nodes in the mediastinum, rectrocural space or axillae.

To ensure uniform interpretation of scans, Lilly will be working with Bioimaging, Inc. Bioimaging will conduct training on collection of CT scans and ongoing quality review of these scans, will prepare the electronic versions of scans for review, will set up workstations at the reviewing sites, and will develop a worksheet for reviewers. Each reviewer will follow the same protocol for review of scans.

Appendix 1

# Appendix 1
# Pharmacokinetic Figures and Tables

**Table 1. Mean (%CV) LY231514 Pharmacokinetic Parameters**

| Study Number | Route of Administration Dosage Form | Dose ($mg/m^2$) | $C_{max}$ ($\mu g/mL$) | $T_{max}$ (hr) | $V_d/F$ ($L/m^2$) | $AUC_{0-\infty}$ ($\mu g \cdot hr/mL$) | $T_{1/2}$[a] (hr) | Urinary Excretion (% of dose) | $Cl_p/F$ ($ml/min/m^2$) | $Cl_r$ ($ml/min/m^2$) |
|---|---|---|---|---|---|---|---|---|---|---|
| JMAA | IV (10 minute infusion) | 525 (n=3) | 121 (13) | 0.19 (53) | 6.9 (12)[b]<br>13.7 (26)[c] | 231 (32) | 3.9 | 69.9 (29) | 40.7 (33) | 27.4 (52) |
| | | 600 (n=20) | 137 (14) | 0.20 (52) | 7.0 (20)[b]<br>11.5 (40)[c] | 266 (29) | 3.1 | 82.9 (15) (n=4) | 40.0 (24) | 35.9 (41) (n=4) |
| | | 700 (n=5) | 175 (27) | 0.18 (50) | 6.4 (7.7)[b]<br>10.9 (17)[c] | 398 (43) | 3.7 | 87.8 (20) (n=4) | 33.6 (39) | 29.9 (73) (n=3) |
| | Female | 50 - 700 (n=9) | NR | NR | 6.6 (23)[b]<br>13.8 (43)[c] | NR | NR | 90.4 (11) (n=7) | 44.3 (21) (n=9) | 41.0 (29) (n=5) |
| | Male | (n=26) | NR | NR | 7.1 (22)[b]<br>10.3 (22)[c] | NR | NR | 68.4 (27) (n=11) | 40.0 (26) (n=26) | 28.5 (45) (n=11) |
| | All | (n=35) | NR | NR | 6.9 (22)[b]<br>11.2 (34)[c] | NR | NR | 77.0 (24) (n=18) | 41.1 (33) (n=35) | 32.4 (42) (n=16) |
| | Repeat Administration | 450 and 600 (n=4)[d] | 94.5 (18) | 0.3 (64) | 7.4 (4.2)[b]<br>10.0 (12)[c] | 221 (19) | 2.4 | NR | 47.5 (15) | NR |
| JMAB | IV (10 minute infusion) | 10 (n=4) | 2.01 (20) | 0.13 (67) | 6.3 (16)[b]<br>8.4 (16)[c] | 2.57 (50) | 1.27 | NR | 79.2 (49) | NR |
| | | 20 (n=4) | 4.32 (14) | 0.2 (40) | 5.7 (8.6)[b]<br>7.9 (26)[c] | 5.91 (27) | 1.5 | NR | 59.6 (27) | NR |
| | | 30 (n=10) | 7.48 (17) | 0.2 (40) | 5.6 (23)[b]<br>7.5 (22)[c] | 13.6 (35) | 2.1 | NR | 39.6 (24) | NR |
| | | 40 (n=7) | 11.2 (40) | 0.2 (44) | 6.6 (16)[b]<br>9.1 (11)[c] | 14.4 (42) | 2.0 | NR | 52.3 (34) | NR |

NR - not reported

[a] harmonic mean

[b] steady-state volume of distribution

[c] apparent volume of distribution

[d] repeat administration following fourth course

**Table 2. Mean (%CV) LY231514 Pharmacokinetic Parameters**

| Study Number | Route of Administration Dosage Form | Dose ($mg/m^2$) | $C_{max}$ (ng/mL) | $T_{max}$ (hr) | $V_d/F^b$ ($L/m^2$) | $AUC_{0-\infty}$ (ng•hr/mL) | $T_{1/2}{}^a$ (hr) | Urinary Excretion (% of dose) | $Cl_p/F$ (ml/min) | $Cl_r$ ($ml/min/m^2$) |
|---|---|---|---|---|---|---|---|---|---|---|
| BP 001 | IV (10 minute infusion) | 0.2 (n=3) | 28.7 (16) | 0.08 | 7.4 (18)[b]<br>7.8 (14)[c] | 25.4 (46) | 0.6 | NR | 149.9 (42) | NR |
| | | 0.4 (n=4) | 68.8 (36) | 0.08 | 15.1 (48)<br>6.9 (84) | 117.4 (83) | 0.7 | NR | 118.8 (84) | NR |
| | | 0.52 (n=3) | 79.1 (37) | 0.1 (70) | 15.3<br>17.6 (n=1) | 80.9 (n=1) | 1.9 | NR | 107.1 (n=1) | NR |
| | | 0.78 (n=2) | 148.1 | 0.08 | 18.9<br>4.4 | 256.0 | 0.9 | NR | 51.2 | NR |
| | | 1.2 (n=1) | 142.9 | 0.08 | 11.7<br>15.5 | 71.8 | 0.6 | NR | 278.7 | NR |
| | | 1.8 (n=1) | 246.6 | 0.08 | 8.5<br>10.8 | 128.9 | 0.5 | NR | 232.7 | NR |
| | | 2.3 (n=1) | 396.5 | 0.08 | 8.0<br>7.6 | 348.9 | 1.1 | NR | 109.9 | NR |
| | | 3 (n=3) | 466.2 (49) | 0.2 | 11.2 (61)<br>12.5 (54) | 693.3 (49) | 2.1 | NR | 92.9 (68) | NR |
| | | 4 (n=3) | 718.2 (22) | 0.08 | 28.5 (100)<br>6.2 (67) | 1886 (110) | 1.0 | NR | 70.4 (68) | NR |
| | | 5.2 (n=1) | 696.2 | 0.08 | 8.2<br>10.7 | 696.2 | 1.0 | NR | 124.5 | NR |

NR - not reported

[a] harmonic mean

[b] steady-state volume of distribution

[c] apparent volume of distribution

**Table 3. Mean (%CV) LY231514 Pharmacokinetic Parameters**

| Study Number | Route of Administration Dosage Form | Dose ($mg/m^2$) | $C_{max}$ ($\mu g/mL$) | $T_{max}$ (hr) | $V_d/F^b$ ($L/m^2$) | $AUC_{0-\infty}$ ($\mu g \cdot hr/mL$) | $T_{1/2}{}^a$ (hr) | Urinary Excretion (% of dose) | $Cl_p/F$ (mL/min) | $Cl_r$ ($ml/min/m^2$) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JQAC<br>JQAD<br>JQAG<br>JQAH | IV (10 minute infusion) | 600 (n=103) | 101.6 (42) | NR | 15.1 (28) | 213.5 (21) | 2.5 | NR | 88.8 (19) | NR | Population PK (Cycle1) |
| | | (n=72) | 91.2 (49) | NR | 15.5 (29) | 189.4 (26) | 2.5 | NR | 90.5 (19) | NR | (Cycle 3) |

NR - not reported

[a] harmonic mean

[b] steady-state volume of distribution

[c] apparent volume of distribution

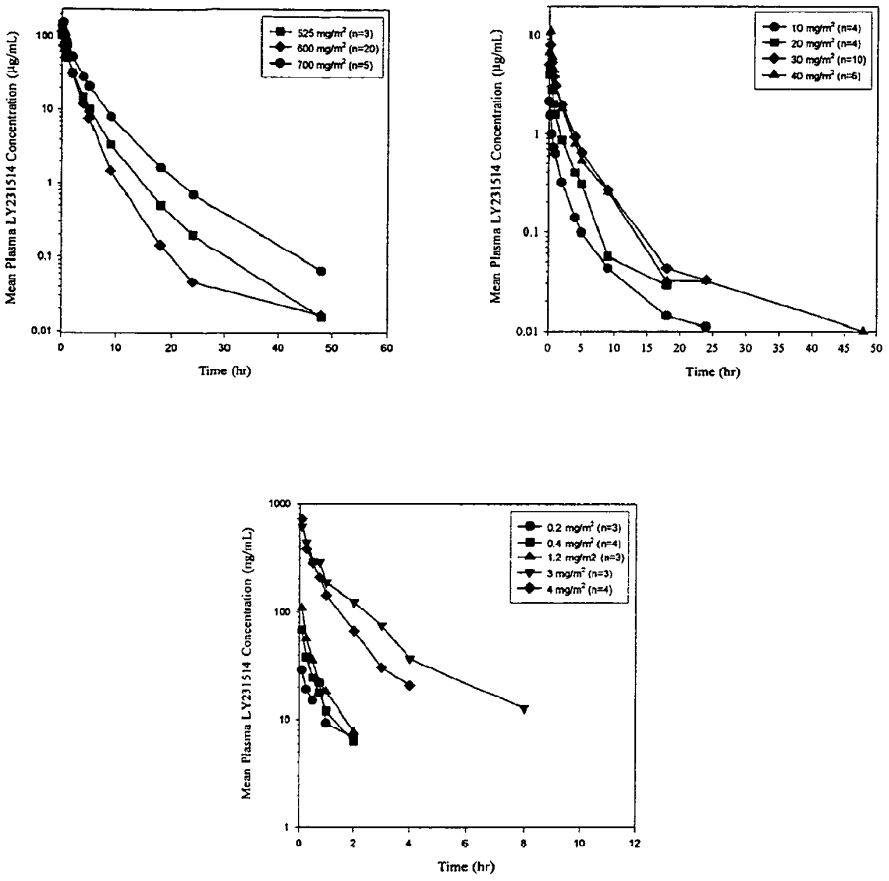



**Figure 1.** **Mean plasma MTA concentration-time profiles following administration of a 10-minute intravenous infusion for Studies JMAA (top left), JMAB (top right), and BP-001 (bottom center).**

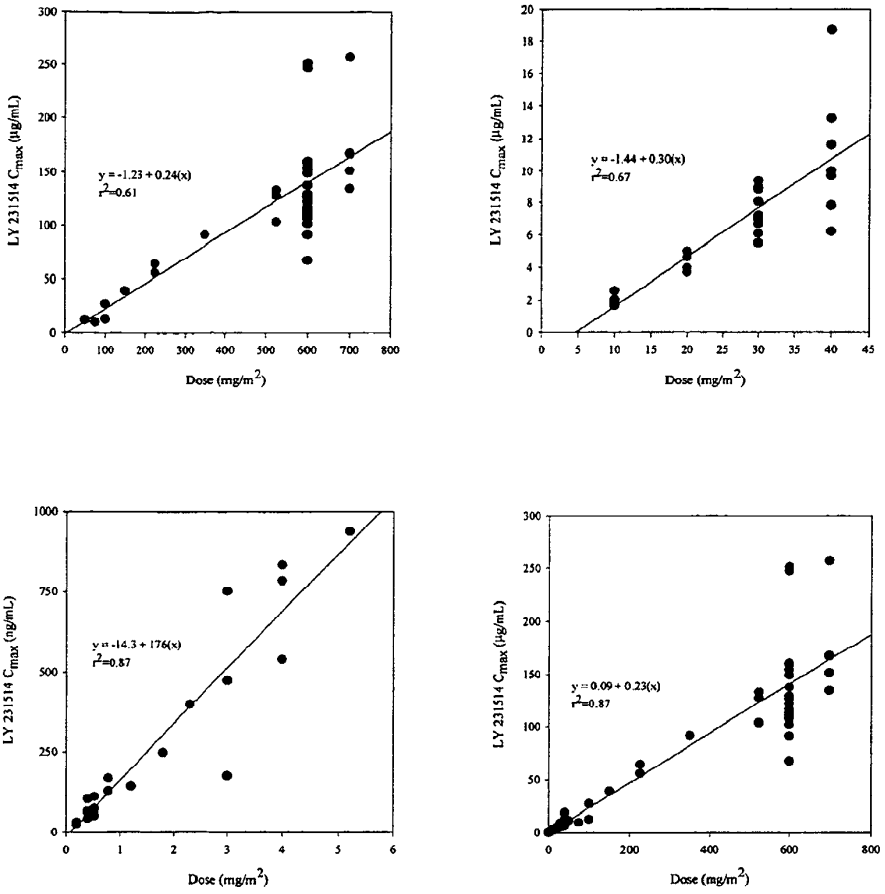



**Figure 2.** **Relationship between $C_{max}$ and BSA-normalized dose following administration of a 10-minute intravenous infusion for Studies JMAA (top left), JMAB (top right), BP-001 (bottom left), and pooled data from all three studies (bottom right).**

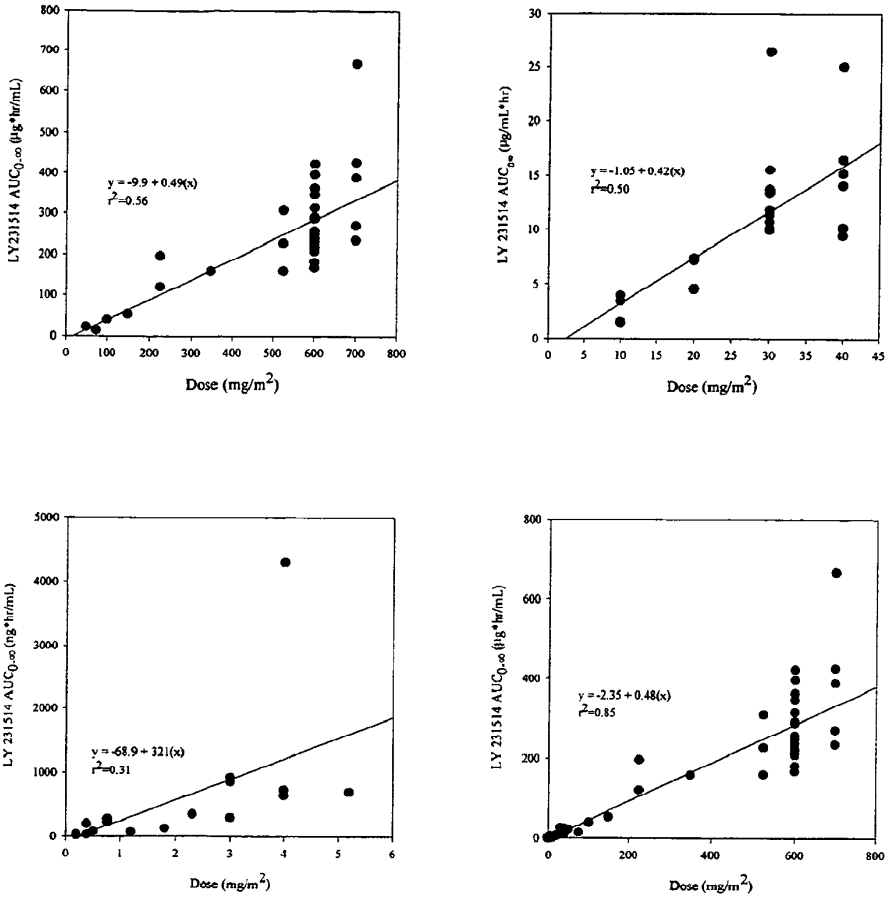



**Figure 3.** **Relationship between total systemic exposure ($AUC_{0-\infty}$) and BSA-normalized dose following administration of a 10-minute intravenous infusion for Studies JMAA, (top left) JMAB (top right), BP-001 (bottom left), and pooled data from all three studies (bottom right).**

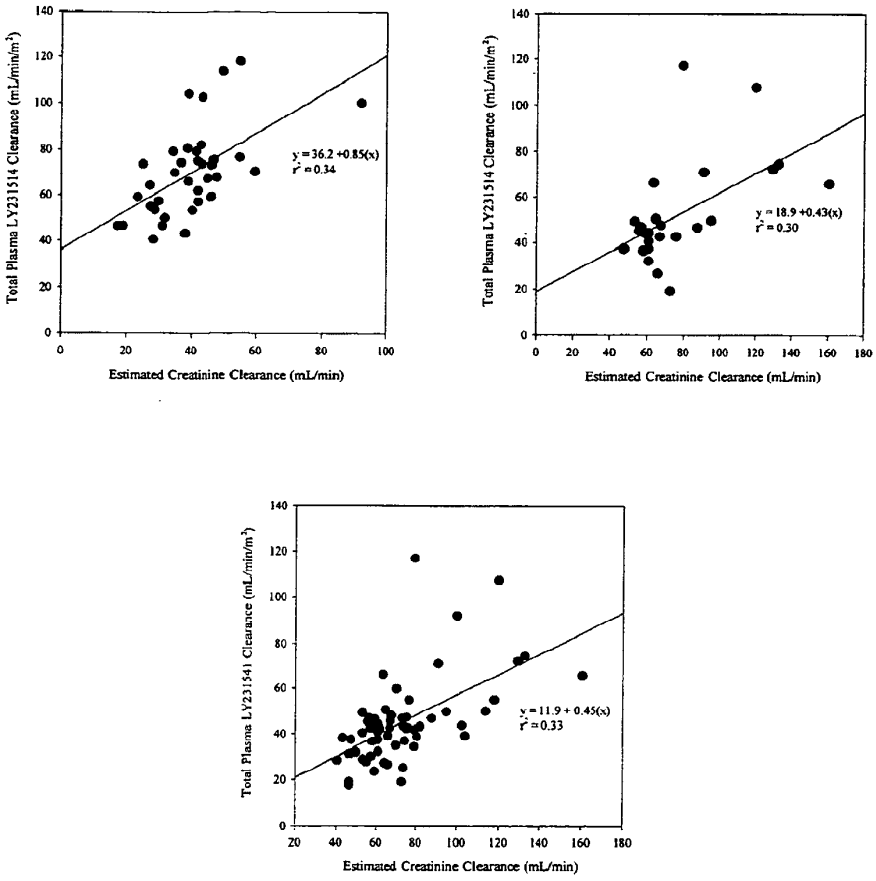



**Figure 4.** **Relationship between total plasma MTA clearance and estimated creatinine clearance (LBW) following administration of a 10-minute intravenous infusion for Studies JMAA (top left), JMAB (top right), and pooled data from both studies (bottom center).**

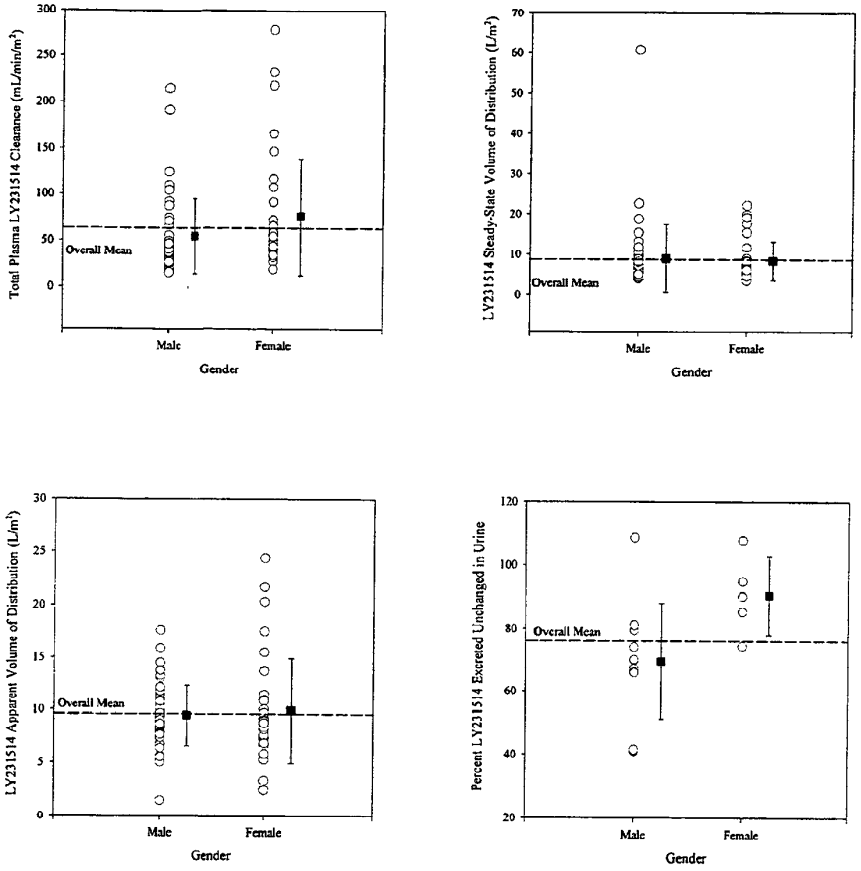



**Figure 5.** **The effect of gender on the total plasma MTA clearance (top left), steady-state volume of distribution (top right), apparent volume of distribution (bottom left), and percent of MTA excreted unchanged in urine (bottom right).**

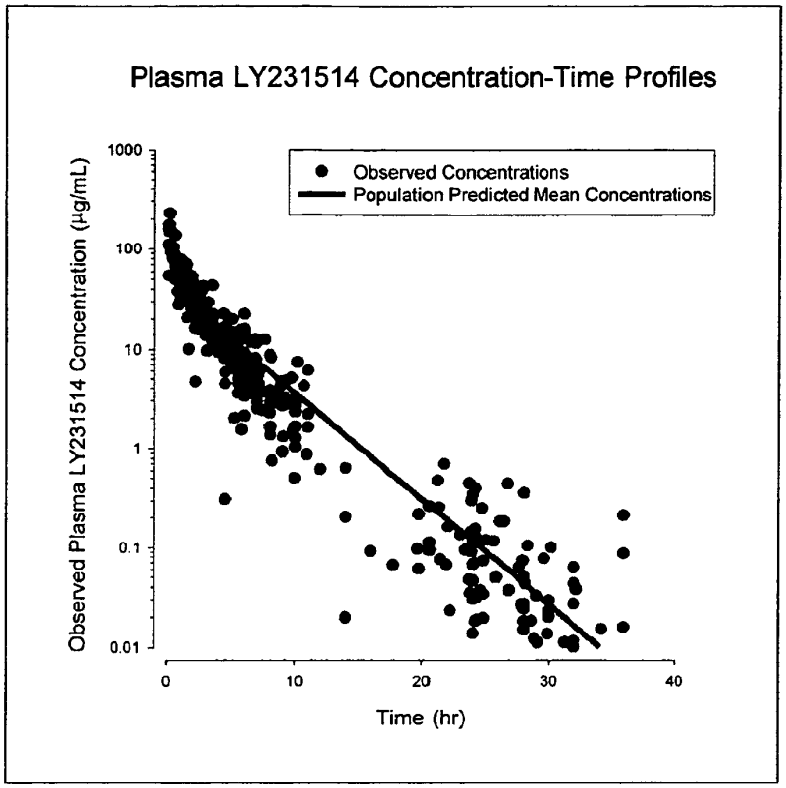
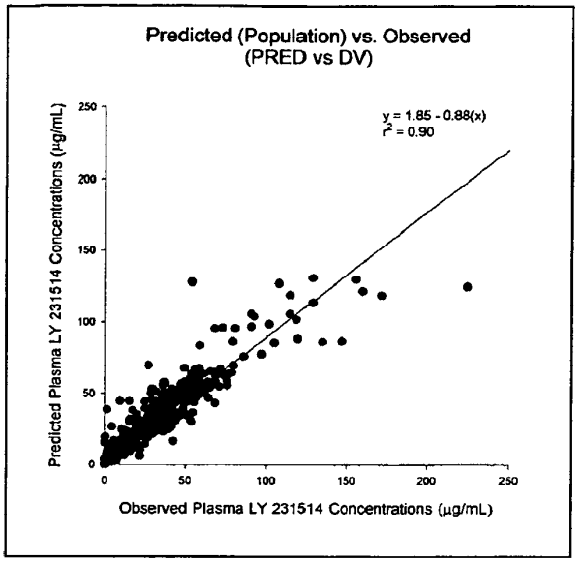



**Figure 6.** **Plasma MTA concentrations as a function of time from Phase 2 studies.**



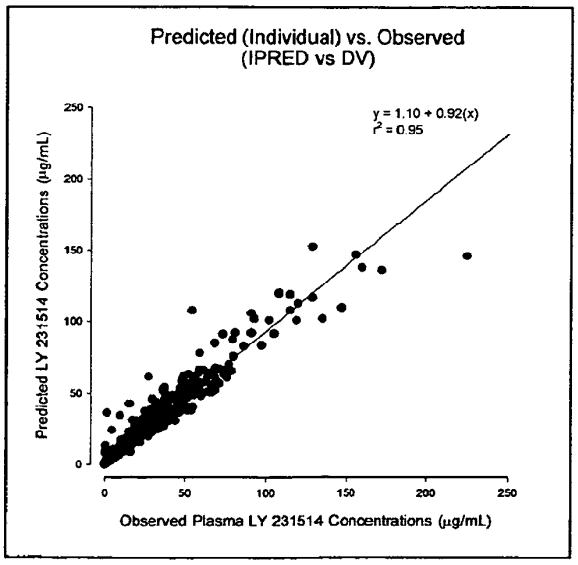
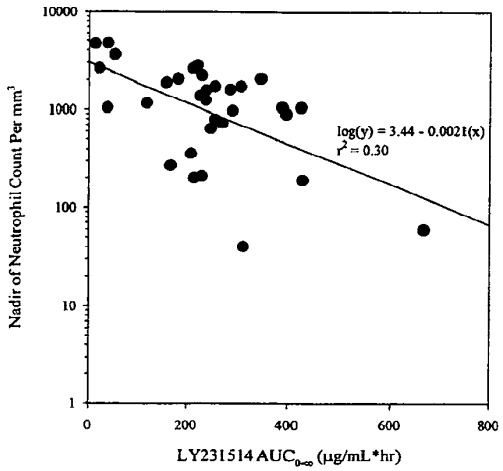




**Figure 7.** **Predicted plasma MTA concentrations from the population model (top) and from post hoc estimates (bottom) as a function of the observed concentrations.**



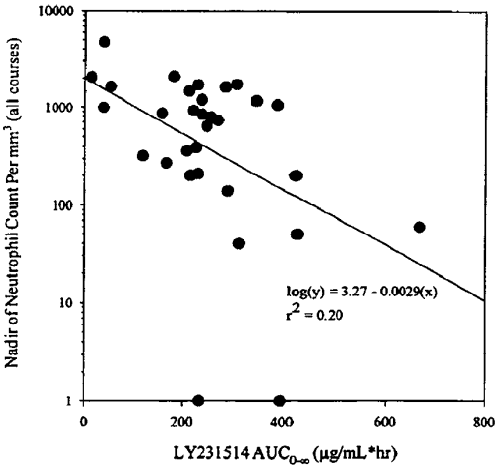
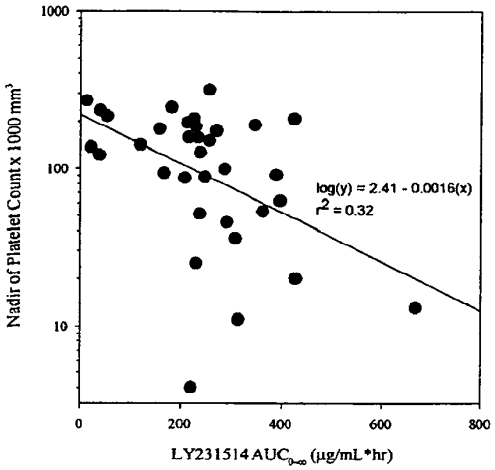




**Figure 8.** **Relationship between the nadir of neutrophil counts and $AUC_{0-\infty}$ from the first cycle (top) and the maximum nadir (worst toxicity) after multiple cycles and $AUC_{0-\infty}$ from the first cycle (bottom).**



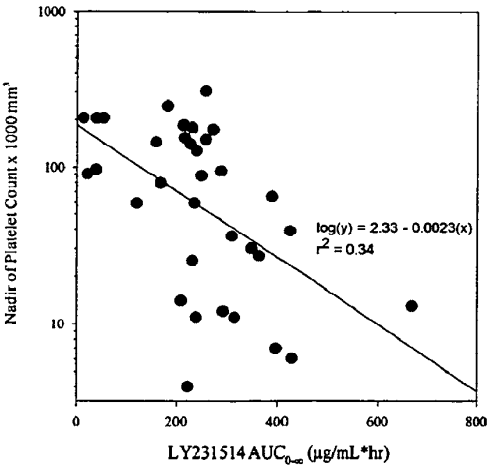




**Figure 9.** **Relationship between the nadir of platelet counts and $AUC_{0-\infty}$ from the first cycle (top) and the maximum nadir (worst toxicity) after multiple cycles and $AUC_{0-\infty}$ from the first cycle (bottom).**

Appendix 2

# Appendix 2
# Phase 1 Studies BP-001 and JMAB

# Initial Phase I Evaluation of the Novel Thymidylate Synthase Inhibitor, LY231514, Using the Modified Continual Reassessment Method for Dose Escalation

By D.A. Rinaldi, H.A. Burris, F.A. Dorr, J.R. Woodworth, J.G. Kuhn, J.R. Eckardt, G. Rodriguez, S.W. Corso, S.M. Fields, C. Langley, G. Clark, D. Faries, P. Lu, and D.D. Von Hoff

**Purpose:** To determine the toxicities, maximal-tolerated dose (MTD), pharmacokinetic profile, and potential antitumor activity of LY231514, a novel thymidylate synthase (TS) inhibitor.

**Patients and Methods:** Patients with advanced solid tumors were administered LY231514 intravenously over 10 minutes, weekly for 4 weeks, every 42 days. Dose escalation was based on the modified continual reassessment method (MCRM), with one patient treated at each minimally toxic dose level. Pharmacokinetic studies were performed in all patients.

**Results:** Twenty-five patients were administered 58 courses of LY231514 at doses that ranged from 10 to 40 mg/m$^2$/wk. Reversible neutropenia was the dose-limiting toxicity. Inability to maintain the weekly treatment schedule due to neutropenia limited dose escalation on this schedule. Nonhematologic toxicities observed included mild fatigue, anorexia, and nausea. At the 40-mg/m$^2$/wk dose level, the mean harmonic half-life, maximum plasma concentration, clearance, and apparent volume of distribution at steady-state were 2.02 hours, 11.20 μg/mL, 52.3 mL/min/m$^2$, and 6.64 L/m$^2$, respectively. No major antitumor responses were observed; however, minor responses were achieved in two patients with advanced colorectal cancer.

**Conclusion:** The dose-limiting toxicity, MTD, and recommended phase II dose of LY231514 when administered weekly for 4 weeks every 42 days are neutropenia, 40 mg/m$^2$, and 30 mg/m$^2$, respectively.

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LY231514 (N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo, 3-d]pyrimidin-5-yl) ethyl]benzoyl]-L-glutamic acid disodium salt) is a novel compound representative of a new class of folate antimetabolites. It has a pyrrole ring that replaces the pyrazine ring in the pterine portion of folic acid, and a methylene group that replaces the benzylic nitrogen in the bridge portion (Fig 1). The primary mechanism of antitumor effect of LY231514 is via inhibition of the enzyme thymidylate synthase (TS), which is the only de novo source of thymidylate for the cell.[1-3] This enzyme catalyzes the reductive methylation of deoxyuridine monophosphate (dUMP), in the presence of a reduced folate cofactor, 5,10-methylene tetrahydrofolate, to deoxythymidine monophosphate (dTMP) and dihydrofolate. Deoxythymidine monophosphate is the precursor of deoxythymidine triphosphate (dTTP), one of the deoxyribonucleotides necessary for DNA synthesis.[4,5] LY231514 undergoes extensive intracellular polyglutamation,[1-3] which with other chemotherapeutic agents, converts the drug from a form that readily effluxes from the cell, to a form that is retained intracellularly for a prolonged period. This produces a more sustained drug effect.[5]

In preclinical models, LY231514 has demonstrated activity against a wide spectrum of tumor types. In vitro, it is highly cytotoxic against CCRF-CEM human leukemia cells in culture, with a 50% inhibitory concentration (IC50) of 0.007 μg/mL. This activity was reversed by the addition of thymidine to the medium.[1-3] LY231514 has also demonstrated substantial in vitro activity against human tumor colony-forming units obtained from patients with colon cancer, renal cancer, hepatoma, carcinoid tumor, and both non–small-cell and small-cell lung cancer (Von Hoff DD, personal communication, August 1995).[6] In animal studies, LY231514 was able to suppress tumor growth completely at doses ≥ 10 mg/kg in mice with two types of transplanted human colon xenografts (VRC5 and GC3) resistant to methotrexate (MTX).[1]

Toxicology studies of LY231514 in mice (CD-1 strain), using daily intraperitoneal doses of up to 150 mg/kg for 2 weeks, were associated with minimal toxicity. There was a dose-related decrease in body weight, reaching a maximum of 20% at the 150-mg/kg level. Moderate decreases in WBC and platelet counts, as well as mild decreases in RBC counts, were also observed. Weekly

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*The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.*

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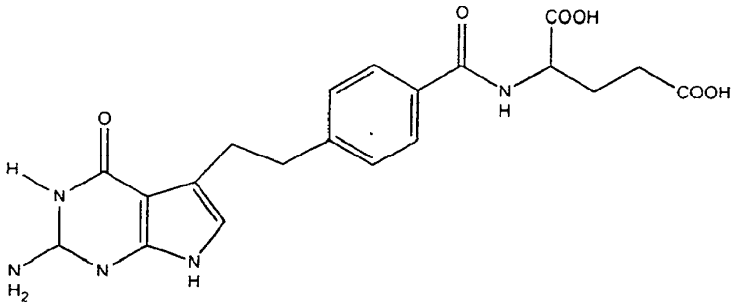
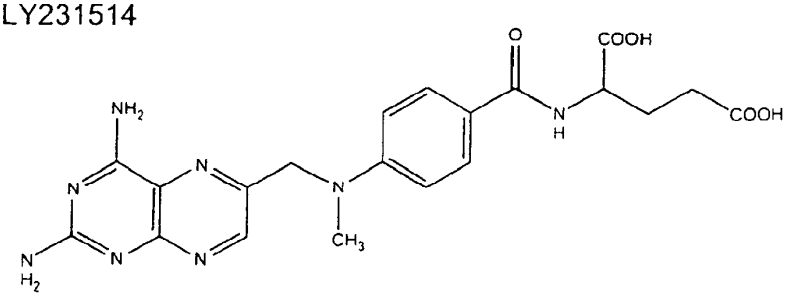


LY231514

Fig 1. Structure of LY231514 and methotrexate.



Methotrexate

doses of 315 mg/kg (944 mg/m$^2$) for 6 weeks was also minimally toxic in mice. The 50% lethal dose ($LD_{50}$) of LY231514 given as a single intravenous dose was more than 1,574 mg/kg.[1]

Beagle dogs were treated on various intravenous dosing schedules to determine toxicity. The weekly schedule began at 105 mg/kg, but the two dogs died after two doses. The dosing was then reduced to 105 mg/kg for one dose, followed by 26.24 mg/kg/wk for five doses. The major toxicities observed were anorexia, emesis, diarrhea, oral mucositis, and weight loss. Neutropenia, lymphopenia, and mild anemia were also observed. By 6 weeks, two of the four dogs died of sepsis, secondary to mucositis in one case and pneumonia in the other. Plasma concentrations of LY231514 increased in a linear fashion with increasing doses. The terminal half-life was approximately 2.3 hours. When comparing the toxicity of the various schedules, modest toxicity was observed in dogs treated with 100 mg/kg as a single dose, 5 mg/kg, twice weekly, and 0.5 mg/kg/d.[1]

In vitro and in vivo, folinic acid has been shown to antagonize the antitumor effect of other TS inhibitors currently undergoing clinical evaluation. This effect appears to be mediated via a competitive inhibition for transport of the agent into the cell and/or intracellular polyglutamation.[7,8] Folinic acid was evaluated as a rescue agent for LY231514. Four beagle dogs were administered potentially lethal intravenous doses (50 mg/kg for two doses, 3 days apart) of LY231514. All dogs developed signs of toxicity characterized by oral mucositis, anorexia, diarrhea, and a decrease in the leukocyte count by 50% to 80% beginning the day after the second dose of LY231514. Folinic acid was administered parenterally for 7 days with total daily doses of 150 mg initially, then tapering to 20 mg/d. The clinical signs resolved within 4 days and the hematologic abnormalities resolved within 6 days of the initiation of folinic acid rescue. At the termination of the study, one dog had a residual healed oral ulcer. The other animals had no gross pathologic evidence of residual tissue damage following folinic acid rescue.[1]

The starting dose of a phase I investigational drug trial is generally one third the toxic-dose-low in the most sensitive large animal species tested, or one tenth the 10% lethal dose ($LD_{10}$) in mice. LY231514 was only minimally toxic in mice. In dogs, deaths occurred in those that received 26.24 mg/kg (525 mg/m$^2$) per week, so one third of this, 175 mg/m$^2$/wk, was not felt to be a safe

starting dose. An initial dose of 10 mg/m²/wk was used to enhance safety. The dose escalation format was based on the modified continual reassessment method (MCRM) proposed by Faries.[9] Using this scheme, a single patient is treated at each minimally toxic dose level and more patients are added to a level when significant toxicity is observed. This dose-escalation format reduces the number of patients treated with lower, possibly less effective doses, while increasing the proportion treated at dose levels closer to the maximal-tolerated dose (MTD). The objectives of this study were to determine the qualitative and quantitative toxicities, the MTD, pharmacokinetic profile, and antitumor effect of LY231514 when dosed weekly for 4 weeks. This schedule will be repeated every 42 days to allow for resolution of toxic effects.

## PATIENTS AND METHODS

### *Patient Selection*

All patients underwent a complete history, physical examination, chest x-ray, and laboratory evaluation. Eligibility criteria included the following: (1) histologic evidence of solid tumor refractory to conventional therapy and other investigational agents of higher priority; (2) at least 18 years of age; (3) World Health Organization (WHO) performance status ≤ 2; (4) life expectancy ≥ 12 weeks; (5) off previous anticancer therapy for at least 3 weeks (at least 6 weeks for nitrosoureas or mitomycin); (6) adequate bone marrow function (WBC count ≥ 3,000/μL or granulocyte count ≥ 1,500/μL, platelet count ≥ 100,000/μL, hemoglobin level ≥ 9 g/dL), hepatic function (bilirubin level ≤ 1.5 mg/dL, AST ≤ two times the upper limit of normal, albumin level ≥ 2.5 g/dL, normal prothrombin/partial thromboplastin time), renal function (creatinine concentration ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min), cardiac function (no dysrhythmias requiring therapy and no myocardial infarction in the previous 6 months), and metabolic function (electrolytes within normal limits unless due to cancer, blood glucose < 200 mg/dL); and (7) written, informed consent. Exclusion criteria included the following: (1) clinical evidence of brain metastases, (2) serious preexisting medical conditions that would prevent full compliance with the study, (3) pregnancy, (4) concomitant anticancer therapy, (5) use of aspirin, or (6) presence of pleural or peritoneal effusions. Patients who required chronic aspirin therapy and those with effusions were excluded due to the structural similarities of LY231514 and MTX (Fig 1). MTX may be displaced from albumin and its renal secretion may be impaired by the concurrent use of aspirin, thereby increasing its cytotoxic effect.[10] MTX also is retained in effusions and released slowly into plasma, causing potentially substantial toxicity.

### *Pharmacokinetics*

Plasma samples for pharmacokinetics were planned for all patients during their first treatment course. A reverse-phase high-performance liquid chromatography (HPLC) assay was developed to determine the concentration of LY231514 in plasma. A quantity of 0.5 to 1 mL of plasma was subjected to a preconditioned solid-phase extraction (SPE) cartridge (Bond Elut Certity II, part no. 1210-2080; Varian, Harbor City, CA). The SPE cartridges were preconditioned with 2 mL of HPLC grade methanol, followed by 2 mL of a pH 7.0 phosphate buffer. Immediately following the addition of the sample, the column was washed with 2 mL of the pH 7.0 phosphate buffer, and then with 2 mL of methanol. The absorbed LY231514 was eluted with 2 mL of 40% acetonitrile and 60% buffer solution. The eluate was evaporated to dryness under nitrogen. The residues were reconstituted with 200 μL of distilled, deionized water, and then filtered with 0.1-μm Ultrafree-MC centrifuge filters (Millipore Inc, Bedford, MA). The extraction efficiency of LY231514 from plasma was 60%. The chromatographic procedure consisted of injecting 150 μL of the filtrate onto an octadecyl column (YMCbasic, 25 cm × 4.6 mm; YMC Inc, Wilmington NC) preceded by a YMCbasic precolumn (23 cm × 4 mm). The mobile phase consisted of 14% acetonitrile and 86% pH 3.0 phosphate buffer solution, pumped at a flow rate of 0.8 mL/min, and monitored by UV detection at 250 nm. The internal standard used was dideazatetrahydrofolate (Lometrexol; Eli Lilly, Indianapolis, IN), with a retention time of approximately 13 minutes. The retention time for LY231514 was approximately 17 minutes. Two calibration curves were used in the assay of the plasma samples. A low concentration range (10 to 400 ng/mL) was used for the 1-mL plasma sample, and a high concentration range (400 to 20,000 ng/mL) for the 0.5-mL plasma sample. Both concentration curves were linear over their respective ranges, with a correlation coefficient more than 0.96. The lower limit of quantitation of LY231514 was 10 ng/mL.

### *Drug Administration*

LY231514 disodium was supplied as a lyophilized powder in 100-mg vials and reconstituted in 10 mL of normal saline. The appropriate dose was then withdrawn and diluted in normal saline to a total volume of 50 mL. This was administered intravenously over 10 minutes, weekly for 4 weeks, repeated every 42 days. To be eligible to receive subsequent weekly doses, all toxicity must have been ≤ grade 1 at the time of treatment. Toxicity was assessed according to the WHO toxicity criteria. Patients were evaluated by a physician weekly during therapy for signs and symptoms of toxicity. The initial patient treated at each dose level was observed for a minimum of 4 weeks before decisions regarding dose escalation were made. Folinic acid would be considered, based on animal rescue data, for grade IV myelosuppression that persisted for 7 days or for grade III/IV nonhematologic side effects. The planned dosing of folinic acid was 50 mg/m² intravenously every 6 hours for 2 days, then 40 mg/m² intravenously every 6 hours for 6 additional days. All serious adverse events were reported to the institutional review board and the study sponsor, Eli Lilly and Co, Indianapolis, IN.

### *Dose Escalation*

Dose levels to be studied were 10, 20, 40, 75, 150, 225, 375, . . . to 1,000 mg/m²/wk. Dose escalation was planned based on the MCRM, with one patient treated at each minimally toxic dose level. Before each new patient was treated, an estimated MTD was calculated based on the toxicity experienced by all previously treated patients. The dose level selected for a new patient was based on the following criteria: at least three patients would be treated at the initial dose level of 10 mg/m²; the dose level for a new patient could not be more than one level above the level assigned to the previous patient; the dose level could not be greater than the estimated MTD; a minimum of three patients would be treated at a level before dose escalation when moderate reversible toxicity (grade III hematologic or grade II nonhematologic toxicity, excluding nausea, vomiting,

and alopecia) occurred; and a minimum of six patients would be treated at a dose level before escalation when unacceptable reversible toxicity (grade IV hematologic or grade III nonhematologic toxicity, excluding nausea, vomiting, and alopecia) occurred.

The MTD was defined as that dose level at which 30% of the patient population developed unacceptable reversible toxicity. The recommended dose for phase II clinical trials on this schedule would be the dose that caused moderate reversible toxicity in most patients, with at least 10 patients treated at this dose level. Intrapatient dose escalation was allowed if the next dose level was completed without unacceptable toxicity.

### *Efficacy Criteria*

Disease assessment was performed every one to two cycles. Standard response criteria were used. A complete response required disappearance of all evidence of disease for at least 4 weeks. A partial response required a ≥ 50% decrease in the sum of the products of the diameters of all measured lesions for at least 4 weeks. There also could be no new lesions or increases in the size of any assessable lesions. A minor response was defined as a ≥ 25% reduction in measurable or assessable disease that did not meet criteria for a response. Progressive disease was defined as a greater than 25% increase in the sum of the products of the diameters of the measured lesions or the appearance of any new lesions. Stable disease was defined as not meeting criteria for a response or progressive disease.

## RESULTS

Twenty-five patients were enrolled onto the study. One patient was not assessable due to the development of a small bowel obstruction, secondary to his malignancy, after a single dose of LY231514. He subsequently declined further treatment. The characteristics of the 24 assessable patients are listed in Table 1. A majority of the patients who participated in the trial had refractory metastatic colon cancer and had received prior chemotherapy; eight had also been treated with radiation therapy. A total of 58 courses of LY231514 were administered, with a range of one to seven courses per patient. Two patients were not fully assessable for toxicity during their first courses of treatment. One was hospitalized during his first two courses with gastrointestinal hemorrhages, due to tumor infiltration of the small bowel. His first fully assessable course was the third cycle. A second patient was diagnosed with brain metastases during the first course, and LY231514 was withheld during radiation therapy. Her first fully assessable course was the second cycle.

**Table 1. Patient Characteristics**

| | |
|---|---|
| No. entered | 25 |
| No. assessable | 24 |
| Male/female | 11/13 |
| Age, years | |
| Median | 59 |
| Range | 20-82 |
| WHO performance status | |
| 0 | 12 |
| 1 | 11 |
| 2 | 1 |
| No. of prior chemotherapy regimens | |
| 1 | 3 |
| 2 | 12 |
| 3 | 7 |
| 4 | 2 |
| Prior radiation therapy | 8 |
| Tumor type | |
| Colorectal | 17 |
| Gastric | 2 |
| Head and neck | 2 |
| Hepatoma | 1 |
| Renal | 1 |
| Sarcoma | 1 |

### *Toxicities*

The dose-limiting toxicity of LY231514 on this schedule was neutropenia. Overall, of 24 assessable patients, four developed grade IV and five grade III neutropenia as their maximal toxicity. Nonhematologic toxicity was relatively mild, with no instances of grade III or IV side effects (Table 2). There was no evidence of cumulative toxicity.

At the 10-mg/m$^2$ dose level, the second patient developed grade III neutropenia and grade IV thrombocytopenia. Three other patients were treated at this dose level with no side effects. Since three of four patients at this dose level had no toxicity, dose escalation proceeded per protocol to the 20-mg/m$^2$ level. The patient tolerated the 20-mg/m$^2$ dosing without side effects. The next patient was treated at the 40-mg/m$^2$ dose level and developed grade IV neutropenia after the second dose. Five additional patients were subsequently treated at this dose level, with both grade IV and grade III neutropenia occurring in two of six patients (Table 3). As a result of the grade IV toxicity at the 40-mg/m$^2$ level, three patients were added at the 20-mg/m$^2$ level to insure tolerability. There were no instances of grade III or IV side effects

**Table 2. Toxicity (course 1)**

| Toxicity | WHO Grade (no. of patients) | | | | |
|---|---|---|---|---|---|
| | 0 | I | II | III | IV |
| Neutropenia | 6 | 1 | 7 | 5 | 5 |
| Thrombocytopenia | 20 | 0 | 2 | 1 | 1 |
| Anemia | 9 | 8 | 7 | 0 | 0 |
| Nausea/emesis | 13 | 9 | 2 | 0 | 0 |
| Fatigue | 13 | 10 | 1 | 0 | 0 |
| Transaminasemia | 20 | 3 | 1 | 0 | 0 |
| Anorexia | 13 | 11 | 0 | 0 | 0 |
| Mucositis | 20 | 4 | 0 | 0 | 0 |
| Dermatitis | 23 | 1 | 0 | 0 | 0 |

Table 3. Neutropenia (course 1)

| Dose Level (mg/m²) | No. of Patients | Doses Given/Planned | WHO Toxicity Grade (no. of patients) 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| 10 | 4 | 14/16 | 3 | 0 | 0 | 0 | 1 |
| 20 | 4 | 15/16 | 3 | 0 | 1 | 0 | 0 |
| 30 | 10 | 30/40 | 0 | 1 | 4 | 3 | 2 |
| 40 | 6 | 18/24 | 0 | 0 | 2 | 2 | 2 |

observed. Since toxicity was minimal at the 20-mg/m² level, but significant at the 40-mg/m² dose level, an intermediate dose level of 30 mg/m² was added, based on the estimated MTD determined by the MCRM. Ten patients were treated at this dose level, with grade IV neutropenia occurring in two of 10 patients. Folinic acid rescue was not required in any patients.

Inability to deliver scheduled doses due to ≥ grade II myelosuppression at the time of treatment limited dose escalation on this schedule (Table 3). At the 10- and 20-mg/m² levels, 29 of 32 planned doses were delivered, and six of eight patients received all doses. At the 40-mg/m² level, 18 of the planned 24 doses were delivered, and at the 30-mg/m² dose level, 30 of the 40 doses were given. Only one patient at each of these dose levels received all four of the scheduled doses during the first course.

Patients with clinically significant pleural or peritoneal effusions were excluded from the study, but five patients had evidence of small effusions by computed tomographic (CT) scan. All were treated at the 30-mg/m² or 40-mg/m² dose levels. There was no apparent difference in toxicity between those with and without these small effusions. Grade III or IV neutropenia occurred in three of five patients with effusions and in six of 11 patients without effusions. The patient who experienced severe myelosuppression at the 10-mg/m² dose level had no evidence of pleural or peritoneal effusions.

Although mild weight loss was evident in animal studies, this was not a significant clinical problem. Five of 24 patients exhibited weight loss greater than 5% (maximum, 8.4%), while three patients gained greater than 5%. There did not appear to be a relationship between dose level and weight loss. Three of 16 patients treated at the 30- or 40-mg/m² levels had weight loss of greater than 5%, compared with two of eight patients treated at the lower levels.

*Pharmacokinetics*

During the first course of therapy, plasma samples were obtained at 5, 15, 30, and 45 minutes, 1, 2, 4, 5, 9, 18, 24, and 48 hours, and weekly before drug dosing. Figure 2 shows the mean concentrations from 10, 20, 30, and 40 mg/m², and Table 4 lists the pharmacokinetic calculations from these data. LY231514 exhibits a relative small vol-

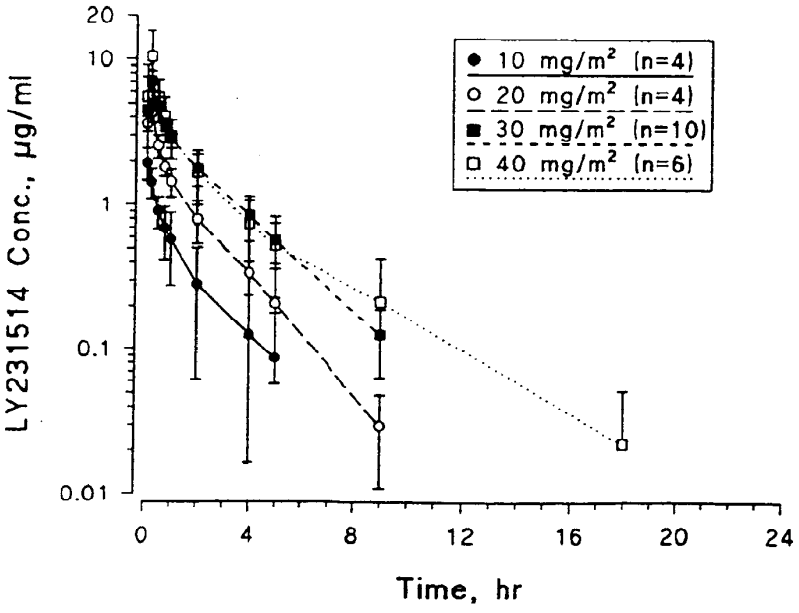



Fig 2. LY231514: mean (± SD) plasma concentrations.

Table 4. LY231514: Mean ± SD Pharmacokinetic Parameters

| Dose mg/m² | N | Age (years) | $C_{max}$ (μg/mL) | $t_{max}$ (hours) | AUC (μg/h/mL) | Half-Life* (hours) | Cl (mL/min/m²) | $V_{SS}$ (L/m²) |
|---|---|---|---|---|---|---|---|---|
| 10 | 4 | 48 ± 21 | 2.01 ± 0.40 | 0.13 ± 0.08 | 2.57 ± 1.27 | 1.27 | 79.2 ± 38.7 | 6.31 ± 1.01 |
| 20 | 4 | 50 ± 17 | 4.32 ± 0.60 | 0.21 ± 0.08 | 5.91 ± 1.58 | 1.53 | 9.6 ± 15.9 | 5.70 ± 0.49 |
| 30 | 10 | 66 ± 9 | 7.48 ± 1.28 | 0.20 ± 0.08 | 13.61 ± 4.82 | 2.11 | 39.6 ± 9.4 | 5.63 ± 1.29 |
| 40 | 6 | 51 ± 13 | 11.2 ± 4.45 | 0.19 ± 0.09 | 14.38 ± 6.00 | 2.02 | 52.3 ± 17.9 | 6.64 ± 1.05 |

Abbreviations: Cl, total systemic clearance; $t_{max}$, time to achieve maximum plasma concentration; $V_{SS}$, steady-state volume of distribution.
*Harmonic mean; range of all values, 0.89 to 3.87 hours.

ume of distribution, which reflects the polar nature of the compound. These data also suggest the compound has a moderate clearance and a relatively short half-life. The clearance varies, with what initially appears to be an inverse relationship to dose. As the dose increases from 10 to 30 mg/m², clearance is almost halved. However, the clearance is higher when the dose increases to 40 mg/m². Figure 3 shows the regressions between dose and both area under the curve (AUC) and maximum plasma concentration ($C_{max}$) values. The AUC values from the 30-mg/m² dose are nearly identical to those from the 40-mg/m² dose. The regression of AUC values with dose is highly variable; the regression between $C_{max}$ values and dose shows less variability and appears linear. Although the regression between AUC values and dose may suggest saturable elimination, the high variability of this regression and the consideration of both regressions together do not fully support saturable behavior. Further inspection of these data suggest that there may be an inverse relationship of drug clearance to patient age, with clearance decreasing as age increases (Fig 4). Although this is not a strong correlation ($R^2$ = .43), it may provide at least a partial explanation of the low clearance values from those patients given the 30-mg/m² dose, as these patients were, on average, older than patients enrolled at the 40-mg/m² dose level (Table 3).

Like other folate derivatives, renal excretion was suspected to be the primary route of excretion for LY231514; however, no urine samples for drug levels were collected in this study. The estimated creatinine clearances (Cockroft and Gault estimation) for each patient appear to correlate with the patient's LY231514 clearance values (Fig 5). The correlation of LY231514 clearance with age may also be influenced by renal function, since there is a known reduction in renal clearance with increasing age. These data suggest that, like other folates, LY231514 is primarily eliminated renally.

Correlations were attempted between pharmacokinetic values and the degree of neutropenia attained after the first cycle. The AUC and $C_{max}$ values were plotted against the neutrophil nadir measured after the first cycle (Figs 6 and 7, respectively). Linear correlations were found, with a reduction in the neutrophil nadir occurring with an increase in AUC or $C_{max}$.

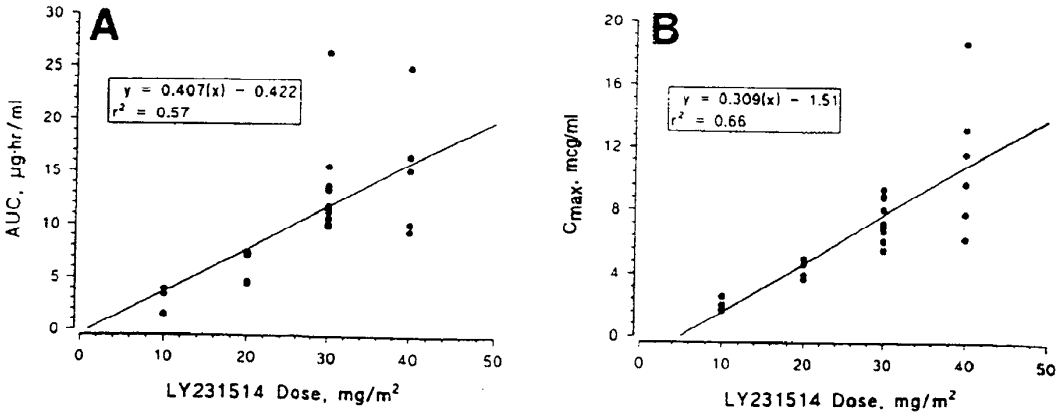



Fig 3. Regression of (A) AUC and (B) $C_{max}$ v Dose.

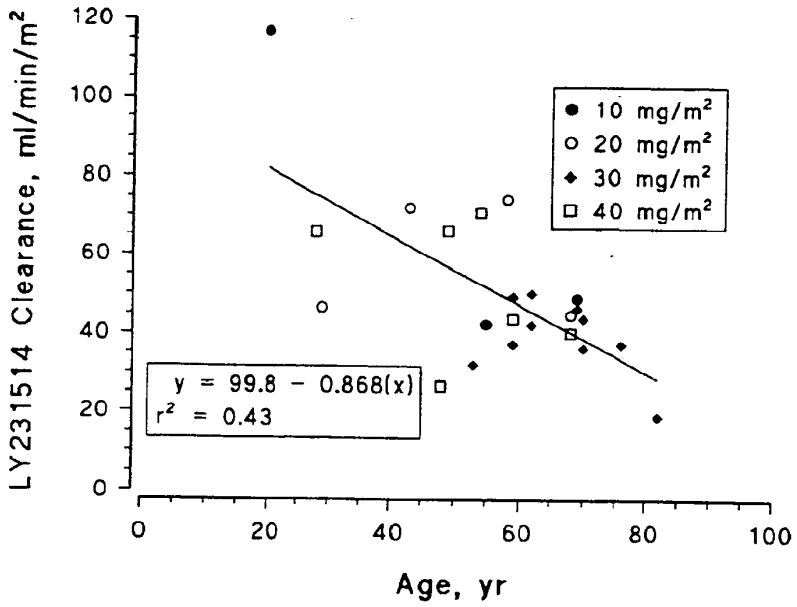



Fig 4. Correlation between LY231514 clearance and patient age.

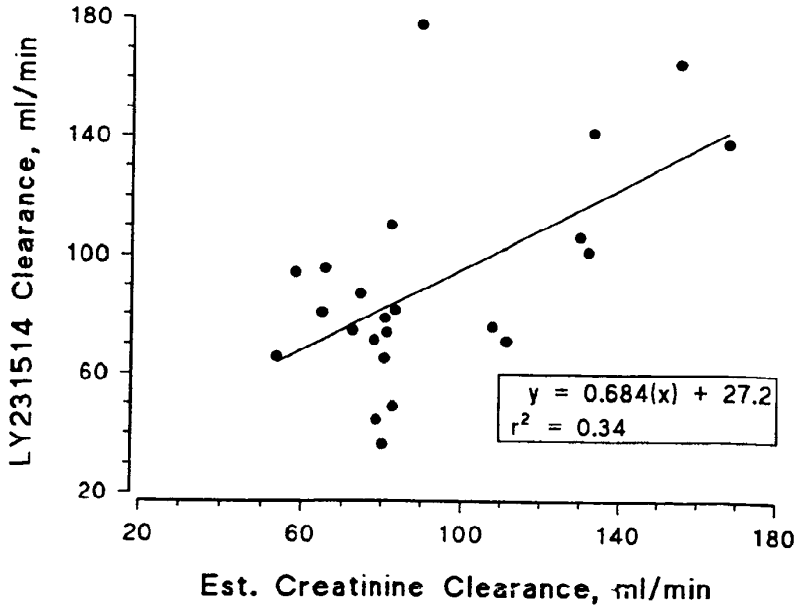



Fig 5. Correlation between LY231514 clearance and estimated creatinine clearance.

*Antitumor Activity*

No major responses were observed; however, minor responses were achieved in two patients with advanced, refractory colon cancer. A 59-year-old woman who had failed to respond to treatment with fluorouracil (5-FU) and folinic acid exhibited a 34% reduction in her measurable disease after two courses at the 40 mg/m$^2$ dose level. She developed progressive disease by her next CT scan 6 weeks later. A 76-year-old man with assessable liver metastases, treated at the 30-mg/m$^2$ level, exhibited a decline in his carcinoembryonic antigen (CEA) level from 945 ng/mL prestudy to 271 ng/mL after three courses of treatment. Of note, he had been previously treated with 5-FU and levamisole, 5-FU and folinic acid, and intrahepatic artery 5-FU and interferon.

## DISCUSSION

LY231514 is a novel inhibitor of the enzyme TS. In preclinical studies, it has demonstrated activity against a wide spectrum of tumor types. Toxicities observed in animal studies have included neutropenia, anemia, anorexia, weight loss, emesis, diarrhea, and mucositis. Folinic acid has been shown to be an effective agent in alleviating toxic effects of LY231514 in animals.[1-3,7]

A unique aspect of this phase I clinical trial was an attempt to use the MCRM for dose escalation. The traditional dose-escalation design of a phase I investigational drug clinical trial involves a minimum of three patients at a dose level before dose escalation. When significant reversible toxicity is observed, more patients are added to that dose level. This proceeds until the MTD is determined. The recommended dose for phase II clinical trials is generally the MTD or the dose level below the MTD, depending on the specific side effects and their severity.[11,12] The Continual Reassessment Method (CRM), proposed by O'Quigley et al,[13] uses a Bayesian format to estimate the MTD, based on toxicity data from all previously treated patients. Patients are then added at the dose level established at the commencement of the trial that is closest to the estimated MTD. The MCRM, proposed by Faries,[9] combines the more rapid dose-escalation plan of the CRM, with the more conservative, traditional dose-escalation schedule. The MCRM offers the advantages of reducing the number of patients treated with lower, and thus possibly less effective doses, and increases the proportion treated at dose levels closer to the MTD. However, it is without the potential large incremental dose escalations of the CRM.[13] The dose-escalation format planned for this trial was based on the MCRM, with the exception of treating additional patients at a dose level if moderate toxicity was observed, rather than a single patient as planned by the MCRM, to enhance safety.

The dose-limiting toxicity of LY231514 on this schedule was neutropenia, with an MTD of 40 mg/m$^2$/wk. Nonhematologic toxicity of LY231514 was relatively mild, with no instances of grade III or IV side effects. The recommended dose for phase II clinical trials of

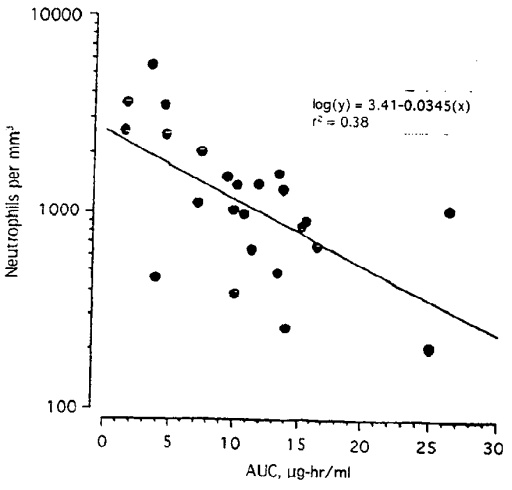



Fig 6. Neutrophil nadir count v AUC, 10 to 40 mg/m$^2$.

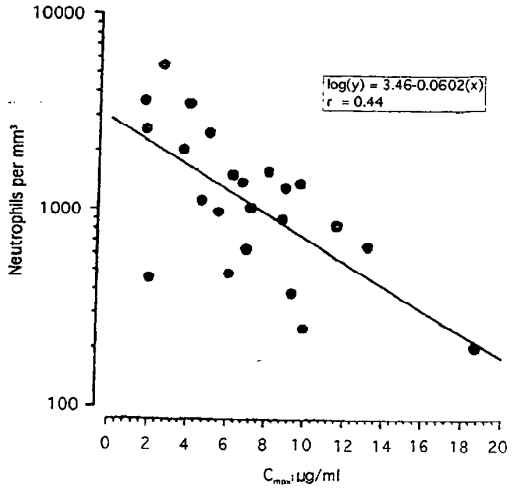



Fig 7. Neutrophil nadir count v $C_{max}$, 10 to 40 mg/m$^2$.

LY231514 on this schedule is 30 mg/m²/wk. It was difficult to use the MCRM optimally to predict the MTD with this weekly dosing schedule. One fourth of all planned doses at the 30- and 40-mg/m² dose levels were omitted due to ≥ grade II neutropenia at the time of scheduled treatment.

Correlations were made between the degree of toxicity and the pharmacokinetic behavior of LY231514. The log-linear correlations are consistent with a non–phase-specific toxicity existing with this compound.[14] These data allow pharmacokinetic measurements to be predictive of a toxic response.

No complete or partial responses were observed in this group of 24 patients. However, signs of antitumor activity were observed in two patients with advanced, previously treated colon cancer. In conclusion, LY231514 administered weekly for 4 weeks every 42 days was well tolerated. The dose-limiting toxicity, MTD, and recommended phase II dose of LY231514 when dosed weekly for 4 weeks every 42 days are neutropenia, 40 mg/m², and 30 mg/m², respectively. Reversible neutropenia, which occurs predominantly at week 3 or 4, limited dose escalation on this schedule. Alternative phase I schedules are being explored in an attempt to achieve greater dose-intensity.

## ACKNOWLEDGMENT

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# A Phase I and Pharmacokinetic Study of LY231514, the Multitargeted Antifolate

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## ABSTRACT

**LY231514 is a novel antifolate that principally inhibits thymidylate synthase, but with additional folate-dependent enzyme targets. A Phase I study of single-agent LY231514 administered as a daily i.v. infusion over 10 minutes for 5 days, repeated every 3 weeks, was conducted to evaluate the maximum tolerated dose, pharmacokinetic profile, and antitumor activity of the drug using this schedule. Thirty-eight patients with advanced malignancies that were refractory or not amenable to standard therapy were treated with a total of 116 courses of LY231514, escalating treatment doses through 10 dose levels, from 0.2–5.2 mg/m²/day. No objective clinical responses were observed, although minor antitumor activity not fulfilling the response criteria was seen in three patients.**

**A maximum tolerated dose of 4.0 mg/m²/day was determined, with neutropenia as the predominant dose-limiting toxicity. Reversible disturbances of liver biochemistry, fulfilling the protocol definitions of dose-limiting toxicity, were also observed. Other toxicities included diarrhea, mucositis, skin rash, and fatigue. Pharmacokinetic studies were performed at all treatment levels. Analysis showed a linear relation between administered dose and both maximum plasma concentration ($C_{max}$) and area under the plasma concentration/time curve. The drug was cleared with a day 1 total body clearance of 108.9 ± 38.8 ml/min/m², with plasma concentrations declining with a mean harmonic terminal half-life of 1.4 ± 0.98 h. When given by this schedule, LY231514 is tolerable, and Phase II studies are in progress.**

## INTRODUCTION

LY231514 (*N*-[4-[2-(2-amino-3,4-dihydro-4-oxo-7H-pyrollo[2,3-d]pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid disodium salt) is a novel antifolate with a pyrrole ring replacing the pyrazine ring in the pterine portion of folic acid, and the benzylic nitrogen in the bridge portion substituted by a methylene group. LY231514 has been developed as an inhibitor of TS[2] (1) but also has important secondary enzymatic targets; this feature may confer a therapeutic advantage over other folate analogues.

The biochemical locus of LY231514 is TS (1, 2), a folate-dependent enzyme catalyzing the conversion of dUMP to dTMP, the precursor of the nucleotide dTTP. TS is a two-substrate enzyme, and this reaction requires the presence of the reduced folate cofactor 5,10-methylenetetrahydrofolate; TS is the only *de novo* intracellular source of thymidylate. *In vitro* work has shown that LY231514 also inhibits additional folate-dependent enzymes (2) including dihydrofolate reductase and GARFT involved in *de novo* purine synthesis. Furthermore, end product reversal experiments using the CCRF-CEM human leukemia cell line suggest that these alternative targets are relevant to the cytotoxicity of LY231514, because both thymidine and hypoxanthine are required to circumvent LY231514-induced cell death (2).

LY231514 gains entry to the cell predominantly via the reduced folate carrier and, once localized intracellularly, is an excellent substrate for polyglutamation by the enzyme folylpolyglutamate synthase. Pentaglutamate forms, the predominant intracellular species, acquire approximately an 80-fold gain in affinity for human TS ($K_i$ $glu_5$ = 1.3 nM; parent compound = 109 nM) and a 140-fold gain in affinity for murine GARFT ($K_i$ $glu_5$ = 65 nM; parent compound = 9300 nM; Ref. 2). In addition, polyglutamation confers polarity on the molecule, increasing intracellular retention.

LY231514 has demonstrated good activity in preclinical model systems, exhibiting potent *in vitro* cytotoxicity toward the CCRF-CEM human leukemia cell line ($IC_{50}$ = 7 ng/ml) and, in animal studies, exhibiting growth suppression of the methotrexate-resistant VRC5 and GC3 human colon xenografts by 80–94% (1).

Animal toxicology has been studied in mice and beagle dogs and is described in more detail elsewhere (3). In mice, the single i.v. dose producing death in 50% of animals was greater than 1574 mg/kg, possibly due to this species' high circulating

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[2] The abbreviations used are: TS, thymidylate synthase; MTD, maximum tolerated dose; PK, pharmacokinetic; GARFT, glycinamide ribonucleotide formyltransferase; DLT, dose-limiting toxicity; CTC, Common Toxicity Criteria; AUC, area under the curve; 5-FU, 5-fluorouracil.

plasma thymidine level, which will affect end product reversal of the drug. In dogs, several schedules were used, and the observed toxicities were predominantly gastrointestinal (anorexia, oral mucositis, emesis, diarrhea, dehydration, and weight loss) and hematological (leukopenia). Marked schedule dependency was noted, and a 34-fold increase in dose intensity was found to be feasible, using once-per-week dosing as opposed to daily dosing. Folinic acid treatment commenced 24 h after a potentially fatal single i.v. dose of LY231514 abrogated the anticipated lethality, suggesting a role for folinic acid in the treatment of severe drug-induced toxicity. PK parameters were studied in both animal systems, and rapid, predominantly renal excretion was observed with a terminal half-life in the dog of 2.3 h. Based on animal data, the initial daily and weekly doses in man were estimated at 0.2–0.65 mg/m$^2$ and 10.0 mg/m$^2$, respectively.

Given the schedule dependency observed in animal models and early clinical evidence suggesting therapeutic advantage in favor of prolonged antimetabolite exposure (4), it was proposed that initial Phase I studies of LY231514 would be conducted using several schedules of drug administration. Reported here are the results of the administration of LY231514 by daily i.v. injection for 5 days, repeated every 21 days. Other schedules studied have comprised one injection/week, repeated every 21 days (5), and one weekly injection given for 4 weeks, repeated every 42 days (3).

## MATERIALS AND METHODS

**Patient Selection.** All patients had a baseline history and a full physical, radiological, and laboratory evaluation. Eligibility criteria included: (*a*) histologically confirmed solid malignancy refractory or not amenable to conventional therapy; (*b*) age over 18 years; (*c*) WHO performance status ≤ 2; (*d*) life expectancy ≥ 3 months; and (*e*) adequate hematopoietic (total WBC count ≥ 3.0 × 10$^9$/liter; neutrophils ≥ 1.5 × 10$^9$/liter; hemoglobin ≥ 10 g/dl; and platelets ≥ 100 × 10$^9$/liter), metabolic (electrolytes within 10% of reference range; bilirubin within reference range, aspartate transaminase and alanine transaminase ≤ 2 × upper limit of normal; alkaline phosphatase ≤ 2.5 × upper limit of normal; and normal coagulation profile), and renal function (serum creatinine ≤ 120 μmol/liter, with calculated or $^{54}$Cr-EDTA clearance ≥ 60 ml/min). The study was fully approved by local institutional ethics committees, and all patients gave written informed consent.

Major exclusion criteria included: (*a*) cytotoxic treatment within the previous 4 weeks (6 weeks if treated with nitrosoureas or mitomycin C); (*b*) pregnancy or lactation; (*c*) significant concomitant medical conditions; (*d*) central nervous system malignancy; (*e*) simultaneous treatment with folate supplements or antifolate drugs; and (*f*) a third space fluid collection (pleural effusion, ascites).

**PKs.** Plasma sampling for PKs was planned for all patients during the first course of treatment, sampling on days 1 and 5. A reverse-phase high-performance liquid chromatography assay was used to measure plasma concentrations of LY231514 as described previously (3), and standard noncompartmental methods were used to assess LY231514 PKs.

**Drug Dosage and Administration.** LY231514 was supplied as a lyophilized powder in 10- and 100-mg vials and reconstituted using 10 ml of normal saline. It was further diluted in normal saline to a total volume of up to 100 ml and administered i.v. over 10 min by slow infusion, daily for 5 consecutive days. Patients were evaluated weekly, and toxicity was assessed using the CTC. The first patient treated at each dose level was observed over the first treatment course (3 weeks) before a second and third patient were similarly treated.

Dose escalation was considered once all three patients at a given dose level had completed at least one treatment course without DLT (CTC grade 4 hematological or grade 3 nonhematological toxicity). If such toxicity was observed in one or more of the three patients, a minimum of five patients in total were treated at the same dose level. Folinic acid rescue was considered for any patient developing life-threatening toxicity secondary to LY231514. Dose escalations, made in increments of 30–50%, would only proceed provided no more than one-third of the patients experienced DLT. The MTD was defined as the dose at which 30% of the patient population experienced DLT. Disease assessment was performed every two cycles, and standard WHO response criteria were used.

*Table 1* Patient characteristics

| | |
|---|---|
| Total enrolled | 38 |
| Male/female | 19/19 |
| Performance status | |
| 0 | 7 |
| 1 | 26 |
| 2 | 5 |
| Median age (range; yr) | 53 (33–73) |
| Prior therapy | |
| None | 6 |
| Radiotherapy | 12 |
| Chemotherapy | 29 |
| Tumor types | |
| Colorectal | 20 |
| Pancreas | 4 |
| Melanoma | 3 |
| Lung | 2 |
| Gall bladder | 2 |
| Others | 7 |

## RESULTS

Thirty-eight patients were enrolled in the study. Their clinical characteristics are listed in Table 1. The patients recruited were typical of Phase I studies. There was a predominance of large bowel tumors, and the majority had previous exposure to cytotoxics. Twelve patients had previously received radiation therapy.

A total of 116 courses of LY231514 were administered, the median number of courses received/patient was 2 (range, 1–10). Three patients with responding or stable disease received 10 courses of LY231514. Dose escalation proceeded from 0.2 mg/m$^2$ to 5.2 mg/m$^2$ through 10 dose levels. Unacceptable toxicity was observed in one of two patients treated at 5.2 mg/m$^2$ and in an additional patient treated at 4 mg/m$^2$. This patient, the sixth receiving this dose, developed DLT, establishing 4 mg/m$^2$/day for 5 days as the MTD.

**Toxicities.** Major toxicities are listed in Tables 2–4. Of the 38 patients treated, 1 receiving 0.4 mg/m$^2$ failed to complete

*Table 2* Hematological toxicity

| Dose level (mg/m²) | No. of patients | Hematological toxicity per dose level (frequency of worst CTC grade during entire treatment) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Neutrophil count | | | | | Platelets | | | | |
| | | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| 0.2–1.8 | 22 | 21 | | 1 | | | 18 | 4[a] | | | |
| 2.3 | 3 | 1 | | 1 | 1 | | 3 | | | | |
| 3.0 | 5 | | 1 | 3 | 1 | | 4 | | 1 | | |
| 4.0 | 6 | 1 | 2 | 1 | 1 | 1 | 4 | 2 | | | |
| 5.2 | 2 | | 1 | | | 1 | | 1 | | 1 | |

[a] One of the four cases of grade 1 thrombocytopenia developed in patient with previously unrecognized chronic liver disease.

*Table 3* Biochemical toxicity

| Dose level (mg/m²) | No. of patients | Biochemical toxicity per dose level (frequency of worst CTC grade during entire treatment) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Transaminases | | | | | Alkaline phosphatase | | | | | Bilirubin | | | | |
| | | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| 0.2–1.2 | 17 | 11 | 4 | 1 | 1[a] | | 7 | 7 | 2 | 1[a] | | 15 | 1 | | | 1[a] |
| 1.8 | 5 | 1 | 3 | | 1 | | 4 | | 1 | | | 5 | | | | |
| 2.3 | 3 | 2 | | | 1 | | | 1 | 1 | 1 | | 2 | 1 | | | |
| 3.0 | 5 | 1 | 3 | 1 | | | 3 | 1 | 1 | | | 3 | 1 | 1 | | |
| 4.0 | 6 | | 2 | 3 | 1 | | 2 | 3 | 1 | | | 3 | | 2 | 1 | |
| 5.2 | 2 | 1 | 1 | | | | 1 | | 1 | | | 1 | | 1 | | |

[a] Liver enzyme disturbance subsequently attributed to chronic liver disease.

*Table 4* Gastrointestinal toxicity, irrespective of cause

| Dose level (mg/m²) | No. of patients | Gastrointestinal toxicity per dose level (frequency of worst CTC grade during entire treatment) | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mucositis | | | | | Nausea | | | | | Vomiting | | | | | Diarrhea | | | | |
| | | 0 | 1 | 2 | 3 | 4 | 0 | 1–2 | 3 | 4 | | 0 | 1–2 | 3 | 4 | | 0 | 1–2 | 3 | 4 | |
| 0.2–1.8 | 22 | 17 | 4 | 1 | | | 15 | 5 | 1 | 1[a] | | 13 | 6 | 2 | 1[a] | | 14 | 8 | | | |
| 2.3 | 3 | 3 | | | | | | 3 | | | | 1 | 2 | | | | 2 | | | | 1 |
| 3.0 | 5 | 5 | | | | | 4 | 1 | | | | 2 | 2 | 1 | | | 3 | 2 | | | |
| 4.0 | 6 | 4 | 2 | | | | 1 | 5 | | | | 3 | 3 | | | | 2 | 4 | | | |
| 5.2 | 2 | 1 | | | 1 | | | 1 | 1 | | | 1 | | 1 | 0 | | 1 | | 1 | | |

[a] Nausea and vomiting attributed to disease-related bowel obstruction; patient failed to complete one course of LY231514 treatment.

a first course, having developed a disease-related bowel obstruction after 1 injection. A second received four courses of LY231514 at 0.78 mg/m$^2$; although CTC grade 3 hepatic enzyme disturbances observed in later cycles were initially attributed to LY231514, previously unrecognized chronic liver disease was subsequently found to be the probable cause of these changes.

The DLTs of LY231514 on this schedule were myelosuppression and perturbations of liver biochemistry. Of the five patients experiencing CTC grade 3–4 neutropenia, the neutrophil nadir was observed at day 8 in three cases and at day 15 in two patients. Significant (>CTC grade 2) myelosuppression was not seen in patients treated at doses less than 2.3 mg/m$^2$. One of three patients receiving 2.3 mg/m$^2$ developed uncomplicated grade 3 neutropenia during a second course of treatment. At 3.0 mg/m$^2$, one of the initial three patients treated experienced grade 3 neutropenia and grade 2 thrombocytopenia. No further DLT was observed in the remaining four patients treated at this dose.

At 4.0 mg/m$^2$, one of five patients developed CTC grade 3 hepatotoxicity (bilirubin), defined as dose limiting, and a second patient developed grade 3 neutropenia. With one of five patients treated at 4.0 mg/m$^2$ having experienced DLT, the treatment dose was then escalated to 5.2 mg/m$^2$, and the first patient treated experienced no significant toxicity. A second patient, however, suffered grade 4 neutropenia, grade 3 thrombocytopenia, and grade 4 gastrointestinal toxicities (stomatitis, diarrhea, and vomiting) on day 8 of treatment course 1, complicated by neutropenic septicemia. This proved fatal despite aggressive medical management, including the use of i.v. folinic acid, and prompted the reevaluation of the 4.0-mg/m$^2$ dose. An additional single patient was treated at this level, who developed uncomplicated but dose-limiting CTC grade 4 neutropenia and grade 3 liver enzyme disturbance (alanine aminotransferase). The MTD was therefore established at 4 mg/m$^2$, with two of six patients developing DLT as defined above.

Perturbation of liver biochemistry tests was frequently observed: minor disturbance (CTC grade 1–2) of hepatic transaminases was seen in 17 patients across the dosing range. These disturbances arose most frequently during either the first (six patients) or second (nine patients) course of treatment, with a median time to onset of 29 days (range, 5–105 days). Such disturbances persisted without deterioration until LY231514 cessation in most (12) cases and resolved spontaneously in the remainder.

Significant (≥ CTC grade 3) hepatic enzyme perturbation was seen in four patients, all of whom received ≥1.8 mg/m$^2$. CTC grade 3 transaminase elevations were seen in two patients receiving 1.8 mg/m$^2$ and 4 mg/m$^2$, respectively. Grade 2 transaminase changes accompanied by grade 3 elevation of serum bilirubin were observed in an additional patient treated at 4 mg/m$^2$. One patient treated at 2.3 mg/m$^2$ developed grade 3 changes in both transaminases and alkaline phosphatase, with grade 2 changes in bilirubin (see below). These alterations of liver biochemistry tests, although fulfilling protocol definitions of DLT, were unaccompanied by clinical sequelae of hepatic dysfunction in any patient. Overall, liver enzyme changes occurred with equal frequency in patients with (8 of 16) and without (10 of 20) hepatic metastases: minor increases in prothrombin time (≤CTC grade 2) were seen in 4 of 16 patients with liver metastases and in 9 of 20 patients without liver metastases.

Gastrointestinal toxicities were mild but seemed to be dose related (see Table 4). Antiemetics were not routinely prescribed, and symptomatic nausea or vomiting responded well to simple antiemetics. Fourteen patients experienced CTC grade 1–2 diarrhea, which was also seen more frequently at higher doses. Only three patients required additional symptomatic treatment with antidiarrheal medication, and none underwent hospitalization.

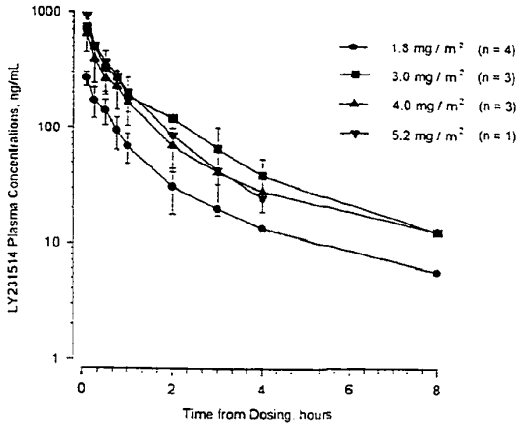


*Fig. 1* Plasma concentration/time profile of LY231514.

Two additional patients had grade 3–4 gastrointestinal toxicity: the first, a male with pancreatic cancer, received LY231514 at 2.3 mg/m$^2$. After a second cycle of treatment, he developed rectal bleeding, heralding a fatal gastrointestinal hemorrhage. Coagulation parameters and platelet count were normal throughout the time on study, although grade 3 changes in alkaline phosphatase and hepatic transaminases were noted in association with the acute event. Postmortem examination showed extensive inflammatory changes throughout the large intestine, with no focal bleeding source identified and only microscopic evidence of residual tumor. The etiology of this event remains unclear; however, a relation to LY231514 could not be excluded. The second patient experiencing significant gastrointestinal toxicity received LY231514 at 5.2 mg/m$^2$ and is detailed above.

**PKs.** PK samples were obtained during the first course of treatment from 29 patients. On days 1 and 5, samples were taken at 0, 5, 15, 30, and 45 min and 1, 2, 3, 4, 8, 12, and 24 h after dosing. Additional single samples were taken on days 2, 3, and 4 and days 8 and 15. Fig. 1 details the day 1 mean plasma concentration/time profiles of patients treated at the higher dose levels (1.8, 3.0, 4.0, and 5.2 mg/m$^2$), and Table 5 summarizes these PK parameters.

Mean AUC and maximum plasma concentration ($C_{max}$) vary in a linear fashion with dose (Fig. 2, *a* and *b*). No time dependency for PK parameters was found; normalized day 1 and 5 AUC values were comparable (Fig. 3). LY231514 is cleared rapidly from the plasma with a mean day 1 clearance of 108.9 ± 38.8 ml/min. Plasma levels declined with a mean harmonic terminal half-life of 1.4 ± 0.98 h. Volume of distribution is small, (8.04 ± 4.1 liters/m$^2$), reflecting the polarity of the compound. There was a weak correlation between day 1 plasma drug clearance and both pretreatment serum creatinine ($r^2$ = 0.26; $P$ = 0.01; Fig. 4*a*) and calculated creatinine clearance ($r^2$ = 0.22; $P$ = 0.02; Fig. 4*b*). There was no significant correlation observed between drug clearance and patient age ($r^2$ = 0.13; $P$ = 0.13) or the neutrophil nadir of cycle 1 and either day 1 AUC ($r^2$ = 0.13; $P$ = 0.12) or $C_{max}$ ($r^2$ = 0.15; $P$ = 0.09).

**Antitumor Efficacy.** No objective tumor responses to LY231514 treatment were recorded; however, antitumor effects were observed in three patients. The first, a 62-year-old female with metastatic non-small cell lung cancer previously treated with platinum, received LY231514 at 3 mg/m$^2$. After six courses of LY231514, there was symptomatic and radiological improvement, sustained for an additional four treatments. The second, a 33-year-old male with metastatic colon cancer, demonstrated a reduction in a nonmeasurable hepatic metastatic lesion, insufficient to qualify as partial tumor response after four courses of treatment with LY231514 at 4 mg/m$^2$. The third, with a 4 × 4-cm tumor in the pancreas, received two courses of LY231514 at 2.3 mg/m$^2$. Four weeks after a second course, the patient developed fatal gastrointestinal bleeding as described above. No macroscopic tumor was seen at necropsy; however, microscopic tumor was found in biopsies taken from the original site of disease.

An additional eight patients had stable disease on LY231514; of these, two had metastatic large bowel cancer actively progressing through 5-FU-based therapy before achieving disease stabilization of 3- and 6-months duration, respectively, on LY231514.

## DISCUSSION

When given as a daily 10-min infusion for 5 days, repeated every 3 weeks, LY231514 proved to be well tolerated, with a MTD of 4 mg/m$^2$/day. Myelosuppression was the principal DLT; liver biochemistry perturbations were also observed, and although such changes were by definition dose limiting, there was no evidence of clinically significant compromise of hepatic function. Similar changes have been seen in patients receiving other antifolates, including CB 3717, ralitrexid (6), and methotrexate. Nonhematological toxicities were generally mild and easily manageable. Weight loss, observed in animal models, was not seen in the current study.

PK studies showed the PK profile of LY231514 to be linear when related to drug dose. As with other antifolates, excretion is thought to be principally renal, and correlation between drug dosage and both serum creatinine and calculated (modified) creatinine clearance (7) was observed, similar to that found in other early clinical studies of the compound (3). However, these observed associations are weak, possibly due to the ineligibility of patients with renal impairment from study entry. Additionally, we found no pharmacodynamic correlation between myelotoxicity and PK parameters, contrary to previous findings (3). These contrasting results are likely related to the differing schedules of drug administration used, with drug half-life a stronger determinate of total drug exposure when using an intermittent injection schedule than when using repeated daily injections. Furthermore, given the 10-fold variation in single-day drug dosage between these two schedules and the relatively low plasma drug concentrations (approaching the limits of quantitation) achieved with the daily × 5 schedule, caution should be exercised in interpretation of PK data from this schedule. Such low levels of measurable drug may potentially lead to an overestimation of drug clearance and underestimation of drug half-life.

Several features make TS an attractive target for antineoplastic drugs, its central role in the *de novo* synthesis of TTP, an

*Table 5* PK parameters, mean ± SD

| Dose (mg/m²) | n | Age (yr) | $C_{max}$ (ng/ml) | AUC (ng/h/ml) | Half-life (h) | Clearance (ml/min/m²) | $V_{ss}$ (liters/m²) |
|---|---|---|---|---|---|---|---|
| 1.8 | 4 | 59.5 ± 10.5 | 290.2 ± 84.2 | 315.0 ± 94.6 | 2.0 ± 1.4 | 103.9 ± 39.6 | 8.57 ± 3.6 |
| 3.0 | 3 | 54.0 ± 4.4 | 544.4 ± 320.9 | 767.5 ± 299.8 | 2.1 ± 0.4 | 75.0 ± 37.7 | 9.5 ± 5.9 |
| 4.0 | 3 | 52.3 ± 16.8 | 654.9 ± 207.1 | 605.7 ± 227.4 | 1.1 ± 0.5 | 121.8 ± 47.9 | 8.25 ± 1.3 |
| 5.2 | 1 | 56 | 936.7 | 752.0 | 1.13 | 115.2 | 7.8 |

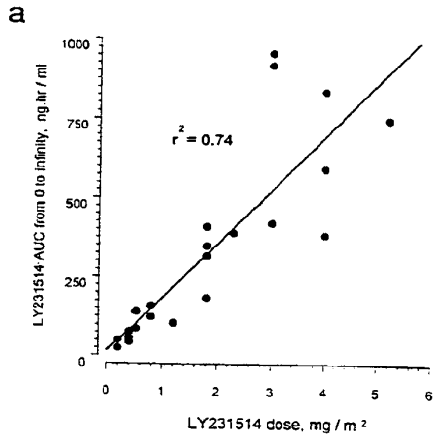


*Fig. 2* Regression of (*a*) AUC and (*b*) $C_{max}$ as a function of LY231514 dose.

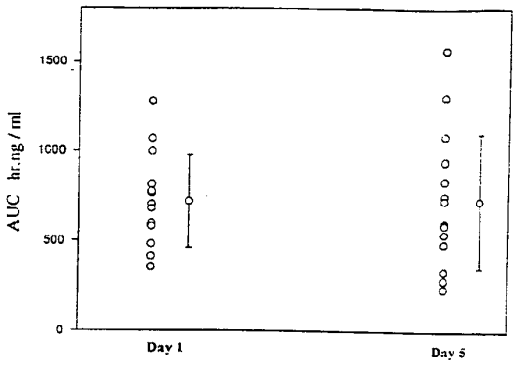


*Fig. 3* Day 1 and 5 AUC for a normalized dose of 4 mg/m².

essential DNA component, together with the recognition of enhanced TS inhibition as the mechanism underlying the increased activity of folinic acid-modulated 5-FU (8), emphasizes its importance in tumor cell growth. TS is overexpressed in colon cancer, and the clinical chemosensitivity of both this tumor and breast cancer are associated with the degree of enzyme inhibition achieved (9, 10). Furthermore, in one study, the outcome of adjuvant 5-FU-based therapy in rectal cancer has been found to correlate with TS expression (11).

TS can be inhibited by the use of fluoropyrimidines or folate analogue compounds. 5-FU is a drug with an established role in the treatment of several tumor types, alone or in combination. However, it does not target TS in isolation and also inhibits RNA synthesis. The folate analogues may provide more specific enzyme inhibition, and the complex structure of the tetrahydrofolate molecule permits a range of modifications for the design of compounds within this class of novel antagonists. CB3717 was the first selective folate analogue inhibitor of TS, and although antitumor activity was observed in early clinical trials (detailed in Ref. 6), unpredictable toxicities, principally nephrotoxicity, precluded its further development. The activity of CB3717, together with the recognition of TS and associated folate pathways as important targets for anticancer agents, maintained interest in this area, and anticipation of the clinical potential of less toxic folate analogues stimulated the development of additional compounds capable of inhibiting TS (reviewed in Refs. 6 and 12). LY231514 is one such novel inhibitor of TS, but one that additionally targets other folate-dependent enzymes including dihydrofolate reductase and GARFT (2). This spectrum of multitargeted enzyme inhibition is unique among this class of compounds and may confer an advantage over other compounds of this type.

Although the plasma PK profile of the compound suggests possible therapeutic advantage in favor of repeated drug exposure, the long-term retention of polyglutamate forms of the drug within the cell would favor less frequent drug dosing. The treatment schedule outlined in this report is one of three in which LY231514 has been evaluated. Comparison of these schedules reveals the effects of LY231514 to be strongly schedule dependent, with up to a 30-fold difference in maximum dose

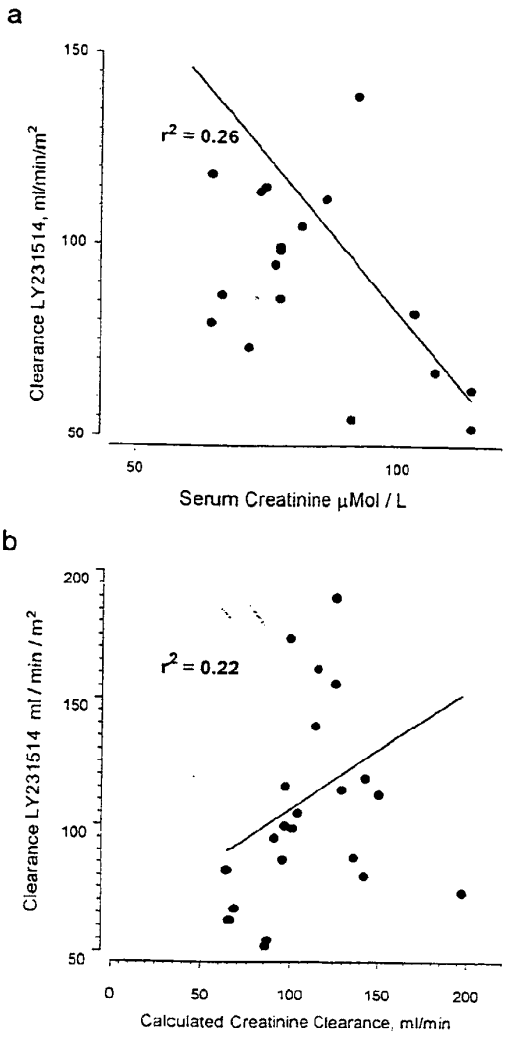


*Fig. 4* Correlation of LY231514 clearance with (*a*) serum creatinine and (*b*) calculated creatinine clearance.

intensity achievable; when given as a single i.v. injection once every 21 days, an MTD of 600 mg/m$^2$ was established (*5*), with myelosuppression and fatigue being dose limiting. Four partial tumor responses in pancreatic and colorectal cancer were observed in this study of 37 patients, with an additional 6 minor responses seen in patients with colorectal cancer. When administered once/week for four consecutive weeks, repeated every 42 days, a MTD of 40 mg/m$^2$ was established. Myelosuppression was again dose limiting (3). Difficulties in maintaining dosing according to schedule due to neutropenia in subsequent courses were observed in this regimen. Other toxicities found in both series included reversible liver transaminase elevation, nausea, diarrhea, mucositis, and skin rash.

Given the ease of administration of a single injection every 3 weeks, the dose intensity achievable using this regime, and the antitumor activity observed in early clinical trials using this schedule, current Phase II studies of LY231514 are focused on a 3-weekly single injection schedule of administration and are underway in a range of tumor types. However, this study indicates that a treatment schedule of daily × 5, every 21 days, using 4 mg/m$^2$ as a daily dose, is feasible and shows some evidence of antitumor activity. More detailed evaluation of both antitumor activity and treatment tolerance at 4 mg/m$^2$/day × 5 is now being undertaken in Phase II studies.

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Appendix 3

# Appendix 3
# Summary of Deaths

## Death Summaries

In 748 patients treated with MTA to date, there have been 22 deaths which are clearly treatment related (2.9%). Thirteen of these 22 patients died of septic complications of myelosuppression, and in an additional 3 patients, neutropenia is thought to have contributed to the patients' deaths. Five of the 22 patients died due to events secondary to diarrhea (3 with renal failure, 1 with hypotensive shock, 1 with metabolic shock). Two patients had both gastrointestinal toxicity and neutropenia; one of these expired of acute respiratory distress syndrome. The remaining death occurred in a patient with a prior history of cardiac failure, including 3 prior infarcts. He had severe MTA-related anemia which was thought to have contributed to his fatal cardiac failure while on therapy. Seven of these 22 treatment-related deaths occurred in Phase 1 studies, of which 2 occurred secondary to treatment with the combination of MTA and cisplatin. To date, there have been no treatment-related deaths in Phase 2 MTA combination studies, or in other Phase 1 combination studies. At the time of preparation of this document, we are seeking additional information on two patients (JMBR-401-4012 and JMBR-403-4048), but for the purposes of this analysis, have ascribed these deaths to MTA at this time.

**Treatment Related Deaths in MTA Studies**

| Type of Study | Number of Patients | Number of Deaths |
|---|---|---|
| Phase 1 Single Agent | 100 | 5 |
| Phase 1 Combination | 109 | 2 |
| Phase 2 Single Agent | 504 | 15 |
| Phase 2 Combination | 35 | 0 |

The following is a list of deaths associated with treatment with MTA or MTA in combination. These have been characterized as follows: 1)Deaths clearly related to therapy with MTA in Phase 1; 2) Deaths clearly related to therapy with MTA in Phase 2. In addition, we have provided information on patients in whom the balance of probability is that they died of other causes. These are divided into those deaths occurring in Phase 1 and those occurring in Phase 2. For completeness, we have also provided death summaries for patients who died on study from other causes or within 30 days of study drug administration and whose deaths are clearly not study drug related. Again, these are divided into patients treated in the Phase 1 and Phase 2 settings. For an analysis of risk to benefit ratio, please see Section 7 of the main briefing document.

**Patients are designated by [Study Code-Investigator Number-Patient Number].**

**Deaths related to therapy with MTA in Phase 1:**

**H3E-BP-001, Pt 37 Death date: 1 Feb 96**

Patient 37 was a 55-year-old male, and had been diagnosed with colon cancer. He received 5 mg/m2 of MTA daily for 5 days every 21 days. After Cycle 5 of MTA (at 5.2 mg/m2), he was hospitalized with Grade 4 mucositis, dehydration, diarrhea, thrombocytopenia, and febrile neutropenia. The patient was treated intravenously with IV antibiotics, but deterioration of renal function occurred, with reduced urine output, hypotension, and subsequent death. Cause of death was therefore secondary to MTA.

**JMAA-1-167 Death date: 21 Sep 94**

Patient 1-167 was a 66-year-old male who received three cycles of MTA, starting on 11 July 1994, at the following dose levels: 700 mg/m2, 525 mg/m2, and 350 mg/m2, respectively. After Cycle 3, the patient became pancytopenic (Grade 4), and developed mucositis. As a consequence of his myelosuppression and compromised gastrointestinal mucosa, he became septic, which led to his death. Thus, death was due to septic complications of MTA therapy.

**JMAA-1-183 Death date: 8 Aug 95**

Patient 1-183 was a 66-year-old female who received eight cycles of MTA for adenocarcinoma of the colon, starting on 2 February 1995. The first six cycles were dosed at 600 mg/m2, and the last two cycles were at 450 mg/m2. After Cycle 8, the patient was hospitalized with intractable nausea/vomiting, dehydration, diarrhea, mucositis, and hematologic toxicities of neutropenia and thrombocytopenia. On Day 21 of inpatient hospitalization, her mental status worsened, and she developed respiratory problems. The investigator's opinion was that prior toxicities predisposed her to acute respiratory distress syndrome (ARDS). Hence, the patient died on Day 24 of hospitalization of ARDS, secondary to MTA therapy.

**JMAA-1-173 Death date: 8 Dec 94**

Patient 1-173 received four cycles of MTA, the fourth cycle was at a reduced dose of 350 mg/m2 (Cycles 1 through 3 were at 600 mg/m2), for a diagnosis of colon cancer, starting on 9 September 1994. Following Cycle 4, the patient developed febrile neutropenia, which persisted for >7 days. Due to the neutropenia, fungal pneumonia with associated fungal sepsis occurred (blood cultures were positive for fungus). Despite aggressive therapy, the patient died from this complication of therapy.

**JMAP-401-0048 Death date: 5 Mar 98**

This event concerns a 64-year-old male (Patient 401-0048) with an advanced transitional cell carcinoma, and a second primary, an invasive well-differentiated spinocellular epithelioma (found on biopsy of bronchus), and was being treated with MTA (500

mg/m2) and cisplatin (75 mg/m2), starting on 2 February 1998. Six days after Cycle 2 of MTA/cisplatin, the patient developed Grade 4 diarrhea, dehydration, oral mucositis with bleeding, and was hospitalized with a diagnosis of metabolic shock. The patient was admitted to the intensive care unit, intubated and sedated, and treated with dopamine for hypotension. At the time of hospitalization, he was found to be leukopenic and thrombocytopenic (Grade 4 - white blood cell count on 3 March 0.1; platelets on 3 March 41K, on 4 March 14K). Despite support with artificial ventilation and inotropic medications, the patient became anuric and died on 5 March 1998. The cause of death was listed as septic metabolic shock and multi-organ failure. Hence, the patient died of complications of treatment with MTA.

**JMAP-401-0053 Death date: 10 Mar 98**

This series of events concern Patient 401-0053 who was a 55-year-old male with head and neck cancer, and a history of chronic alcoholism who received one cycle of MTA/cisplatin on 23 February 1998. Symptoms developed on 1 March 1998, with increasing dysphagia, dehydration, and poor oral intake. The patient was hospitalized, and intravenous hydration was initiated. Grade 4 mucositis developed, and the patient was treated with a "cocktail" of hydrocortisone, lidocaine, nystatin, acyclovir intravenously, and TPN. On 5 March, the white blood cell count was 0.6 (ANC 468), and the patient was afebrile. Platelet count on 5 March was 46K (by 9 March it was 6K). Fever developed on 7 March and blood cultures were done, which were positive for Staph aureus (consideration made of an infected venous access device). A chest x-ray indicated left bronchial pneumonia, and antibiotics were started on 7 March. At this point, the patient became increasingly somnolent, and was transferred to the intensive care unit. A CT scan indicated signs of toxic/metabolic encephalopathy. The patient died on 10 March 1998. The cause of death was listed as sepsis. Autopsy revealed a small tumor, indicating death was not from progressive disease. Mucositis may have been related to prior radiotherapy or alcohol consumption. Neutropenia, fever, and sepsis may have been related to central line sepsis. However, the balance of probability was the patient died of MTA complications.

**JMAW-100-5002 Death date: 13 Jul 98**

This patient was a 79 year old male with prostate cancer who was enrolled in our renal impaired study. He was enrolled in cohort 4 (GFR<20). He received 150 mg/m$^2$ of MTA on 24 June 1998. On 30 June 1998 he was admitted to the hospital for grade 4 mucositis, leukopenia and neutropenia. He also developed anemia and thrombocytopenia on 2 July 1998. Further labs showed and elevated BUN (98 mg/dL) and elevated creatinine (4.5 mg/dL). He was confused and his oxygen saturation was 96%. He was treated with Filgrastim, Leucovorin and Thymidine and his counts did begin to recover. He had a feeding tube placed and received 2 units of packed red blood cells. He developed diarrhea and lethargy and remained confused. His mucositis improved. Investigator states cause of death is renal failure resulting from MTA.

**Deaths related to therapy with MTA in Phase 2:**

**JMAC-4-155 Death date: 27 Dec 95**

This was a 77 year old patient with colorectal cancer who received MTA from 12Oct95 to 12Dec95 at a dose of 600 mg/m2. The patient was admitted on 21Dec95 with a 4 day history of vomiting and diarrhea. The patient was jaundiced and afebrile and lab results showed an absolute neutrophil count of 80, a WBC of 0.4 and a bili of 7.21. Blood cultures were not obtained. Soon after admission the patient developed a fever and antibiotics were started. The patient remained febrile and expired after five days. Although the bilirubin was elevated no diagnostic studies were performed to assess tumor status. The investigator believes this death to be from neutropenic sepsis

**JMAC-5-202 Death date: 24 Sep 96**

Patient 5-202 was a 64-year-old male with adenocarcinoma of the colon with metastasis to the small intestine and the lung, and a history of atrial fibrillation. He received study drug 600 mg/m2 from 2 July 1996 to 17 September 1996. The patient developed dizziness, diarrhea, and abdominal pain of 4 days' duration, and presented to the hospital with neutropenia, fever, and diffusely distended bowel 6 days following Cycle 4. An abdominal CT showed air in the biliary system. The patient developed progressive abdominal distention and subsequent paroxysmal supraventricular tachycardia and increasing respiratory distress. He died 24 September 1996, 7 days after receiving his last dose of MTA. Autopsy showed infarction of small and large bowel, and multiple bowel adhesions. The cause of death was most likely bowel infarction resulting from multiple factors (therapy, obstruction secondary to adhesions, ischemia related to hypotension just before death). The balance of probability is that the infarct was disease-related. However, the infarction occurred in the setting of neutropenia, secondary to MTA. Therefore, one has to conclude that MTA played a role in this patient's death.

**JMAF-100-2 Death date: 01 Oct 97**

Patient 100-2 was a 60-year-old male with gastric cancer. He received study drug 500 mg/m2 from 29 July 1997 to 26 August 1997. He was hospitalized on 4 September 1997 (Day 8 of Cycle 2) for acute abdominal pain. He also presented with neutropenia, fever, pneumonia, and enteritis. Counts were: hemoglobin 5.9, white blood cell count 0.7, and platelets 46K. He received antibiotics and G-CSF. On 29 September 1997 he complained of worsening respiration, and x-rays showed a massive bilateral pneumonia. He died on 1 October 1997 due to pneumonia. Autopsy showed bilateral pneumonia, multiple liver metastasis, peripancreatic metastasis, and left heart hypertrophy. This death is felt to be due to study drug.

**JMAF-101-31 Death date: 16 Dec 97**

Patient 101-31 was a 76-year-old male with gastric cancer with a history of three previous MI's (1975, 1978, 1985). He also had a pacemaker placed in 1996. He received his one and only dose of MTA (500 mg/m2) on 27 November 1997, and presented to the hospital 5 days later complaining of dyspnea. He had an increase in cardiac enzymes which showed the occurrence of a heart attack (thought to have occurred immediately before hospitalization). While hospitalized, he developed hemorrhagic stomatitis (2 December), anemia (2-15 December), confusion, and melena (2-15 December). Labs done on 4 December showed hemoglobin 6.6; white blood count 0.75, neutrophils 23.7%, and platelets 204K. On 11 December labs were: hemoglobin 8.2, white blood count 13.4, neutrophils 76%, and platelets 129K, after transfusions and G-CSF. Following the heart attack, the patient received parenteral nutrition and antibiotic therapy. He developed hematemesis on 5 December and a new episode of heart failure. The patient died on 16 December, as a result of the latest episode of heart failure. No autopsy was performed. Although the patient had a prior history of cardiac events and his counts recovered prior to death, the investigator considered there to be a causal relationship between MTA and heart failure, due to the development of severe anemia following MTA therapy.

**JMAF-106-186 Death date: 29 Oct 97**

Patient 106-186 was a 66-year-old male with gastric cancer who received MTA 500 mg/m2 on 17 September 1997 and 9 October 1997. After the infusion of the second dose, the patient developed vomiting and diarrhea, which led to dehydration and pre-renal insufficiency. Serum creatinine on 28 October 1997, was 4.0. The patient also had leukopenia for which he was hospitalized. While hospitalized the patient developed anuria, metabolic acidosis, and renal failure, with subsequent death. Autopsy showed necrosis of the gastric lesion and hepatic metastasis. It is believed that study drug contributed to this patient's vomiting and diarrhea, and therefore, to his acute renal failure, based on the lab results. There was no prior history of renal disease. Hence, this death must be considered study-drug related.

**JMAG-804-849 Death date: 4 Oct 97**

Patient 804-849 was a 58-year-old female with adenocarcinoma of the breast. She received study drug (600mg/m2) every 21 days from 10 July 1997 to 21 August 1997. Toxicity during Cycle 2 included Grade 2 hemoglobin (8.7), Grade 3 white blood cell count (1.1), and Grade 3 neutrophils (0.6). The patient was admitted to the hospital on 25 August 1997 with shortness of breath, hypotension, and metabolic acidosis, as well as sepsis due to urinary tract infection. She died on 27 August 1997 from metabolic acidosis. The investigator does not feel that this death is study-drug related. However, given that the patient developed sepsis in the setting of neutropenia, and metabolic acidosis was secondary to sepsis, this death should be considered study-drug related (at least until further information is received to the contrary).

**JMAH-505-29 Death date: 12 Dec 96**

Patient 505-29 was a 54-year-old male, with esophageal cancer and received three cycles MTA (600 MG/M2) from 23 September 1996 to 12 November 1996. After Cycle 3 he had relatively low nadirs of hemoglobin (7.7), white blood cell count (1.6), neutrophils (0.7), and platelets (3K). With the exception of white blood cell count and platelets, his counts had started to recover on Visit 4 after Cycle3 (hemoglobin 8.9, white blood cell count 1.6, neutrophils 0.8, platelets 3K). The patient had a 1-day dose delay for Cycle 4, and blood tests showed anemia and thrombocytopenia. His condition deteriorated and he was admitted to the hospital. He received two units packed cells, but his condition continued to deteriorate, and he died on 12 December 1996, with leukopenia, uremia, increased serum creatinine, and dyspnea. The patient's dysphagia was worsening as a consequence of progressive disease. The ivestigator stated that this patient died of progression of his esophageal cancer, but that drug toxicities were contributing factors.

**JMAH-802-19 Death date: 31 Aug 96**

Patient 802-19 was a 70-year-old male with esophageal cancer. He received one dose of MTA (600 MG/M2) on 14 August 1996. On the first visit for follow-up lab work, the hemglobin was 8.9, white blood cell count 1.0, neutrophils 0.3, and platelets 133K. At the next lab follow-up the counts were hemglobin 10.3, white blood cell count 1.71, neutrophils 1.3, and platelets 9K. He was hospitalized on 21 August 96 with neutropenia, fever, and dehydration. He became septic, developed renal failure, and died on 31 August 1996. Post-mortem exam showed death from a gastrointestinal hemorrhage, secondary to stomach cancer. Although the death was not thought to be study-drug related by the investigator, it occurred in the setting of myelosuppression, secondary to MTA.

**JMAI-404-51 Death date: 24 Dec 97**

Patient 404-51 was a 63-year-old male with metastatic renal cell carcinoma (to liver, adrenals, mediastinum, lung, thyroid, and bone). He was treated with MTA 500 $mg/m^2$ from 31 October 1997 to 12 December 1997, after which he experienced severe diarrhea and kidney failure. He was hospitalized on 22 December 1997 with renal failure and cardiac arrhythmia (prior history of cardiac arrhythmia), and subsequently died on 24 December. The death was due to renal failure, secondary to diarrhea.

**JMAJ-301-3003 Death date: 2 Mar 98**

Patient 301-3003 was a 60-year-old male with mouth cancer and received MTA 500 $mg/m^2$ on study from 23 December 1997 to 24 February 1998. After his last cycle he developed fever and chills, and was hospitalized 4 days later with severe dyspnea, dehydration, hypotension, hypoxia, cardiac dysrhythmia, and cachexia. In addition, he was neutropenic with a neutrophil count of 500, and a white blood cell count of 800. Despite treatment with antibiotics, hydration, and oxygen, the patient died of septic shock related to study drug.

**JMAK-603-6045 Death date: 13 Jun 97**

Patient 603-6045 was a 76-year-old male with bladder cancer. He received study drug (500 mg/m$^2$) every 21 days from 6 February 1997 to 22 May 1997. He developed Grade 2 mucositis on 29 May and Grade 3 diarrhea on 4 June. He also exhibited kidney insufficiency, hematuria, Grade 3 asthenia, and hypoalbuminemia around 7 June 1997. The patient's death on 13 June 1997 was a result of multiple organ dysfunction with metabolic acidosis from malnutrition, diarrhea-induced dehydration, and subsequent pre-renal dysfunction. There was no neutropenic sepsis related to this death (most recent complete blood count on 6 June 1997 results: white blood cell count 60.4 with 90% neutrophils). The phenomena leading to the renal failure was thought to have been a catabolic situation induced by tumor progression, worsened by the toxic diarrhea, and further exacerbated by the disease progression in the lungs (which cannot be confirmed or denied by chest x-ray). Chest x-ray showed a mixed alveolar interstitial pattern bilaterally, and gasimetry indicated a mixed metabolic/respiratory acidosis. The investigator considers that the renal insufficiency was a result of diarrhea, and is related to study drug.

**JMAM-505-1009 Death date: 4 Jul 97**

Patient 505-1009 was a 47-year-old female who received MTA (600 mg/m$^2$) from 14 April 1997 to 26 June 1997. On 1 July 1997, she presented with a 2-day history of nausea, vomiting, and diarrhea, and was dehydrated upon admission to the hospital. On 3 July the diarrhea developed into bloody diarrhea. Intravenous hydration, antibiotics, and leukovorin were given, but the patient's condition deteriorated into a frank rectal hemorrhage. The patient was not neutropenic or thrombocytopenic at the time (platelets on 25 June 1997 was 490; white blood cell count 3.4; and neutrophils 8). The patient went into hypotensive shock, and died on 4 July 1997. The investigator expressed the opinion that this death was study-drug related, since it was secondary to MTA-related diarrhea.

**JMBR-401-4012 Death date: 16 Jul 98**

This patient was a 49 year old female who received MTA (800 mg) on 25 June 1998 for squamous cell carcinoma of the lung. Within the following three weeks the patient experienced pulmonary infection and increasing dyspnea and died. The investigator ascribes the patient's death to MTA. *We are awaiting further information on this patient, but for now are assuming that this patient died of neutropenic sepsis.*

**JMBR-403-4048 Death date: 7 Jul 98**

Patient 403-4048 was a 58 year old male who received MTA (1053 mg) on 27 June 1998 for NSCLC. He experienced acute sepsis in the setting of neutropenia secondary to MTA and died some hours later. *We only have preliminary information at this time and are gathering further details.*

**JMBR-720-7001 Death date: 21 Jan 98**

Patient 720-7001 was a 52-year-old male with NSCLC who received MTA (500 mg/m$^2$) from 8 December 1997 to 9 January 1998. After his first dose of MTA he developed pneumonia and was found to be positive for pneumococci on bronchoalveolar lavage. He received antibiotics and recovered. The second dose of MTA was given on 9 January 1998, and the patient was again hospitalized with pneumonia on 16 January 1998. Labs on 16 January were: white blood cell count 0.8 and platelets 8K. He received antibiotics, G-CSF, and platelets, with no response. The patient died on 21 January 1998. The investigator feels that death from pneumonia was possibly related to study drug since the patient was neutropenic at the time. There was no evidence of disease progression at the time of death.

**Deaths possibly related to MTA in Phase 1:**

**H3E-BP-001, Pt 25 Death date: 6 Apr 95**

Patient 25, was a 66-year-old male with pancreatic cancer who received MTA (4.4 mg) from 20 February 1995 to 24 March 1995. He died of a rectal hemorrhage of unknown etiology while on study. Per the investigator, the event is considered to be possibly related to study drug, by process of elimination on post-mortem exam. No thrombocytopenia was present at the time of the rectal hemorrhage and death. The autopsy also revealed the presence of enteritis and hepatitis.

**JMAB-1-125 Death date: 21 Nov 93**

Patient 1-125 was a 69-year-old male with colon cancer who had received three doses MTA (30 mg/m$^2$) on Cycle 1 (22 October 1993 to 5 November 1993), when he experienced multiple symptoms of toxicity. For an unrelated condition, he had received Fortaz, and developed a rash, which persisted, although the drug had been given several weeks prior. Upon admission to the hospital on 8 November 1993, his condition continued to deteriorate, with fever, lower extremity edema, and progression of the rash. He also developed renal insufficiency (creatinine 4.9). On 17 November 1993 the patient became neutropenic (Grade 3) and thrombocytopenic (Grade 4), which was treated symptomatically, and improved without complications. Renal function improved as well as the rash, with the administration of steroids (given for possible interstitial nephritis), but the patient experienced an acute central nervous system event on 20 November 1993, which caused severe mental incapacitation. The cause of the neurologic dysfunction and death was not clear, but was thought unlikely to be due to MTA, as it had been discontinued 2 weeks earlier. However, a role of MTA in this patient's death cannot be totally excluded.

**Deaths possibly related to MTA in Phase 2:**

**JMAL-509-1041 death date: 31 May 97**

Patient 509-1041 was a 65-year-old male with NSCLC with brain metastasis. He was treated with 600 mg/m2 MTA every 21 days from 18 September 1996 to 6 May 1997 (total 12 cycles). He developed nausea, diarrhea, and intermittent vomiting on Day 2 of Cycle 12 and was presented to the emergency room on Day 7 of Cycle 12. The patient died while hospitalized from pancreatitis. The investigator believes that the pancreatitis may possibly be related to MTA.

**JMBR-720-7000 Death date: 12 Feb 98**

Patient 720-7000 was a 77-year-old male with NSCLC. He received the last dose of MTA (500 mg/m$^2$) (Cycle 3) on 15 January 1998, and 11 days later developed a fever. Chest x-ray revealed pneumonia, and the patient was hospitalized for intravenous antibiotics, although the patient was not neutropenic at the time. Lab values were: hemoglobin 100, red blood cell count 3.57, white blood cell count 2.6, neutrophils 61.1, platelets 235K. Blood cultures were not done. A CT scan done in February 1998 was positive for disease progression. The patient died of pneumonia, which was diagnosed within 109 days of the most recent MTA infusion. Althugh there was no neutropenia, and the patient had other risk factors for pneumonia (including prior cholecystectomy), the relationship of the death to study drug cannot be excluded. The investigator considered that relationship to be possible, rather than probable.

**JMBR-720-7003 Death date: 19 Dec 97**

Patient 720-7003 was a 65-year-old female who was histopathologically diagnosed with poorly differentiated NSCLC on 11 September 1997. She was treated only once with MTA (500 mg/m$^2$) on 5 December 1997. She was hospitalized on 14 December with asthenia. Her counts were: hemglobin 119, red blood cell count 4.03, white blood cell count 7.3, platelets 179K. She was discharged after 3 days. She was re-admitted into the intensive care unit on 19 December with acute dyspnea, pneumonia, and lung edema. Labs on 19 December were: hemoglobin 122, and white blood cell count 14.6. The patient died that day. The autopsy report indicated that advanced pancreatic cancer was the main cause of death, but pneumonia was the immediate cause of death. The report also indicated that the lung lesions were metastatic from the pancreatic tumor. The patient was not neutropenic at the time of developing pneumonia, but the pneumonia was diagnosed within 10 days of MTA infusion. The investigator states that although there was no neutropenia, and the fact that the patient had other risk factors for pneumonia (malignancy), the relationship to study drug cannot be totally excluded.

**JMBZ-0002** **Death date: 01Jun98**

Patient 0002 was a 66 year old male with NSCLC who received one dose of MTA 500 $mg/m^2$ and Cisplatin $75mg/m^2$ on 28May98. He had a history of angina, hypertension,hypercholesterolemia and no previous history of cardiac events.

**Deaths from other causes in Phase 1: (deaths on study from any cause, or within 30 days of study drug administration, and not related to any toxicity )**

**H3E-BP-001, Pt 33 Death date: 21 Oct 95**

Patient 33 was a 63-year-old male with pancreatic cancer, who received 6.8 mg of MTA from 18 September 1995 to 22 September 1995. He was hospitalized on 26 September 1995 for right-sided weakness and right arm edema. Evaluation by a neurologist determined a diagnosis of acute plexopathy from neuritis, secondary to neoplasia and chemotherapy. The patient died several weeks later of progressive disease.

**JMAB-1-107 Death date: 19 Oct 93**

Patient 1-107 was a 54-year-old male with colon cancer. He received MTA, 40 $mg/m^2$ weekly, for 3 weeks, followed by 3 weeks of rest from 27 April 1993 to 20 September 1993. He was removed from the study on 30 September 1993 due to progressive disease. He died of progressive disease on 19 October 1993. The investigator feels this death was disease-related, but because of the timing of events has included it in the list of on-study deaths.

**JMAB-1-110 Death date: 13 Jan 94**

Patient 1-110 was a 29-year-old female with metastatic colon cancer (to lung and brain), who died after receiving five cycles MTA (30 $mg/m^2$) on JMAB. Dates of MTA doses were from 1 June 1993 to 21 December 1993. This patient was scheduled to receive her sixth dose of drug on 10 January 1994, but did not keep her appointment due to an ear infection. On 13 January 1994, while bathing she suffered a respiratory arrest. She was rushed to the hospital by emergency medical service, at which point she was pronounced dead on arrival. No autopsy was performed. Given the interval between the last administration of study drug and the patient's date of death, and considering the patient had metastatic disease to the lung and brain, the balance of probability is that the respiratory arrest was secondary to progressive disease, rather than study drug.

**JMAP-401-2 Death date: 1 Apr 96**

Patient 401-2 was a 57-year-old male with NSCLC who received study drug on 20 February 1996. He was hospitalized with pneumonia (in the absence of neutropenia), on 12 March 1996, and treated with antibiotics. A bronchoscopy was performed and a lavage showed staphylococcus, streptococcus, and enterococcus. He was removed from study on 22 March 1996 because of disease progression. His condition subsequently deteriorated, and he died of respiratory failure. His death was determined to be a consequence of disease progression.

**JMAP-401-0012 Death date: Unknown**

Patient 401-0012 was a 61-year-old male who was treated with MTA from 14 May 1996 to 4 June 1996. On 26 May 1996 and 7 June 1996, the patient had episodes of "collapse" with loss of consciousness for brief periods followed by dizziness and feelings of weakness. He was hospitalized for these events and was found to have mild arrhythmias that may have been related to study drug or to his history of CHF. Study drug was discontinued at this time. He experienced febrile neutropenia 21 June 1996 and later died of tumor progression sometime after this hospitalization. Date of death is not known and investigator feels that death was related to progressive disease.

**JMAS-102-135 Death date: 19 Apr 98**

Patient 102-135 was a 55 year-old female with pancreatic cancer. She received the first dose of MTA (925 mg/m$^2$) on 5 March 1998. On Day 7 (12 March), she was hospitalized with severe anemia, neutropenia, and thrombocytopenia (hemoglobin 6.8, white blood cell count 1.15, platelets 63K). On 13 March she developed hematemesis and bloody stools, thought to be related to a prior history of colitis. The patient had positive blood cultures (for gram positive cocci, yeast, and gram positive bacilli, in three different culture media), and intravenous antibiotics were started. She also received leucovorin and thymidine for Grade 3 mucositis. By 19 March 1998, the lab values had all improved, and gastrointestinal bleeding had diminished. Labs on 24 March were: hemoglobin 8.6, platelets 67K, and white blood cell count 18.0. On 25 March 7 liters ascites fluid was drained from her abdomen, and she was discharged to home hospice on 26 March. The patient died at home on 19 April 1998, of disease progression. She had recovered from all MTA-related pancytopenia and other toxicities.

**Deaths from other causes in Phase 2:**

**JMAC-4-157** **Death date: 17Apr96**

This patient was a 57 year old with colorectal cancer who received MTA 600 mg/m2 from 12Dec95 to 4Apr96. She had a history of valvular heart disease which her physician stated was devere enough that she would have been a candidate for surgery. She decided against surgery upon learning of her metastatic cancer. She was admitted to the hospital on 17Apr96 with weakness. She had experienced 7-8 episodes of diarrhea per day for the three days prior to admission and these stools were heme positive. She was taken to the ICU where pnuemonia was ruled out and where her stools were heme negative. She died there and the investigator feels that the outcome was a result of her underlying valvular heart disease.

**JMAH-505-28** **Death date: 05 Dec 96**

Patient 505-28 was a 63-year-old male who had esophageal carcinoma and received 600 $mg/m^2$ of study drug from16 September 1996 to 28 November 1996. He was admitted to the hospital on 3 December 1996, for dehydration related to disease progression. He did not respond to supportive therapy and died 2 days later. This death is not thought to be study drug related.

**JMAI-404-0056** **Death date: 24 Mar 98**

This event involves a 63-year-old male patient (Patient 404-0056) with renal cell carcinoma, which was diagnosed in February 1998. He received one cycle of MTA (600 $mg/m^2$) on 9 March 1998. On Days 6-7, the patient became neutropenic and thrombocytopenic, but without any bleeding or sepsis. The last lab values were: hemoglobin 4.9, hct 228, white blood cell count 1.3, platelets 5K. Disease progression was diagnosed, and the patient was treated with radiotherapy to mediastinum on 16 March 1998. Death occurred on 24 March 1998 due to progression of disease. An autopsy confirmed presence of remarkable metastases to mediastinum and lungs, which led to cardiopulmonary failure.

**JMAK-602-6023** **Death date: 31 Oct 96**

Patient 602-6023 was a 76-year-old male with bladder cancer and a history of diabetes mellitus since 1972, and hypertension since 1994. He received MTA (600 mg/m2) on 24 September 1996. This patient progressed to lung and bone and died on 31 October 1996. The investigator does not consider the events leading up to the death, or the death itself, related to study drug, but rather to poor patient condition.

**JMBB-100-1021** **Death date: 11 Jul 97**

Patient 100-1021 was a 51-year-old male, admitted to the hospital with diarrhea, fever, anemia, thrombocytopenia, and chest wall bleeding, which at the time were thought to be

attributed to study-drug administration. He had been treated with 500 mg/m$^2$ of MTA on 19 June. All toxicities resolved by 10 July, at which time the patient was taken off-study due to progressive disease documented by CT scan in which the patient's liver was virtually replaced by metastatic disease. The death occurred on 11 July 1997, and was determined by the investigator to be due to disease progression.

**JMBM-100-2001 Death date: 18 Apr 98**

This death is reported on Patient 100-2001, a 66-year-old male patient with colorectal cancer, who received 500 mg/m$^2$ of MTA from 26 May 1997 to 11 March 1998. On 16 April 1998, he underwent a colonoscopy, where biopsy was attempted to investigate a possible recurrence of disease. During the procedure the bowel was perforated, which led to diaphragmatic compression, respiratory failure, and subsequent cardiac arrest. He was intubated and transferred to the intensive care unit, where his condition deteriorated. The diagnosis of septic shock was made, with accompanying anuria, acidosis, and positive blood cultures. Death occurred on 18 April 1998, attributed to septic shock from the bowel perforation.

**JMBM-109-2171 Death date: 19 Sep 97**

Patient 109-2171 was diagnosed with colorectal cancer and received 500 mg/m$^2$ of MTA on 28 August 1997, the first and only dose received. On 8 September the patient was hospitalized with anasarca, dyspnea, and profound weakness. Upon admission, this 79-year-old male was found to be thrombocytopenic, with a platelet count of 10,000. A chest x-ray demonstrated partial collapse of the right lower lobe, with bilateral pleural effusions. While hospitalized he was transfused, and paracentesis was done twice for massive ascites, which was present at the time he enrolled in the study. The patient's disease progressed during the hospitalization, and he subsequently died on 19 September. By the time of death, the thrombocytopenia and dyspnea were both resolved (platelets 567,000 on 19 September), but the ascites remained. No scans were done to document disease progression, but blood chemistries diagnosed liver metastases (SGOT 90, alkaline phosphatase 612). The investigator and Lilly physician both consider this death as due to disease progression.

**JMBN-100-3026 Death date: 13 Oct 97**

Patient 100-3026 was a 55-year-old male, with an advanced malignancy, and received 4 mg/m$^2$ of study drug every day for 5 days in two cycles on 15 September 1997 and 10 October 1997. He was hospitalized on 11 October 1997 with increased weakness and respiratory distress and was found to have progressive disease. On 12 October the patient was found to have a pneumothorax, and a chest tube was placed. That day he went into respiratory arrest and was transferred to the intensive care unit, where he was intubated. By patient wishes, only comfort care was provided, and he died on 13 October 1997. It was the investigator's opinion that the patient died of respiratory distress related to progressive disease.

**JMBN-100-3038 Death date: 29 Nov 97**

Patient 100-3038 was a 53-year-old male with colorectal cancer. He received MTA (4 $mg/m^2$) every day for 5 days for two cycles (Cycle 1 starting 20 October 1997 and Cycle 2 starting 14 November 1997). Initial scan prior to receiving drug showed 30-40 lesions that were being followed. A CT scan done in November showed more than 100 lesions. In addition, the patient had hepatomegaly when seen on 20 November 1997. He died on 29 November, of progressive disease, according to the investigator.

**JMBN-107-3141 Death date: 21 Sep 97**

Patient 107-3141 was a 61-year-old male with colorectal cancer, who received two cycles MTA (4 $mg/m^2$ every day times 5 days). During the study he had experienced the following toxicities: Grade 3 mucositis, Grade 4 bleeding rash, elevated bilirubin (2.7), elevated LDH (to 3576 U/L), Grade 2 neutropenia, Grade 4 thrombocytopenia, and Grade 3 anemia. These toxicities were MTA-related, and abated after discontinuation of therapy (the last dose was given on 25 August 1997). The patient was taken off study on 11 September 1997, due to documented progression in the liver. The patient died of disease on 27 September 1997.

**JMBN-107-3143 Death date: 21 Sep 97**

Patient 107-3143 was a 68-year-old male with colorectal cancer, who received two cycles MTA at 4 mg/m2 daily for 5 days, 21 days apart. He was hospitalized on Day 7 of Cycle 2 with severe weakness, reduced oral intake (without vomiting), and 4+ pitting edema with weeping blisters on bilateral lower extremities, but no neutropenia (white blood cell count 23.1, ANC 19.8). His condition deteriorated progressively, despite intravenous hydration, antibiotics, and steroids. Although the patient was afebrile by 20 September, and the ANC was rising, the renal function continued to deteriorate (rising BUN and creatinine), and he died 2 days after admission (Day 9 of Cycle 2). No autopsy was done. Disease progression was diagnosed, but no scans were performed to confirm. The presence of ascites and abnormal lab values were used to document progression. The analysis statement for the death: the renal failure was more than likely related to disease progression, which caused this patient's death.

**JMBP-401-4001 Death date: 30 Dec 97**

Patient 401-4001 was a 60-year-old female who received 600 $mg/m^2$ of study drug once every 21 days from 16 October 1997 to 7 November 1997. She was hospitalized for 5 days with increasing abdominal pain and icterus on 23 October 1997 (this occurred again on 6-8 November 1997). She was removed from study 26 November 1997, because of lack of efficacy. The patient died on 30 December 1997 of cardiovascular failure, secondary to metastatic breast cancer. She had not received study drug for approximately 6 weeks.

**JMBP-401-4002 Death date: 7 Feb 98**

Patient 401-4002 was a 38-year-old female who received her first and only dose of MTA (600 mg/m$^2$) on 12 January 1998 for metastatic breast cancer. She was hospitalized on 21 January for malaise and hyperbilirubinemia (2.4 MG%), which the investigator considered related to study drug. At that time, she was taken off study because she had progressive disease with lung metastasis. She died on 7 February 1998.

**JMBP-802-8021 Death date: 28 Feb 98**

Patient 802-8021 was a 56-year-old female with breast carcinoma who received MTA 600 mg/m$^2$ from 30 July 1997 to 14 January 1998, at which time a chest x-ray and liver ultrasound showed disease progression. She was hospitalized 25 February 1998 with jaundice, increased breathlessness, and nausea. She was also found to have a low platelet count with no obvious bleeding. Her condition continued to deteriorate, and her level of consciousness dropped 27 February 1998. Chemistries were within normal limits, with the potassium at upper level of normal (7.5). She died 28 February 1998. It is the investigator's opinion that death was either due to a cardiac event secondary to hyperkalemia, or a cerebral bleed, but not study drug.

**JMBR-401-4006 Death date: 09 Mar 98**

Patient 401-4006 was a 62-year-old male with non-small cell carcinoma of the lung. He received the first and only cycle of MTA (500 mg/m$^2$) on 13 February 1998. He was hospitalized on 16 February with a left humerus fracture, thought to be related to bone metastases. The patient was taken off study at that time due to documented disease progression, and died of disease on 9 March 1998. The investigator does not believe that there is a relationship between the study drug and the death.

**JMBR-508-6001 Death date: 28 Apr 98**

Patient 508-6001 was a 66-year-old male with NSCLC who received two cycles of 500 mg/m$^2$ of MTA, (4 March and 25 March, respectively). On 21 April he was hospitalized and found on CT to have cerebral metastases. His condition deteriorated, and he died on 28 April 1998 of metastatic progressive disease.

**JMBR-720-7009 Death date: 28 May 98**

Patient 720-7009 was a 68-year-old male with NSCLC and a history of cerebral infarct in Jan 1998. He was treated with MTA 500 mg/m2 from 17 April 1998 to 8 May 1998. He was hospitalized on 18 May 1998 with a fever of 38.0 C. Lab results showed mild leukopenia and an elevated CRP. His CRP was elevated before starting the study. No infection was detected and blood culture was negative. He received IV antibiotics and was descharged afebrile on 30Apr98. On 18May98 he was rehospitalized with a fever of 38 degrees C and lab tests showed elevated platelets and CRP. He was not neutropenic and no infection was found. He received IV antibiotics again and fever resolved on 21May98. He then became confused and a CT of his brain revealed a cerebral infarct and small hemorrhage. His condition deteriorated rapidly and he died 28 May 1998 of his

cerebral infarcts. The investigator does not believe the cerebral infarcts are related to MTA.

Appendix 4

# Appendix 4
# Serious Adverse Event Listing

## List of Serious Adverse Events

### Serious, Unexpected, Possibly Related Trial Events

| Event Terms | Cumulative 1 March 1983 to 11 May 1998 | Most Recent 12 January 1998 to 11 May 1998 |
|---|---|---|
| **Body as a Whole** | | |
| Abdominal Pain | 32 | 5 |
| Abscess | 2 | 1 |
| Accidental Injury | 4 | 2 |
| Accidental Overdose | 1 | 1 |
| Allergic Reaction | 1 | 0 |
| Ascites | 8 | 0 |
| Asthenia | 39 | 7 |
| Back Pain | 5 | 1 |
| Carcinoma | 60 | 10 |
| Cellulitis | 9 | 0 |
| Chest Pain | 16 | 3 |
| Chills | 14 | 0 |
| Face Edema | 1 | 0 |
| Fever | 137 | 25 |
| Flu Syndrome | 3 | 0 |
| Headache | 5 | 1 |
| Hernia | 1 | 0 |
| Hypothermia | 2 | 1 |
| Infection | 28 | 3 |
| Malaise | 7 | 2 |
| Mucous Membrane Disorder | 14 | 1 |
| Neck Pain | 1 | 1 |
| Neoplasm | 2 | 0 |
| Overdose | 3 | 0 |
| Pain | 32 | 6 |
| Pelvic Pain | 1 | 1 |
| Radiation Injury | 1 | 0 |
| Sepsis | 13 | 3 |
| Suicide Attempt | 1 | 0 |
| Surgical Procedure | 13 | 0 |
| **Cardiovascular System** | | |
| Angina Pectoris | 1 | 0 |
| Arrhythmia | 1 | 1 |
| Arterial Thrombosis | 1 | 1 |
| Atrial Fibrillation | 7 | 1 |
| Atrial Flutter | 1 | 0 |
| Cardiovascular Disorder | 1 | 0 |
| Cerebral Infarct | 1 | 0 |
| Cerebrovascular Accident | 5 | 0 |

## Serious Trial Events (cont'd)

| Event Terms | Cumulative 1 March 1983 to 12 January 1998 | Most Recent 12 January 1997 to 11 May 1998 |
|---|---|---|
| **Cardiovascular System** | | |
| Congestive Heart Failure | 2 | 1 |
| Deep Thrombophlebitis | 9 | 2 |
| Electrocardiogram Abnormal | 1 | 0 |
| Heart Arrest | 3 | 1 |
| Heart Block | 1 | 1 |
| Heart Failure | 2 | 0 |
| Hypotension | 7 | 3 |
| Myocardial Infarct | 1 | 0 |
| Pallor | 1 | 1 |
| Pericardial Effusion | 1 | 1 |
| Pulmonary Embolus | 3 | 0 |
| Pulmonary Thrombosis | 1 | 0 |
| Shock | 7 | 3 |
| Supraventricular Tachycardia | 1 | 0 |
| Syncope | 6 | 0 |
| Tachycardia | 1 | 0 |
| Thrombophlebitis | 4 | 0 |
| Thrombosis | 5 | 0 |
| **Digestive System** | | |
| Anorexia | 11 | 3 |
| Carcinoma of the mouth | 1 | 0 |
| Cholecystitis | 1 | 0 |
| Cholelithiasis | 1 | 0 |
| Cholestatic Jaundice | 1 | 0 |
| Colitis | 1 | 0 |
| Constipation | 8 | 1 |
| Diarrhea | 67 | 6 |
| Dilation of Stomach | 1 | 0 |
| Dysphagia | 9 | 2 |
| Enteritis | 1 | 0 |
| Enterocolitis | 1 | 0 |
| Esophageal Hemorrhage | 1 | 0 |
| Esophagitis | 2 | 0 |
| Fecal Impaction | 1 | 0 |
| Flatulence | 2 | 1 |
| Gastroenteritis | 3 | 0 |
| Gastrointestinal Carcinoma | 104 | 10 |
| Gastrointestinal Disorder | 7 | 0 |
| Gastrointestinal Hemorrhage | 15 | 2 |
| Hematemesis | 3 | 1 |
| Hepatic Failure | 2 | 0 |
| Hepatitis | 1 | 0 |

## Serious Trial Events (cont'd)

| Event Terms | Cumulative 1 March 1983 to 12 January 1998 | Most Recent 12 January 1998 to 11 May 1998 |
|---|---|---|
| **Digestive System** | | |
| Hepatorenal Syndrome | 1 | 0 |
| Ileus | 4 | 1 |
| Intestinal Obstruction | 21 | 2 |
| Intestinal Perforation | 2 | 1 |
| Jaundice | 7 | 1 |
| Liver Damage | 2 | 1 |
| Liver Function Tests Abnormal | 6 | 3 |
| Melana | 1 | 0 |
| Nausea | 73 | 6 |
| Nausea and Vomiting | 6 | 1 |
| Nausea Vomiting and Diarrhea | 1 | 0 |
| Pancreatitis | 3 | 0 |
| Rectal Disorder | 1 | 1 |
| Rectal Hemorrhage | 3 | 0 |
| Stomatitis | 20 | 3 |
| Vomiting | 89 | 7 |
| **Endocrine System** | | |
| Diabetic Coma | 1 | 0 |
| **Hemic and Lymphatic System** | | |
| Anemia | 63 | 7 |
| Bleeding Time Increased | 1 | 0 |
| Hemolysis | 1 | 0 |
| Hypochromic Anemia | 2 | 0 |
| Leukocytosis | 3 | 1 |
| Leukopenia | 162 | 23 |
| Marrow Depression | 3 | 0 |
| Pancytopenia | 6 | 2 |
| Petechia | 1 | 0 |
| Thrombocytopenia | 56 | 7 |
| WBC Abnormal | 1 | 1 |
| **Metabolic and Nutritional Disorders** | | |
| Acidosis | 4 | 0 |
| Alkaline Phosphatase Increased | 1 | 0 |
| Bilirubinemia | 7 | 2 |
| BUN Increased | 2 | 0 |
| Cachexia | 2 | 1 |
| Creatinine Increased | 3 | 0 |
| Dehydration | 54 | 4 |
| Diabetes Mellitus | 1 | 1 |
| Edema | 6 | 0 |
| Generalized Edema | 2 | 0 |

**Serious Trial Events (cont'd)**

| Event Terms | Cumulative 1 March 1983 to 12 January 1998 | Most Recent 12 January 1998 to 11 May 1998 |
|---|---|---|
| **Metabolic and Nutritional Disorders** | | |
| Gout | 1 | 0 |
| Hypercalcemia | 5 | 2 |
| Hyperglycemia | 2 | 2 |
| Hyperkalemia | 1 | 1 |
| Hypernatremia | 1 | 1 |
| Hypochloremia | 1 | 0 |
| Hypoglycemia | 2 | 0 |
| Hypokalemia | 11 | 1 |
| Hyponatremia | 4 | 0 |
| Hypoproteinemia | 1 | 0 |
| Hypovolemia | 4 | 0 |
| Lactic Dehydrogenase Increased | 1 | 0 |
| Peripheral Edema | 6 | 0 |
| SGOT Increased | 2 | 1 |
| SGPT Increased | 3 | 0 |
| Water Intoxication | 1 | 0 |
| Weight Gain | 1 | 0 |
| **Musculoskeletal System** | | |
| Arthralgia | 1 | 1 |
| Leg cramps | 1 | 1 |
| Myalgia | 1 | 0 |
| Myasthenia | 1 | 0 |
| **Nervous System** | | |
| Acute Brain Syndrome | 2 | 1 |
| Anxiety | 1 | 0 |
| Aphasia | 1 | 0 |
| Cerebral Hemorrhage | 1 | 1 |
| CNS Depression | 1 | 0 |
| Coma | 2 | 0 |
| Confusion | 9 | 1 |
| Convulsion | 1 | 0 |
| Delirium | 1 | 0 |
| Depression | 1 | 0 |
| Dizziness | 6 | 0 |
| Hemiplegia | 2 | 1 |
| Hypokinesia | 1 | 0 |
| Insomnia | 1 | 0 |
| Neuropathy | 1 | 1 |
| Paralysis | 2 | 0 |
| Paresthesia | 1 | 0 |
| Somnolence | 5 | 0 |

## Serious Trial Events (concluded)

| Event Terms | Cumulative 1 March 1983 to 12 January 1998 | Most Recent 12 January 1998 to 11 May 1998 |
|---|---|---|
| **Nervous System** | | |
| Speech Disorder | 1 | 0 |
| Stupor | 1 | 0 |
| Thinking Abnormal | 1 | 0 |
| Tremor | 2 | 0 |
| **Respiratory System** | | |
| Atelectasis | 1 | 0 |
| Apnea | 5 | 1 |
| Carcinoma of Lung | 39 | 11 |
| Cough Increased | 2 | 2 |
| Dyspnea | 55 | 9 |
| Epistaxis | 2 | 0 |
| Hemoptysis | 4 | 0 |
| Hyperventilation | 1 | 1 |
| Hypoxia | 3 | 2 |
| Lung Disorder | 5 | 0 |
| Lung Edema | 2 | 1 |
| Pharyngitis | 2 | 0 |
| Pleural Disorder | 1 | 0 |
| Pleural Effusion | 8 | 0 |
| Pneumonia | 23 | 7 |
| Pneumothorax | 5 | 2 |
| Pulmonary Embolus | 3 | 0 |
| Respiratory Disorder | 5 | 0 |
| **Skin and Appendages** | | |
| Alopecia | 1 | 0 |
| Maculopapular Rash | 3 | 0 |
| Pruritis | 2 | 0 |
| Rash | 32 | 3 |
| Skin Discoloration | 1 | 0 |
| Sweating | 5 | 0 |
| Urticaria | 1 | 0 |
| **Special Senses** | | |
| Amblyopia | 1 | 1 |
| Deafness | 1 | 0 |
| Tinnitus | 1 | 0 |
| Urinary Retention | 2 | 0 |
| **Urogenital System** | | |
| Acute Kidney Failure | 1 | 0 |
| Anuria | 2 | 1 |
| Bladder Carcinoma | 3 | 1 |
| Breast Carcinoma | 16 | 2 |

| Event Terms | Cumulative 1 March 1983 to 12 January 1998 | Most Recent 12 January 1998 to 11 May 1998 |
|---|---|---|
| **Urogenital System** | | |
| Cervix Carcinoma | 2 | 1 |
| Dysuria | 1 | 0 |
| Epididymitis | 1 | 0 |
| Hematuria | 3 | 0 |
| Kidney Failure | 5 | 0 |
| Kidney Function Abnormal | 2 | 0 |
| Kidney Tubular Disorder | 1 | 0 |
| Nephritis | 1 | 0 |
| Orchitis | 1 | 0 |
| Scrotal Edema | 1 | 1 |
| Urinary Retention | 2 | 0 |
| Urinary Tract Infection | 5 | 1 |
| Urine Abnormality | 2 | 0 |
| Vaginal Hemorrhage | 1 | 0 |
| | | |

Appendix 5

# Appendix 5
# Detailed Methodology for Multivariate Analysis

## Methods for Multivariate Analysis

### 1. *Why Multivariate Analysis Approach to MTA Clinical Research Questions?*

A patient complains of coughing, chest pain, and fever. The physician does not make a diagnosis based upon any one of these signs or symptoms by itself.

- Coughing may suggest a common cold
- Chest pain may suggest heart attack
- Fever could indicate pneumonia

The physician considers all three indicators in combination. A statistician calls fever, cough, and chest pain three variables, because their severities can vary from one patient to another, and even vary from time to time within the same patient.

The physician will usually seek information about additional variables.

- What is the appearance of the sputum?
- What does chest x-ray show?
- What is the white blood cell (WBC) count?

When a physician knows the value of only one variable for a patient, such as severity of fever, he has univariate data. When he knows the value of two or more variables, such as severity of fever, presence or absence of pain, and WBC count, he has multivariate data. We practically always have multivariate data in clinical research and practice.

A syndrome is a group of signs and symptoms that occur together and characterize a particular abnormality. Univariate statistical procedures scrutinize each sign or symptom in isolation as if no others existed; multivariate statistical procedures look for syndromes.

Medical scientists should no more think of limiting their analysis of multivariate data to univariate statistical procedures than a physician would diagnose pneumonia from knowledge of only one symptom.

Univariate statistical techniques examine each variable by itself, ignoring variables' relationships to other facts about a patient. That is contrary to the way the clinicians typically approach problems. Multivariate statistical techniques harmonize naturally with

clinicians' habits of thought, because multivariate procedures search for significant combinations and patterns in data, just as clinicians do.

When evaluating results of treatment in a clinical trial, one measure of outcome seldom suffices by itself to tell the whole story. In cancer, for example, even a simple criterion like survival after 5 years may need to be supplemented by other variables such as measures of quality of life, severity of adverse effects of therapy, and total days of hospitalization. Multivariate statistical procedures allow us to examine several outcome measures jointly to learn if any combination of them differentiates one treatment from another. They can reveal relationships buried in data which univariate procedures could overlook.

## 2. *A Road Map for the Multivariate Analysis of MTA Data*

Before we discuss the details of the multivariate analysis and interpretation of MTA data, it is useful to discuss a road map of the analysis strategy. We first discuss how "discriminant analysis" is used to predict clinical outcome(s) such as toxicity or efficacy following treatment with MTA. We then show how discriminant analysis is also used to develop a screening technique for clinical outcome such as toxicity following treatment with MTA. Here, special attention will be paid to patients who have been misclassified to see if they are carriers of special messages that should not be ignored. We will finally use "canonical correlation analysis" to unravel correlation that may exist between prespecified potential predictors and a set of clinical outcomes following treatment with MTA.

### 2.1. Use of Discriminant Analysis to Predict Clinical Outcome

***The Problem***

An investigator treats a fixed number of patients with MTA. He evaluates their clinical outcomes profile such as toxicity/efficacy profiles after their treatment with the drug. It is determined that n patients of N experienced a given clinical outcome and (N-n) patients did not. The investigator wonders if several facts he knew about the patients before treatment could have predicted their response to the drug.

The above question will addressed in four steps:

**Step 1:**

For a given clinical outcome of interest, a list of k items of prior information which may predict a given patient's response to the drug is established as illustrated in Table 1.

**Table 1. Information About a Patient Prior to Treatment**

| Possible Predictor Variables | Short Name |
|---|---|
| Predictor Variable 1 | PRED1 |
| Predictor Variable 2 | PRED2 |
| Predictor Variable 3 | PRED3 |
| ..... | ..... |
| Predictor Variable *k* | PRED*k* |

**Step 2:**

We will examine the k predictor variables one by one, performing k individual statistical significance tests, to see if any one of the variables by itself predict which patient will experience a specific toxicity/efficacy outcome and which will not. This will be achieved by examining resulting individual p-values. It is possible, in fact very likely in some cases, that each of the k predictor variables by itself does not predict who will experience toxicity/efficacy and who will not. For this reason, we will take the next step.

**Step 3:**

Discriminant analysis examines all k predictors in combination, drawing its strength from hidden or not so obvious relationships that may exist between them, and yields a single p-value. The critical question to answer here is whether the ***k*** predictor variables, taken together, predict better than chance who will experience toxicity/efficacy from treatment.

It is worth pointing out one of the key strengths of multivariate statistical procedures. Even though individual, univariate tests may have indicated that none of the predictor variables chosen is significant, there is a chance that a combination of the ***k*** variables predicts toxicity/efficacy significantly better than chance (significant p-value) if they truly have something to do with the toxicity/efficacy outcome of interest. This observation can be compared, in clinical investigation and practice, to the fact that for a clinician an individual sign or individual symptom may not be sufficient to make a diagnosis of a given condition but that a combination of signs and symptoms are more likely to lead to more accurate diagnosis.

## 2.2. Classification analysis

Once we know which of the k variables predict significantly better than chance who, among future MTA patients, will experience a given toxicity/efficacy outcome following treatment, the next task will be to see how good the prediction is by implementing a classification analysis. Here, the central idea is as follows.

Given that a patient who was treated with MTA did (or did not) experience a given toxicity/efficacy outcome, how well would we have been able to predict it beforehand had we known values of the identified predictor variables on the patient at baseline (or during the course of treatment)? Posterior probability of membership in each group is

calculated using generalized square distance function. This probability is used to create a discriminant function that allows us to generate the following summary table.

**Table 2. Number and Percent of Patients Classified into Group**

| From Group | Outcome Predicted | Outcome Not Predicted | TOTAL |
|---|---|---|---|
| Outcome Experienced | n1 | n2 | n1+n2 |
| | (%) | (%) | (%) |
| Outcome Not Experienced | m1 | m2 | m1+m2 |
| | (%) | (%) | (%) |
| TOTAL | n1+m1 | n2+m2 | N |
| % | % | % | (100%) |

The essential role of this table is to give us a gauge of how well our classification procedure works when using known baseline predictors of a specific clinical outcome.

Discriminant analysis is indeed used here to develop a front end "screening technique" for toxicity/efficacy following treatment with MTA. Now that we have used patients already treated with MTA to identify predictor variables, we want to use this information to develop a screening technique for identifying which future MTA patients will experience a given safety/efficacy outcome. To accomplish this, we will study the MTA database as illustrated below.

**Step 1:**

Suppose, for the sake of illustration, that to date there are 200 patients treated with MTA and that, of those, 20 have experienced a given toxicity. We will know that 20/200 or 10% of MTA patients experienced the outcome. This is called the "prior probability", because the fact that 10% of patients with identified characteristics experienced toxicity is known prior to any further statistical investigation of the database.

Without doing any medical investigation at all, we might say that each patient is free from experiencing toxicity once treated with MTA, and we would be right 90% of the time. A 90% accuracy sounds impressive but does not, by itself, help us because classifying each patient as toxicity-free following MTA treatment would not identify ANY of the patients who will experience toxicity. To be useful for the MTA program, a screening technique must correctly identify some of the patients whom we know have experienced toxicity. Perhaps it should correctly identify most of the patients whom we know have experienced toxicity.

**Step 2:**

We will measure and obtain, for each patient, values at baseline of prospectively identified k predictor variables for a given clinical outcome. We will perform, for each

predictor variable, a univariate statistical test to see whether the predictor variable significantly differentiates the two groups (clinical outcome experienced versus not experienced). But, chances are that the combination of the k predictor variables might differentiate groups more clearly than either measure alone. Should the screening technique fail to identify a sufficiently "high" percentage of patients who experienced toxicity, we will then build in ways to improve our multivariate procedures so that we correctly identify more of the patients with the toxicity of interest.

**Step 3:**

Discriminant analysis will produce a "discriminant score" for each patient—a combination of the k predictor variables, weighted so as to maximize the difference between patients who experience toxicity and those who do not, following treatment with MTA. The magnitude of a patient's discriminant score determines whether he is classified as having toxicity or not. We will use special multivariate techniques using these discriminant scores to improve the performance of the screening technique. Two observations should be made before we conclude the classification analysis plan.

1) It is critical at this stage to pay special attention to patients who have been misclassified. This is because these patients may be sending messages that perhaps there are other predictor variables that may have been overlooked.

2) Use of a large database will produce stable results for the purpose of discrimination in future cases. However, we should expect less accurate discrimination technique for future cases by sheer nature of underlying statistical models. To bring in an analogy, predicting the weather becomes less accurate as forecasters extend their predictions farther into the future. Just as weather forecasters improve weather prediction accuracy by updating the meteorological database, so are we going to improve our screening, discrimination, and classification techniques by reanalyzing MTA database as more data are gathered over time.

## 2.3. Additional Exploratory Analyses

Additional multivariate exploratory analyses will be undertaken. For example, there may be strong scientific reasons to believe that a set of variables exert some influence on certain toxicities following treatment with MTA. Lacking specific hypotheses, we may wonder if potential predictor variables are significantly related to a given set of toxicities. Canonical correlation analysis will be performed to discover any correlation between prespecified potential predictor variables and a given set of toxicities. A new and potentially better performing screening technique could then be developed.

Appendix 6

# Appendix 6
# Protocol H3E-MC-JMBQ

**MTA (LY231514)**

**Protocol H3E-MC-JMBQ(a)**

# A Phase 2/3 Trial of MTA vs Vinorelbine in Patients Previously Treated with Only One Platinum Plus Taxane-Based Regimen for Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Protocol Approved by the Sponsor: 16 June 1998
Amendment (a) Approved by the Sponsor: 17 July 1998

**A Phase 2/3 Trial of MTA vs Vinorelbine in Patients Previously Treated with Only One Platinum Plus Taxane-Based Regimen for Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)**

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**A Phase 2/3 Trial of MTA vs Vinorelbine in Patients Previously Treated with Only One Platinum Plus Taxane-Based Regimen for Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)**

# 1. Introduction

## 1.1. Non-Small Cell Lung Cancer (NSCLC)

Lung cancer, one of the most common malignancies in the world, continues to rise in incidence. It is the leading cause of cancer death in men in the United States, and since the late 1980s, it is also the leading cause of cancer death in women. An estimated 177,000 new cases will be diagnosed in 1998, accounting for approximately 13% of all cancer diagnoses and 29% of all US cancer deaths (Landis et al. 1998). The majority of these deaths will be due to metastatic NSCLC.

Almost 80% of lung cancers can be classified as NSCLC, with 65% to 75% of cases presenting as locally advanced (Stage III) or metastatic disease (Stage IV) (Walling 1994; Shepherd 1993; Ihde 1992). Patients diagnosed with Stage IIIa disease generally receive chemotherapy as part of standard multimodality treatment, whereas Stage IIIb and IV disease patients typically receive chemotherapy as first-line standard therapy.

### *1.1.1. Chemotherapy for NSCLC*

Several individual chemotherapy agents have been tested in advanced or metastatic NSCLC, with only moderate activity reported (response rates of about 15% are considered active). No single agent has been definitively identified as standard therapy (Ginsberg et al. 1997). While cisplatin has historically been considered the most active agent in NSCLC, it and other active agents (eg, mitomycin-C, ifosfamide, vindesine, vinblastine, and etoposide) have achieved median survival times of only 6 to 8 months (Ginsberg et al. 1997).

Vinorelbine was recently approved for first-line treatment in advanced NSCLC as a single agent and in combination with cisplatin. It has been associated with response rates of over 20%, although increases in long-term survival have been more modest (Dancey et al. 1997; Hainsworth et al. 1995; Rigas 1997; Crawford et al. 1996). When used in combination with cisplatin, both increased response rates and survival advantage have been noted compared to either agent alone (Wozniak et al. 1996; Le Chevalier et al. 1994). In one study, the vinorelbine-cisplatin combination showed an increased advantage in 1-year survival of 33% versus 12% for cisplatin alone (Wozniak et al. 1996). When vinorelbine plus cisplatin was compared to vinorelbine alone, the 1-year survival advantage was 35% versus 30% in favor of the combination (Le Chevalier et al. 1994).

As recently as March 1998, the US FDA's oncologic drug advisory committee (ODAC) voted to recommend two new agents, paclitaxel and gemcitabine, for the treatment of NSCLC (Scrip No 2320, 1998). By some estimates, paclitaxel in combination with cisplatin or other platinum drugs is already the standard regimen in roughly 40% of all newly diagnosed NSCLC cases. The ODAC recommended approval for paclitaxel as first-line therapy for advanced NSCLC based predominantly on results from a single well-controlled trial comparing paclitaxel/cisplatin, high-dose paclitaxel/cisplatin, and a cisplatin/etoposide regimen. The sponsor reported a median survival for paclitaxel patients of 9.7 months, compared with 7.4 months for the control group, and an estimated 15% reduction in the risk of death for patients receiving paclitaxel. Although the differences were not considered statistically significant by the FDA, the reported 1-year survival rates were 36% for the low-dose combination and 40% for high-dose paclitaxel with cisplatin, compared with 32% for the etoposide/cisplatin arm. In addition, the FDA said that paclitaxel produced a significant tumor response rate of 21% to 24%.

The committee also recommended approval of gemcitabine as a first-line treatment of patients with locally advanced or metastatic NSCLC, both in combination with cisplatin and as a single agent, palliative treatment (Scrip No 2320, 1998). Approval of the combination therapy was based on pivotal trial results which showed a 1- year survival rate of 39% for gemcitabine/cisplatin versus 28% for cisplatin alone, with median survival times of
9 and 7.5 months, respectively. Additional values reported by the sponsor were tumor response rates of 32% (combination) versus 10% (cisplatin), and median times to progressive disease of 5.8 versus 3.7 months, respectively. Due to its reduced toxicity profile, single-agent gemcitabine is likely to be an attractive alternative for elderly or other patients who cannot tolerate platinum combination therapy.

In spite of the pending FDA approval of two new therapies for NSCLC, patients who fail first-line chemotherapy still have a poor prognosis with a life expectancy of only a few months. Response to second-line therapy is unlikely, perhaps because of poorer patient performance status, as well as an acquired or inherent chemotherapy resistance (Pronzato et al. 1994; Fossella 1997). As a result, new combination and single-agent chemotherapies are still needed to salvage patients who progress after their initial therapeutic regimens.

## 1.2. MTA (LY231514)

### *1.2.1. Background and Phase 1 Results*

Inhibition of the enzyme thymidylate synthase (TS) may be the primary mechanism of action of MTA, a folate antimetabolite (Lilly Research Laboratories 1997; Shih et al. 1992; Grindey et al. 1992). Thymidylate synthase, a folate-dependent enzyme, catalyzes the transformation of deoxyuridine monophosphate (dUMP) to deoxythymidine

monophosphate (dTMP). Inhibition of TS results in decreased thymidine necessary for DNA synthesis (Grem 1990; Schilsky 1992).

MTA also inhibits dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT), a folate-dependent enzyme that is involved in purine synthesis (Shih et al. 1996). These targets are related to the cytotoxicity of MTA since both thymidine and hypoxanthine are required to circumvent cellular death caused by MTA (Schultz et al. 1996). MTA gains entry to the cell via the reduced folate carrier and once localized is an excellent substrate for folypolyglutamate synthase (FPGS). The pentaglutamate form of MTA is the predominant intracellular form and is >60-fold more potent in its inhibition of TS than the monoglutamate (Chen et al. 1996).

MTA exhibits highly cytotoxic in vitro activity against the CCRF-CEM human leukemia cell line and has shown significant antitumor activity against thymidine-and hypoxanthine-deficient murine tumor cell lines as well as two human colon xenografts resistant to methotrexate. Several dose schedules were studied in dogs with the predominant toxicities being gastrointestinal and hematological. Marked schedule dependency was noted, with a 34-fold increase in dose intensity found using a once weekly compared to daily dosing. Folinic acid treatment initiated 24 hours after a potentially fatal dose prevented lethality, suggesting a role for folinic acid in the treatment of severe, drug-induced toxicity (Lilly Research Laboratories 1997).

Given the schedule dependency observed in animal models, Phase 1 studies were conducted exploring three treatment schedules: daily times 5 every 3 weeks (H3E BP-001), weekly times 4 every 6 weeks (H3E-MC- JMAB), and once every 3 weeks (H3E-MC-JMAA).

Thirty-eight patients were treated at doses ranging from 0.2 to 5.2 mg/m$^2$ daily times 5 every
3 weeks in Study BP-001 (McDonald et al. 1998). The maximum tolerated dose (MTD) was 4 mg/m$^2$/day, with dose limiting toxicities (DLTs) on this schedule of reversible neutropenia and liver enzyme disturbance. Other toxicities included mucositis, diarrhea, rash, fatigue, and elevated transaminases. Minor responses were observed in two patients with colorectal cancer and NSCLC.

In study JMAB, 24 patients were treated with a 10-minute infusion of MTA once a week for
4 weeks, with cycles repeated every 6 weeks (Rinaldi et al. 1995). Doses ranged from 10 to 40 mg/m$^2$/week. The DLT was myelosuppression, particularly leukopenia and granulocytopenia. Neutropenia prevented weekly dosing in some patients. Nonhematologic toxicities included mild fatigue, anorexia, and nausea. DLT was observed at 40 mg/m$^2$/week, and the recommended dose for Phase II evaluation was 30 mg/m$^2$/week. The weekly schedule was not pursued in Phase 2 trials.

In study JMAA, MTA was administered to 37 patients as a 10-minute infusion once every

3 weeks at doses ranging from 50 to 700 mg/m$^2$ (Rinaldi et al. 1996). The DLTs on this schedule were neutropenia, thrombocytopenia, and fatigue. Of the 20 patients treated at 600 mg/m$^2$, Common Toxicity Criteria (CTC) Grade 4 neutropenia and CTC Grade 4 thrombocytopenia occurred in 4 and 1 patients, respectively, during the first cycle. CTC Grade 2 toxicities at that dose level included rash, mucositis, nausea, vomiting, fatigue, anorexia, and elevations of liver transaminases. Ten patients who developed rashes received dexamethasone 4 mg twice daily for 3 days starting 1 day prior to treatment with MTA which improved or prevented the rash during subsequent cycles of therapy. There was evidence of cumulative toxicities of neutropenia, thrombocytopenia, and mucositis which may have been due to the prolonged intracellular half-life of the polyglutamate of MTA and decreasing renal function over time with decreased renal drug clearance. Based on this study, the recommended dose for Phase 2 studies was 600 mg/m$^2$. Partial responses were observed in two patients with pancreatic cancer and two patients with advanced colorectal cancer. Three of the four patients with partial responses had failed previous treatment with thymidylate synthase inhibitors including either 5-FU, FUDR, or raltitrexed.

The pharmacokinetics of MTA have been determined in three Phase 1 studies, with dosing given once a week for 3 consecutive weeks and also once every 3 weeks (Rinaldi et al. 1995, 1996). Doses were given as 10-minute infusions in all studies. Doses ranged from 10 to 40 mg/m$^2$ weekly for 3 weeks in the first study, 50 to 700 mg/m$^2$ as a single administration every 3 weeks in the second study, and 0.2 to 5.2 mg/m$^2$ given daily for 5 consecutive days, every 3 weeks in the third study.

Pharmacokinetic determinations were made in 20 patients with various cancers (primarily colorectal cancer) on the every 3-week schedule at the MTD (600 mg/m$^2$). A mean maximum concentration of 137 μg/mL was attained, with a mean half-life of 3.1 hours (range, 2.2 to
7.2 hours). Mean respective clearance and steady-state volume of distribution values of 40 mL/min/m$^2$ and 7.0 L/m$^2$ were also measured. This mean clearance value is similar to that of creatinine clearance in the age range of the patients enrolled (approximately 45 to 55 mL/min/m$^2$), and the volume of distribution reflects limited distribution outside the bloodstream.

Samples collected after the first dose in each course of therapy showed the disposition of MTA to be linear over the entire dose range (0.2 to 700 mg/m$^2$). The clearance of the compound is primarily renal, with 80% or greater of the dose recovered unchanged in the urine during the first 24 hours after dosing. No accumulation appears to occur with multiple courses, and the disposition of MTA does not change after multiple doses. MTA clearance does appear to decrease with age, although this decrease is most likely related to decreasing renal function associated with aging.

### 1.2.2. Phase 2 Results

Two Phase 2 studies in colorectal cancer, one in pancreas cancer, two in NSCLC, and one in breast cancer began in late 1995. These studies were designed to include patients with advanced disease who were either chemo-naive or had received limited prior chemotherapy in the metastatic setting, with a starting dose of 600 mg/m$^2$ once every 21 days. Results from these studies are preliminary.

Clinical activity of MTA in metastatic colorectal carcinoma has been demonstrated in two multicenter trials performed in Canada and the United States. Prior adjuvant chemotherapy was allowed if completed at least 1 year prior to study entry. In the Canadian study, the starting dose of 600 mg/m$^2$ was reduced to 500 mg/m$^2$ after dose reductions were required in 5 of the first
8 patients. Toxicities leading to these reductions included rash, mucositis, neutropenia, and febrile neutropenia. Responses were seen at this reduced dose in 5 patients for an overall response rate of 17% (95% CI: 6 to 36%) (Cripps et al. 1997). In the US colorectal study, objective tumor responses were seen in 6 of 41 patients for an overall response rate of 15%
(95% CI: 6 to 31%) (John et al. 1997).

Two responses, one complete and one partial, were observed in 35 evaluable patients in the pancreatic cancer Phase 2 study for an overall response rate of 6% (Miller et al. 1997). Importantly, there were 13 additional patients with stable disease lasting for over 6 months of treatment, suggesting a clinical benefit not immediately apparent from objective tumor measurements. Median time to progressive disease was 3.9 months and 31% of patients were alive at 1 year.

A Phase 2 study in patients with locally advanced and/or metastatic breast cancer is ongoing and includes patients who have received prior adjuvant chemotherapy as well as one prior therapy for metastatic disease. Twenty-eight of 36 patients had received prior chemotherapy, 16 as adjuvant treatment, 12 for metastatic disease, and 5 patients who received both. Of the 36 patients evaluable for response, one complete and 10 partial responses have been documented for an overall response rate of 31%. Responses have been seen in pulmonary and hepatic metastases. Three of the responding patients had received recent prior therapy with paclitaxel, docetaxel or an anthracycline for metastatic disease (Smith et al. 1998).

One multi-institutional study in NSCLC has been completed in Canada (Rusthoven et al. 1997) and an additional study is ongoing in Australia and South Africa (Clarke et al. 1997). All patients were chemo-naive. The majority of patients on the Canadian study used the lower starting dose of 500 mg/m$^2$, which was reduced from 600 mg/m$^2$ during the course of the study after one of the first 3 patients experienced CTC Grade 3 mucositis and Grade 4 vomiting and myalgia. Seven partial responses have been observed in 30 evaluable patients for an overall response rate of 23.3% (95% CI: 9.9 to

42.3%) (Rusthoven et al. 1997). All responding patients were treated at the 500 mg/m$^2$ dose level.

The second NSCLC study, which is being carried out jointly between Australia and South Africa, has enrolled 61 patients to date, with 42 evaluable for response. All patients are receiving
600 mg/m$^2$ every 3 weeks in this study. Seven partial responses have been noted for an overall response rate of 17% (Clarke et al. 1998). The initial Phase 2 experience is summarized in Table JMBQ.1.

**Table JMBQ.1 Phase 2 Experience**

| Study | JMAC | JMAD | JMAN | JMAO | JMAG | JMAL |
|---|---|---|---|---|---|---|
| Site | US | US | Canada | Canada | UK | Aus/S Africa |
| Tumor site | colorectal | pancreas | NSCLC | Colorectal | breast | NSCLC |
| No. evaluable patients | 41 | 35 | 30 | 29 | 36 | 42 |
| Median cycles | 4 | 2 | 3 | 3 | 4 | 4 |
| (Range) | (1 -12) | (1-12) | (1-8) | (1-8) | (1-9) | (1-9) |
| CR | 1 | 1 | 0 | 0 | 1 | 0 |
| PR | 5 | 1 | 7 | 5 | 10 | 7 |
| Overall RR (%) | 15 | 6 | 23 | 17 | 31 | 17 |
| (95% CI, %) | | | (9.9-42.3) | (8-39.7) | | |

A total of 209 patients have been treated on the once every 3 weeks schedule in the Phase 2 setting at 600 mg/m$^2$ and are evaluable for safety analysis. The most frequent, serious toxicity has been hematologic in nature. CTC Grade 3 and 4 hematologic toxicity included neutropenia (25% and 26%, respectively) and thrombocytopenia (7% and 10%, respectively). Although severe neutropenia is common, the frequency of serious infection has been low (CTC Grade 4 infection 2%). Likewise, thrombocytopenia has been apparent, and yet serious episodes of bleeding have been rare (<1%). While 8% of patients experienced CTC Grade 3 (4% with
Grade 4) skin rash, prophylactic dexamethasone is reported to ameliorate or prevent the rash in subsequent cycles. Other Grade 3 and 4 nonhematologic toxicities included stomatitis, diarrhea, vomiting, and infection. As seen in clinical studies of other antifolates, transient Grade 3 and 4 elevation of liver transaminases are common but not dose limiting. There have been no cases of persistent transaminase elevation. Tables JMBQ.2 and JMBQ.3 summarize the laboratory and non-laboratory toxicity data from the Phase 2 studies conducted at a starting dose of 600 mg/m$^2$.

Toxicity at 600 mg/m$^2$ has recently been compared to that at 500 mg/m$^2$. For hematologic parameters there appears to be no difference between the incidence of Grade 3 and 4 toxicity or Grade 4 toxicity alone. For nonhematologic parameters there is also no difference except for rash, fatigue, stomatitis, and vomiting, which appear to exhibit an improved toxicity profile at 600 mg/m$^2$. Of note, patients who were administered

MTA 500 mg/m2 in previous trials received concomitant dexamethasone after the onset of toxicity, whereas patients at the
600 mg/m2 dose level were given dexamethasone prophylactically. The reduced toxicity profile at the 600 mg/m2 dose level is thus likely a result of concomitant corticosteroid administration, and is not considered a dose response effect of MTA treatment.

**Table JMBQ.2 Laboratory Toxicity (n=209)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| ANC | 9 | 21 | 24 | 24 |
| Leukocytes | 14 | 28 | 35 | 10 |
| Platelets | 31 | 6 | 6 | 9 |
| Hb | 34 | 43 | 12 | 2 |
| ALT | 33 | 26 | 22 | 0 |
| AST | 42 | 30 | 10 | 0 |
| Bilirubin | 0 | 18 | 7.3 | 2 |
| Creatinine | 13 | 5 | 0 | 0 |
| Alk phos | 49 | 13 | 4 | 0 |

**Table JMBQ.3 Non-laboratory Toxicity (n=209)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Cutaneous | 19 | 39 | 11 | 5 |
| Diarrhea | 17 | 11 | 4 | 3 |
| Infection | 13 | 8 | 2 | 2 |
| Nausea | 33 | 30 | 9 | 0.5 |
| Fatigue | 13 | 11 | 6 | 0 |
| Pulmonary | 0.5 | 7 | 2 | 2 |
| Stomatitis | 23 | 16 | 6 | 1 |
| Vomiting | 13 | 30 | 2 | 3 |

## *1.2.3. Folate Metabolite Correlations*

Studies with other antifolates have suggested that a patient's nutritional folate status may play a role in the development of toxicity. In order to assess the nutritional folate status of patients, the vitamin metabolites homocysteine, cystathionine and methylmalonic acid were measured in
139 patients at baseline and once each cycle thereafter (Niyikiza et al. 1998).
Multivariate statistical analyses of the data were conducted, including stepwise regression modeling, analysis of variance, and discriminant analysis to assess the relationship of vitamin metabolites, drug exposure and other prespecified patient characteristics to toxicity following one course of treatment with MTA. Baseline prognostic factors

considered were age, gender, prior treatment, baseline albumin, liver enzymes, ANC, platelet counts, vitamin metabolite levels, and AUC.

Results showed that statistically significant predictors of Grade 4 neutropenia (n=21 patients) were found to be albumin (p=0.0006) and homocysteine (p=0.0012), while Grade 4 thrombocytopenia (n=8) was highly predicted by homocysteine (p<0.0001) and pretreatment AST (p=0.0012). Grade 3 and 4 mucositis, diarrhea, rash, and fatigue were also highly correlated with baseline homocysteine (p=0.0014). Grade 4 neutropenia was predicted by homocysteine alone in 70% of cases. Homocysteine levels above a threshold concentration of
10 μM predicted Grade 4 neutropenia in the first cycle 75% of the time. Homocysteine was found to be better than albumin at predicting severe hematologic and nonhematologic toxicities. Homocysteine and albumin levels did not appear to change from baseline during treatment with MTA.

Thus, elevated baseline homocysteine levels (≥ 10 to 12 μM) highly correlated with severe hematologic and nonhematologic toxicities following treatment with MTA. The importance of repleting patients with folate, B12, and B6 to improve their nutritional status will be determined by prospectively studying a group of patients taking folate and comparing toxicity with a randomized control group not taking supplementation.

## 1.3. Vinorelbine

Vinorelbine is a vinca alkaloid that binds with tubulin to disrupt microtubular assembly in the mitotic metaphase. Unlike other vinca alkaloids, vinorelbine exhibits less affinity for axonal microtubules and is associated with less severe neurotoxicity. Vinorelbine response rates of
12 to 44% have been reported in first-line therapy and vinorelbine has been approved for first-line treatment in advanced NSCLC as a single agent and in combination with cisplatin (Crawford et al. 1996; Wozniak et al. 1996; Le Chevalier et al. 1994; Depierre et al. 1989, 1991, 1994; Furuse et al. 1996). Vinorelbine has shown limited efficacy as a second-line treatment in advanced NSCLC in several small studies. In 59 patients receiving vinorelbine, excluding those from Yokoyama's study, two partial responses were observed at 30 mg/m$^2$ and no responses were seen at lower doses (Pronzato et al. 1994; Yokoyama et al. 1992; Santoro et al. 1994; Rinaldi
et al. (Lung Cancer) 1994; Rinaldi et al. (Proc ASCO) 1994). In Yokoyama's study of both pretreated and chemo-naive advanced NSCLC patients, vinorelbine showed no activity in an undisclosed number of pretreated patients but did show activity in chemo-naive patients, with partial responses in 5 of 19 patients (26%) treated with 20 mg/m$^2$ as well as in 8 of 18 patients (44%) treated with 25 mg/m$^2$ (Yokoyama et al. 1992).

Granulocytopenia is the principle dose-limiting toxicity of vinorelbine (hospitalization for fevers/sepsis in 8% and death occurring in approximately 1%). Granulocytopenia is transient and generally reversible and is not cumulative over time. Granulocyte nadirs

occurs 7 to 10 days after the dose, with granulocyte recovery usually within the following 7 to 14 days. Mild to moderate anemia is common, but CTC Grade 3 or 4 anemia occurs in only 1% of patients. Asymptomatic thrombocytopenia is also common, but Grade 3 or 4 thrombocytopenia is reported in only 1% of patients.

Mild to moderate peripheral neuropathies (paresthesias and hypesthesias) are the most common neurotoxicities. Loss of deep tendon reflexes is also reported in less than 5% of patients, and severe peripheral neuropathy, reported in 1% of patients, is generally reversible. Alopecia (usually mild) is reported in 12% of patients, and phlebitis proximal to the injection site is reported in 10% of patients. Vomiting, diarrhea, anorexia, and stomatitis are usually mild or moderate and each are reported in less than 20% of patients. Fatigue (usually mild or moderate) occurs in 27% of patients but tends to increase with cumulative dosing. Chest pain is reported in 5% of patients (myocardial infarction rarely); dyspnea in 3% of patients (severe in 2%) and interstitial pulmonary changes are observed rarely. Vinorelbine undergoes substantial hepatic elimination, as reflected by transient increases in liver enzymes without clinical symptoms (total bilirubin: all grades, 13%; Grade 3, 4%; Grade 4, 3%; and SGOT: all grades, 67%; Grade 3, 2%; Grade 4, 1%). Other reported toxicities from patients in clinical trials and clinical practice include jaw pain, tumor pain, back pain, myalgia, arthralgia, hemorrhagic cystitis, rash, ADH secretion, and systemic allergic reactions.

## 1.4. Study Rationale

MTA has shown clinical activity in Stage III and IV NSCLC in two Phase 2 trials (12 partial responses among 50 evaluable, chemo-naive patients). Vinorelbine has been approved as first-line therapy as a single agent with response rates ranging from 12% to 44% for Stage III and IV NSCLC. Since MTA and vinorelbine have each demonstrated clinical activity as first-line therapies in NSCLC and since no drug or combination of agents has been approved as second-line therapy for this disease, this study will compare their efficacy as single agents in the treatment of NSCLC patients who have received one and only one prior platinum plus taxane-based regimen (ie, no other prior chemotherapy is permitted). Phase 2 of this study is designed to confirm an MTA response rate when administered with or without vitamin supplementation and to select the MTA arm with the best safety profile for use in the Phase 3 portion of this study. Assuming that a superior safety profile can be determined for one of the two MTA arms (ie, with or without vitamin supplementation), Phase 3 will compare time to tumor progression on the selected MTA arm versus vinorelbine.

# 2. Objectives

## 2.1. Phase 2: Primary Objective

The primary objective of the Phase 2 portion of this study is to assess the objective tumor response rate following treatment with MTA with or without vitamin supplementation in patients with locally advanced or metastatic NSCLC who have been previously treated with one platinum plus taxane-based regimen only, and to select the best MTA regimen for Phase 3.

## 2.2. Phase 2: Secondary Objectives

The secondary objectives of the Phase 2 portion of this study are:

- To characterize the quantitative and qualitative toxicities of MTA with and without vitamin supplementation in this patient population.
- To assess the pharmacokinetic/pharmacodynamic parameters of folic acid and of MTA with or without vitamin supplementation in this patient population.

## 2.3. Phase 3: Primary Objective

The primary objective of the Phase 3 portion of this study is to compare the time to tumor progression of patients with advanced or metastatic NSCLC who have been previously treated with one platinum plus taxane-based regimen only, following treatment with MTA, to that of the same patient population following treatment with vinorelbine.

## 2.4. Phase 3: Secondary Objectives

The secondary objectives of the Phase 3 portion of this study are to compare in this patient population:

- Objective tumor response rate of both therapies.
- Time to event efficacy variables of both therapies including:
  - survival
  - duration of response for responding patients
  - time to objective tumor response
  - time to treatment failure
- Changes in patient-assessed disease-related symptoms within the MTA and vinorelbine arms using the EORTC QLQ-C30 and LC13 symptom scale (SS14) from baseline to 2 months.
- Changes in quality of life within the MTA and vinorelbine arms using the EORTC QLQ-C30 and LC-13.
- Relative toxicities encountered following treatment with MTA versus vinorelbine.

# 3. Investigational Plan

## 3.1. Summary of Study Design

This is a randomized, Phase 2/3, controlled, open-label, multicenter study of MTA compared to vinorelbine in patients with locally advanced or metastatic NSCLC who have received prior treatment with one platinum plus taxane-based regimen only (ie, no other previous chemotherapy is permitted). The Phase 2 part of the trial will consist of three arms with 55 evaluable patients per arm: MTA with vitamin supplementation, MTA without vitamin supplementation, and vinorelbine. Patient randomization to treatment arms will be balanced for the following baseline prognostic factors: performance status, response to prior chemotherapy, homocysteine level, time since last chemotherapy, and type of prior platinum regimen.

In the Phase 2 portion of the study, patients with measurable disease will be assessed to determine whether MTA shows sufficient antitumor activity in this patient population. The Phase 2 data will also be used to determine which of the two MTA arms has less associated toxicity. A Data Monitoring Board will assess the response rate and toxicity after 110 patients have been evaluated in the combined MTA arms. If the Phase 2 results indicate a tumor response rate less than 10% in the combined MTA arms, the trial will be stopped and the conclusion drawn that MTA is not worthy of further development for this patient population. Otherwise, the best MTA arm will be selected for further study against the vinorelbine arm in the Phase 3 portion of the trial. The MTA arm selection will be based on a 50% reduction in the incidence of CTC Grade 3 or Grade 4 neutropenia in the first 2 cycles of treatment. Based on historical data, it is anticipated that this incidence will be reduced from approximately 40% to 20%.

The primary objective of the Phase 3 portion of the study will be to compare the time to tumor progression in this same patient population after treatment with either the selected MTA regimen or vinorelbine. An additional 330 eligible patients will be randomized (165 per treatment arm) to the selected MTA arm and vinorelbine, allowing a total of 220 patients per treatment arm for evaluation of time to tumor progression. An interim analysis will be performed under the auspices of a Data Monitoring Board when 50% of all patients have been followed beyond the expected median time to tumor progression (6 months).

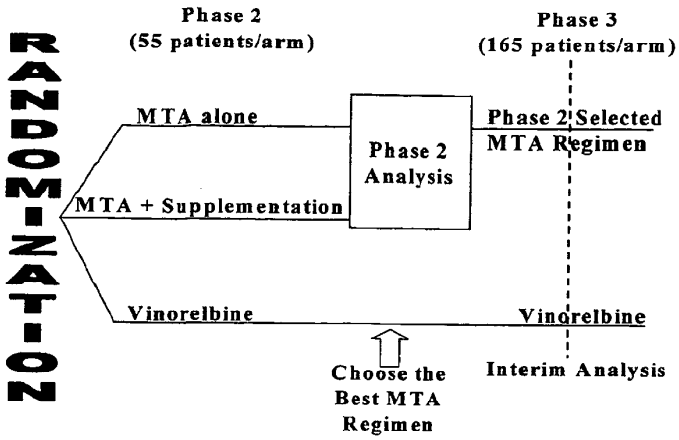


Figure JMBQ.1 Study Design

In Phase 2 and Phase 3, patients receiving treatment with MTA will be given 600 mg/m$^2$ of study drug once every 3 weeks (3 weeks = 1 cycle) according to the dosing guidelines in
Section 3.6.2.1. Those MTA patients who are assigned to receive concomitant vitamin supplementation will also receive two tablets orally, each containing 12.5 mg vitamin B6, 1 mg vitamin B12, and 0.5 mg folic acid, administered daily starting 7 days prior to the first dose of MTA (ie, 1-week lead-in period). The vitamin dosages will be halved (ie, to one tablet) starting on the first day of MTA therapy and will continue daily for as long as the patients remain on study. Patients receiving vinorelbine treatment will be given 30 mg/m$^2$ vinorelbine weekly
(3 weeks = 1 cycle) according to the dosing guidelines in Section 3.6.2.2. For all treatment groups, cycles will be repeated until there is evidence of disease progression, unacceptable toxicity, the patient requests therapy to be discontinued, or the investigator feels that it is not in the patient's best interest to remain on study. Patients can also be discontinued from the study at the sponsor's discretion.

## 3.2. Discussion of Design and Control

According to data examined in a multivariate analysis across a variety of Phase 2 MTA studies, elevated baseline homocysteine levels (≥ 10 μM) strongly correlated with severe hematologic and nonhematologic toxicities following treatment with MTA (Niyikiza et al. 1998). Because of these correlations, this study will provide for balancing the numbers of patients with baseline homocysteine levels ≤10 μM or >10 μM equally across all treatment groups. Additional prognostic factors to be balanced include performance

status, response to prior chemotherapy, time since last chemotherapy, and type of prior platinum treatment regimen.

## 3.3. Investigator Information

In Phase 2, approximately 10 sites with physicians who specialize in oncology will participate as investigators in this clinical study. In Phase 3, approximately 30 sites (including the original
10 sites) with physicians who specialize in oncology will participate as investigators.

The names, titles, and institutions of the investigators are listed in the Contacts for Protocol
H3E-MC-JMBQ provided with this protocol.

If investigators are added after the study has been approved by ILEX™, an ethical review board, or a regulatory agency, these additions will not be considered changes to the protocol, but the Contacts for Protocol H3E-MC-JMBQ will be updated to provide this information.

### *3.3.1. Final Report Signature*

The final report coordinating investigator will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The investigator with the most evaluable patients assigned to treatment will serve as the final report coordinating investigator.

## 3.4. Study Population

### *3.4.1. Entry Procedures*

An informed consent will be obtained from each patient after the nature of the study is explained.

### *3.4.2. Criteria for Enrollment*

**Enter** The act of obtaining informed consent for participation in a clinical study from individuals deemed potentially eligible to participate in the clinical study. Individuals *entered* into a study are those for whom informed consent documents for the study have been signed by the potential study participants or their legal representatives.

**Enroll** The act of assigning an individual to a treatment group. Individuals who are *enrolled* in the study are those who have been assigned to a treatment group.

A person who has been *entered* into the study is potentially eligible to be *enrolled* in the study, but must meet *all* criteria for enrollment specified in the protocol before being *enrolled* (assigned to a treatment group). Individuals who are *entered* into the study but fail to meet the criteria for enrollment are *not* eligible to participate in the study and will not be *enrolled*.

Adverse events are reported for all individuals who receive study drug.

A total of up to approximately 495 qualified patients will be enrolled in the study. The patient population will be patients who have locally advanced or metastatic NSCLC who have been previously treated with one platinum plus taxane-based regimen only (ie, no other prior chemotherapy is permitted).

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion. A change or deletion of a criterion will be indicated by adding a lowercase letter to the existing number of the criterion.

### 3.4.2.1. Inclusion Criteria

Patients may be included in the study only if they meet **all** of the following criteria:

[1] Histologic or cytologic diagnosis of NSCLC with locally advanced or metastatic disease (ie, Stage IIIb or IV).

[2] Patients must have been previously treated with **one** platinum plus taxane-based regimen **only**. **RESPONSE TO THIS ONE PRIOR CHEMOTHERAPY REGIMEN MUST BE DOCUMENTED.** CT films and diagnostic reports from baseline and those denoting best response or progressive disease must be available for review.

[3] **ALL PATIENTS MUST HAVE BASELINE CT OR MRI TO DOCUMENT MEASURABLE DISEASE STATUS, AS DEFINED BELOW.** Medical photographs or chest x-rays alone are not considered sufficient documentation.

*Measurable disease*. Bidimensionally measurable lesions with clearly defined margins by either of the following:

- Computerized tomography (CT), magnetic resonance imaging (MRI), or other imaging scan, with both diameters greater than the distance between cuts of the imaging study.
- Palpation, with both diameters 2 cm or greater.

[4] Prior chemotherapy must be completed at least 4 weeks prior to study enrollment and the patient must have recovered from the acute toxic effects of the **one** previous platinum plus taxane regimen.

[5] Prior radiation therapy allowed to <25% of the bone marrow and patients must have recovered from the acute toxic effects of the treatment prior to study enrollment. Prior radiation to the whole pelvis is not allowed.

[6] Performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) scale (Protocol Attachment JMBQ.1).

[7] Estimated life expectancy of at least 8 weeks.

[8] Patient compliance and geographic proximity that allow adequate follow-up.

[9a] Adequate organ function including the following:

Adequate bone marrow reserve: absolute granulocyte count (AGC) $\geq 1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L, and hemoglobin ≥9 g/dL.

Hepatic: albumin > 2.5 gm/dL, bilirubin ≤1.5 times the upper limit of normal, aspartate transaminase (AST) and alanine transaminase (ALT) ≤3.0 times normal (alkaline phosphatase, AST and ALT ≤5 times normal is acceptable if liver has tumor involvement).

Renal: calculated creatinine clearance ≥45 mL/min (see Protocol Attachment JMBQ.2).

[10] Signed informed consent from patient.

[11] Males or females at least 18 years of age.

[12] Male and female patients with reproductive potential must use an approved contraceptive method (eg, intrauterine device [IUD], birth control pills, or barrier device) during and for 3 months after the study. Females must have a negative serum pregnancy test within 7 days of study enrollment.

### 3.4.2.2. Exclusion Criteria

Patients will be excluded from the study for **any** of the following reasons:

[13] Active infection (at the discretion of the investigator).

[14] Brain metastasis. Patients who are symptomatic for brain metastasis must have a pretreatment CT or MRI of the brain. A patient with documented brain metastasis will be excluded from entering in the study.

[15] Pregnancy.

[16] Breast feeding.

[17] Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator).

[18] Second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or other malignancy treated at least 5 years previously with no evidence of recurrence).

[19] Use of any investigational agent within 4 weeks before enrollment into the study.

[20] Aspirin and other nonsteroidal anti-inflammatory agents should not be administered for 2 days before, the day of, and 2 days after the dose of MTA (5 days prior for long-acting agents such as piroxicam).

[21] Clinically significant effusions (pleural or peritoneal).

[22] Vitamin supplementation on or off prescription.

#### 3.4.2.3. Violation of Criteria for Enrollment

The criteria for enrollment must be followed explicitly. If there is inadvertent enrollment of individuals who do not meet enrollment criteria, these individuals should be discontinued from the study. Such individuals can remain in the study only if there are ethical reasons to have them continue. In these cases, the investigator must obtain approval from the ILEX™ clinical research physician for the study participant to continue in the study.

### *3.4.3. Disease Diagnostic Criteria*

Patients must have a histologic or cytologic diagnosis of locally advanced or metastatic NSCLC, as staged by the American Joint Committee on Cancer (Protocol Attachment JMBQ.3, Mountain 1997).

### *3.4.4. Sample Size*

In the Phase 2 portion of the trial, a total of 55 patients will be randomized to each of the treatment arms: MTA alone, MTA plus vitamin supplementation, or vinorelbine. The selection of the best of the two MTA regimens in this portion of the study will be done using a statistical ranking and selection approach (Gibbons et al. 1977). A sample size of 55 patients per arm will allow the selection of the best of the two MTA regimens with a 98.6% probability of making the correct selection if the best regimen reduces the incidence of CTC Grade 3 and Grade 4 neutropenia in the first two cycles of treatment by half, from 40% to 20%.

In the Phase 3 portion of the study, a total of 165 qualified patients will be randomized to each of the two treatment arms: best MTA regimen or vinorelbine. An overall total of 220 qualified patients will be enrolled on each treatment arm, including the 55 patients per arm from the
Phase 2 part of the trial. This sample size of 220 patients per arm allows the detection of a 33% difference in median time to tumor progression from 3 to 4 months with at least an 84% power, assuming a 1-year accrual and 6-month follow-up period. The final analysis for difference in time to tumor progression will be performed once the median time to tumor progression has been reached with less than a 30% censoring rate in both treatment arms.

## 3.5. Patient Assignment

Patients randomized in the Phase 2 three-arm part of the trial will receive either MTA, MTA plus vitamin supplementation, or vinorelbine. Phase 3 patients will be randomized to receive either the Phase 2 MTA regimen that showed a clear clinical advantage (ie, with or without vitamin supplementation) or vinorelbine.

Randomization will be controlled by a computerized voice response unit at a central location for all study sites. Randomization will be balanced according to seven baseline factors: performance status, response to prior chemotherapy, homocysteine levels, time since last chemotherapy, type of prior platinum treatment regimen, investigational site and stage of disease. For each factor, the following stratifications will be performed:

Performance status will have two strata:

High: Baseline score = 0 or 1

Low: Baseline score = 2

Response to prior chemotherapy will have two strata:

Response to prior chemotherapy

No response to prior chemotherapy

Homocysteine levels will have two strata:

≤10 μmols/L

>10 μmols/L

Time since last chemotherapy category will have two strata:

≤3 months

>3 months

Prior platinum treatment regimen type will have two strata:

cisplatin

carboplatin

Investigational site:

each investigational site will be a stratum

Disease stage will have two strata:

Stage IIIb

Stage IV

Patients will be balanced with respect to the treatment arm in each stratum for each prognostic factor, using the algorithm outlined in Pocok and Simon (Pocok et al. 1975). The randomization probability parameter for the algorithm will be set at 0.75. If the measures of imbalance are equal for both groups, then the probability of allocation to both groups is p = 0.50.

## 3.6. Dosage and Administration

### *3.6.1. Materials and Supplies*

The drug product is composed of MTA disodium and mannitol in a 1:1 ratio. Sodium hydroxide and/or hydrochloric acid solution may have been added during processing to adjust pH. Each vial contains MTA disodium equivalent to 102 or 510 mg of the base compound, MTA. The vials contain a 2% excess to facilitate the withdrawal of the label amount, 100- or 500-mg/vial.

Reconstitute the 100 mg vial with 2 mL to 10 mL sodium chloride solution or water for injection, to give a clear solution at a concentration of 10 mg/mL to 50 mg/mL. Reconstitute the 500 mg vial with 10 mL to 50 mL sodium chloride solution or water for injection, to give a clear solution at a concentration of 10 mg/mL to 50 mg/mL. The reconstituted formulation in sodium chloride solution has been shown to be chemically stable for 72 hours at refrigerated or room temperature. The reconstituted formulation in water for injection has been shown to be chemically stable for 72 hours at refrigerated temperature. Microbial challenge testing has shown MTA to be ineffective at inhibiting microbiological growth and the formulation does not contain a preservative. Therefore, vials of MTA reconstituted with sodium chloride solution or water for injection should be used immediately. For purposes of clinical administration, the reconstituted formulation will be administered as a continuous infusion over approximately 10 minutes.

Vinorelbine (Navelbine® Injection) is a clear, colorless to pale yellow solution in water for injection, containing 10 mg of vinorelbine per milliliter. Vinorelbine is available commercially in single-use 10 mg/1 mL or 50 mg/5 mL clear glass vials. In a syringe, the calculated dose of vinorelbine may be diluted with either 5% dextrose injection, USP or with 0.9% sodium chloride injection, USP to a concentration between 1.5 and 3.0 mg/mL. In an IV bag, the calculated dose of vinorelbine may be diluted to a concentration between 0.5 and 2.0 mg/mL with any of the following solutions: 5% dextrose injection, USP; 0.9% sodium chloride injection, USP; 0.45% sodium chloride injection, USP; 5% dextrose and 0.45 sodium chloride injection, USP; Ringer's injection, USP; and lactated Ringer's injection, USP. Diluted vinorelbine

may be used for up to 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags at 5 to 30°C.

## 3.6.2. Dosage Selection and Administration Procedures

During Phases 2 and 3, MTA 600 mg/m$^2$ will be administered once every 21 days (3 weeks =
1 cycle) as an intravenous infusion over approximately 10 minutes. Dexamethasone 4 mg or equivalent should be taken orally twice a day on the day before, the day of, and the day after each dose of MTA. Cycles will be repeated until there is evidence of disease progression, unacceptable toxicity, or the patient requests therapy to be discontinued.

Those patients assigned to receive MTA with vitamin supplementation (Phase 2 and possibly Phase 3) will also receive two tablets orally containing 12.5 mg vitamin B6, 1 mg vitamin B12, and 0.5 mg folic acid, administered daily starting 7 days prior to the first dose of MTA
(ie, 1-week lead-in period). The vitamin dosages will be halved (ie, to one tablet) starting on the first day of MTA therapy and will continue daily for as long as the patients remain on study. The vitamin supplements will be provided by the sponsor. Patients receiving vitamin supplementation must be reminded to bring their vitamins to each visit.

During Phases 2 and 3, 30 mg/m$^2$ of vinorelbine weekly will be given once a week for 3 weeks
(3 weeks = 1 cycle) as an intravenous injection over approximately 6 to 10 minutes. Precautions should be taken to avoid extravasation of the drug during administration. Cycles will be repeated until there is evidence of disease progression, unacceptable toxicity, or the patient or sponsor requests therapy to be discontinued.

### 3.6.2.1. MTA

#### 3.6.2.1.1. Dose Adjustments for Subsequent Doses

Dose adjustments at the start of a subsequent course of therapy will be based on **nadir** hematologic counts (Table JMBQ.4) or maximal nonhematologic toxicity (Table JMBQ.5) from the preceding course of therapy. AGC must be $\geq 1.5 \times 10^9$/L and platelets $>100 \times 10^9$/L prior to the start of any cycle. Treatment may be delayed up to 3 weeks to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in Tables JMBQ.4 and JMBQ.5. If granulocytes have not exceeded $1.5 \times 10^9$/L or platelets have not exceeded
$100 \times 10^9$/L after a 3-week delay, the patient will be removed from the study.

All patients must have a baseline local and central laboratory calculated creatinine clearance. If results from the central laboratory are not available for treatment decisions, patients may be treated based on calculated creatinine clearance using local serum

creatinine and the formula in Protocol Attachment JMBQ.2. The next cycle will not begin (administration of study drug) until the calculated creatinine clearance value is ≥45 mL/min. Safety analysis will be based on the central serum creatinine and calculated clearance values.

Once a dose reduction of MTA has been made, the patient will not be eligible for any dose escalations of MTA for the remainder of the protocol. A patient who cannot be administered the study drug for 42 days from time of last treatment must be discontinued from the study unless continuation is approved by ILEX™.

Table JMBQ.4. Hematologic Toxicities

| Percent of Full Dose | AGC ($\times 10^9$/L) Nadir | | Platelets ($\times 10^9$/L) Nadir |
|---|---|---|---|
| 100% | ≥0.5 | and | ≥50 |
| 75% | <0.5 | and | ≥50 |
| 50% | <0.5 | and | <50 |
| Discontinue patient from study | | | Recurrence of Grade 3 or 4 after 2 dose reductions |

Table JMBQ.5 Mucositis Following LY231514 Administration

| Toxicity Grade | Dose for Next Cycle (mg/m$^2$) |
|---|---|
| Grade 2 | 75% of previous dose |
| Grade 3-4 | 50% of previous dose |
| Recurrence of Grade 3 or 4 after treatment at 2 dose reductions | Discontinue patient from study |

In the event of diarrhea requiring hospitalization, the drug should be held until resolution to baseline before proceeding. Treatment should be restarted at a 25% dose reduction. For other nonhematologic effects greater than or equal to Grade 3, the drug should be held until resolution to baseline before proceeding. Treatment should restart at a 25% dose reduction if deemed appropriate by the treating physician according to the guidelines in Table JMBQ.5.

### *3.6.2.1.2. Cycle Delay for Subsequent Doses*

Subsequent cycles will not begin until the calculated creatinine clearance value is ≥45 mL/min. Re-testing is recommended at weekly intervals but will be conducted at the investigator's discretion. If a patient's calculated creatinine clearance has not returned to ≥45 mL/min within
6 weeks, the patient must be discontinued from the study unless continuation is approved by ILEX™.

### 3.6.2.2. Vinorelbine

Dose adjustments of vinorelbine are not required for renal toxicity (serum creatinine >2.0 mg/dL). Vinorelbine should be given with caution to patients with hepatic toxicity (Grade 3 to Grade 4) following treatment. After the initial dose, vinorelbine dosage should be adjusted according to hematologic toxicity or hepatic toxicity as described in Table JMBQ.6. In patients with both hematologic and hepatic Grade 3 or 4 toxicity, the lower of the doses determined from Table JMBQ.6 should be administered. If Grade 2 to 4 neurotoxicity develops, vinorelbine will be discontinued at the discretion of the treating physician.

Table JMBQ.6. Vinorelbine Dose Adjustment Based on Hematologic or Hepatic Toxicity

| Hematology/Chemistry[a] | Dose for Next Cycle |
|---|---|
| AGC (x $10^9$/L)[b] | |
| ≥1.5 | 30 mg/m$^2$ |
| ≥1.0 - 1.499 | 15 mg/m$^2$ |
| <1.0 | Do not administer. Repeat AGC in 1 week. If 3 consecutive doses are held for AGC <1.0, discontinue study patient. |
| Platelet (x $10^9$/L)[c] | |
| ≥75 | 30 mg/m$^2$ |
| 50 – 74 | 15 mg/m$^2$ |
| <50 | Do not administer. Repeat platelet count in 1 week. If 3 consecutive doses are held for platelets <50, discontinue study patient. |
| Total bilirubin (mg/dL) | |
| ≤2.0 | 30 mg/m$^2$ |
| 2.1 - 3.0 | 15 mg/m$^2$ |
| >3 | 7.5 mg/m$^2$ |

[a] Within 72 hours prior to treatment.

[b] Patients who experience fever and/or sepsis while granulocytopenic or have 3 consecutive doses held due to granulocytopenia should receive the following subsequent doses: 22.5 mg/m$^2$ for AGC ≥1.5 x $10^9$/L; 11.25 mg/m$^2$ for AGC ≥1.0-1.499 x $10^9$/L.

[c] Patients who experience bleeding while thrombocytopenic or have 3 consecutive doses held due to thrombocytopenia should receive the following subsequent doses: 22.5 mg/m$^2$ for platelet counts ≥75 x $10^9$/L; 11.25 mg/m$^2$ for platelet counts ≥50-74 x $10^9$/L.

## 3.7. Blinding

Phases 2 and 3 of this trial are open label and randomized with the identity of the treatment known to the investigator, patient, and ILEX™.

## 3.8. Concomitant Therapy

Patients are allowed to receive full supportive care therapies concomitantly during the study. No other chemotherapy, immunotherapy, hormonal cancer therapy, radiation therapy, or experimental medications will be permitted while the patients are on the

study. Any disease progression requiring other forms of specific antitumor therapy will be cause for early discontinuation from this study. The following concomitant therapies warrant special attention.

### 3.8.1. Colony Stimulating Factors

Routine use of granulocyte colony stimulating factors (G-CSFs) or granulocyte macrophage colony stimulating factors (GM-CSFs) is not permitted during this study. Patients should not receive G-CSFs or GM-CSFs prophylactically in any cycle. G-CSFs/GM-CSFs may be used only for patients who have AGC $<0.5 \times 10^9$/L for at least 5 days, neutropenic fever, or documented infections while neutropenic. G-CSFs/GM-CSFs must be discontinued at least
24 hours prior to the start of the next cycle of chemotherapy.

### 3.8.2. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Patients taking NSAIDs or salicylates must not take them 2 days before, the day of, or 2 days after receiving MTA. If a patient is taking a NSAID or salicylate with a long half-life
(eg, naproxen, piroxicam, diflunisal, or nabumetone), it should not be taken 5 days before, the day of, or 2 days after receiving MTA.

### 3.8.3. Leucovorin

Leucovorin is not necessary for vinorelbine patients. For patients receiving MTA, leucovorin is allowed for CTC Grade 4 leukopenia, CTC Grade 4 neutropenia lasting greater than 5 days, or CTC Grade 4 thrombocytopenia. Leucovorin should be started for CTC Grade 4 myelosuppression lasting 5 days or more beginning on the fifth day of CTC Grade 4 myelosuppression. Leucovorin should be started immediately if a patient develops CTC Grade 3 or 4 mucositis. The following doses and schedules are recommended for intravenous use; appropriate doses of the oral formulation may also be used at the investigator's discretion.

- Leucovorin 100 mg/m$^2$ intravenously times one; then
- Leucovorin 50 mg/m$^2$ intravenously every 6 hours for 8 days.

**Note:** The primary mode of cytotoxicity of MTA is proposed to be inhibition of thymidylate synthase and it may be more appropriate to provide the end product of TS inhibition as a rescue agent, namely thymidylate. Thymidine has been proposed as a reversal agent for severe toxicity from either 5-fluorouracil (5-FU) or methotrexate but overall the clinical experience is limited (Abelson et al. 1983; Grem et al. 1991). Thymidine has been reported to reverse the severe toxicity associated with 5-FU in a patient with dihydropyrimidine dehydrogenase deficiency (Takimoto et al. 1996). Reversal of methotrexate toxicity has also been reported in patients with normal as well as impaired renal function (Widemann et al. 1997). Recently, one patient treated with

MTA has received thymidine after developing severe toxicity. This patient developed severe myelosuppression as well as somnolence on day 5 following MTA. Myelosuppression is an expected toxicity of MTA but the severity of neurotoxicity is not a common toxicity. Leucovorin was administered for 24 hours, beginning on day 6. Since the leucovorin did not appear to resolve the toxic effects, thymidine was administered for 3 days by continuous infusion at a dose of 8 g/m$^2$/day (Takimoto et al. 1996). Partial resolution of the neurotoxicity was noted after the first day of infusion and by the third day the patient had fully recovered.

### *3.8.4 Therapy for Diarrhea*

In the event of CTC Grade III or IV diarrhea, the following supportive measures are suggested: hydration, octreotide and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) associated with fever or severe neutropenia (Grade III or IV), broad spectrum antibiotics should be prescribed. Patients with severe diarrhea (requiring intravenous rehydration) with severe nausea or vomiting must be hospitalized for intravenous hydration and correction of electrolyte imbalances. Febrile neutropenic patients, with or without diarrhea should also be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

## 3.9. Efficacy, Pharmacokinetic, and Safety Evaluations

See the schedule of events (Protocol Attachment JMBQ.4) and Sections 3.9.1.1 and 3.9.2.2.

### *3.9.1. Efficacy*

#### 3.9.1.1. Efficacy Measures

Within 3 weeks prior to study enrollment each patient will have been assessed by a radiologic imaging study (CT and/or MRI) for tumor measurement. Ultrasound will not be permitted as a method of tumor measurement. The same method used at baseline **will be used consistently** for tumor assessment and will be repeated every 6 weeks (prior to every other cycle). Whenever possible, IV, oral or rectal contrast agents should be used to increase the density between anatomical structures. Contrast should be used consistently for the entire duration of the study. CT or MRI scans should be done with cuts of 10 mm thickness in scans of the chest, abdomen, and pelvis and should be done on soft tissue settings. Lung lesions should be done on both soft tissue and lung settings to

obtain images of all available disease. The settings and slice thickness should be documented at the time of the scan as well as the image number of the lesion being measured. The identical settings should be used on all subsequent studies. When MRI is used for measurement, the image sequence and anatomical plane are to be defined, documented and done consistently for each measurement.

No more than 2 weeks before enrollment into the study, the disease status of each patient will have been assessed with the following procedures:

- Medical history and physical examination, including measurements of height and weight.
- Evaluation of performance status (ECOG Scale, Protocol Attachment JMBQ.1).
- Tumor measurement of palpable or visible lesions.
- Chest x-ray (PA and lateral) and repeated as clinically indicated.

At the stated intervals during the study, efficacy will be assessed in each patient by the following evaluations:

- Prior to each cycle of drug:
  - Weight measurements.
  - Performance status evaluation.
  - Limited medical history and physical examination, including tumor measurements of tumor lesions by physical examination.
  - EORTC QLQ-C30 and LC13 questionnaire completed by the patient **before** chemotherapy is administered and other assessments are discussed with the patient (see Protocol Attachments JMBQ.5 and JMBQ.5a).
- Prior to every other treatment cycle:
  - Radiologic imaging studies used at baseline for tumor measurement. After first documentation of response, the studies should be repeated 4 weeks later to confirm the response.

### 3.9.1.2. Efficacy Criteria

The response status of each patient may be reviewed by a panel of independent investigators and/or by ILEX™. The measurability of a tumor is defined below (Green et al. 1992). **Note: All patients must have measurable disease, documented by CT or MRI, in order to be eligible for this study. Medical photographs alone are not considered adequate documentation.**

**Disease Status**

- Measurable disease: Bidimensionally measurable lesions with clearly defined margins by 1) medical photograph (skin or oral lesions) or plain x-ray, with at least one diameter 0.5 cm or greater (bone lesions not included); or 2) CT, MRI, or other imaging scan, with both diameters greater than the distance between cuts of the imaging study; or 3) palpation, with both diameters 2 cm or greater.
- Evaluable disease: Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease.

- Nonevaluable disease: Pleural effusions, ascites, disease documented by indirect evidence only (eg, by lab values).

All documented lesions are to be followed. If an organ has too many measurable lesions to measure at each evaluation, choose the three largest to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be documented and considered evaluable for the purpose of objective status determination. Included in the evaluations are the following standard criteria:

**Objective status** (to be recorded at each evaluation)

- Complete response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No disease-related symptoms. No evidence of nonevaluable disease, including normalization of markers and other abnormal lab values. All measurable, evaluable, and nonevaluable lesions and sites must be assessed using the same technique as baseline. Refers to clinical CR. When restaging surgery is required, a separate pathologic response variable is incorporated in the response data.
- Partial response (PR): Applies only to patients with at least one measurable lesion. Greater than or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. Nonmeasurable lesions must remain stable or regress for this category. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.
- Partial response in nonmeasurable disease (PRNM): Greater than 50% decrease in estimated area of evaluable, but nonmeasurable, tumor mass, as agreed upon by two independent observers, not to include pleural effusions. (Note: Response in patients with these specific types of evaluable disease and no measurable disease will be reported separately. Patients with both measurable and evaluable disease will be assessed for response according to the above criteria for partial response.)
- Stable/No response: Does not qualify for CR, PR, or progression. All measurable and evaluable sites must be assessed using the same techniques as at baseline.
- Progression: 50% increase or an increase of 10 $cm^2$ (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR reappearance of any lesion which had disappeared, OR appearance of any new lesion/site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). For 'scan-only' bone disease, increased uptake does not constitute clear worsening. Worsening of existing nonevaluable disease does not constitute progression.

  Exceptions: In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond 4 weeks or there must be additional evidence of progression. Lesions which appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
- Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

**Notes**

1) Nonevaluable disease does not affect objective status except in determination of CR (all disease must be absent -- a patient who otherwise has a CR, but who has nonevaluable disease present or not assessed, will be classified as having a PR) and in determination of progression (if new sites of nonevaluable disease develop). Patients with only nonevaluable disease cannot be assessed for response.

2) For evaluable disease other than types specified in PR in nonmeasurable disease, the only objective statuses which apply are CR, stable/no response, progression, and unknown.

3) Objective statuses must stay the same or improve over time until progression (unknown excepted).

4) PR and PRNM cannot apply to the same patient.

**Best Response**

Best response is determined from the sequence of objective statuses. Initial response will be based on baseline tumor measurements. Once a response is noted, this measurement becomes the new baseline. Subsequent responses will be compared to the new baseline.

- Disease assessment every 3 to 6 weeks: Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of PRNM or better before progression, but not qualifying for CR, are required for PRNM. Two determinations of stable/no response or better before progression, but not qualifying as CR, PR, or PRNM, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) will have a best response of increasing disease. Best response is unknown if the patient does not qualify for a best response of increasing disease and if all objective statuses after the first determination and before progression are unknown. **For CR, PR, or PRNM, response must be confirmed; a second assessment should be scheduled for 4 weeks after the first documentation of response.**

#### 3.9.1.3. Definition of Efficacy Measures

A responder will be defined as any patient who exhibits a CR or PR. The duration of a CR or PR is defined as the time from first objective status assessment of CR or PR to the first time of progression or death due to any cause. Time-to-treatment failure is defined as the time from study enrollment to the first observation of disease progression, death due to any cause, or early discontinuation of treatment. Survival is defined as the time from study enrollment to time of death due to any cause.

All responses must be documented using appropriate diagnostic tests which must be repeated every 6 weeks to continue evaluation. The same assessment method used to determine disease status at baseline will be used consistently for efficacy evaluation throughout the study.

### *3.9.2. Safety*

Investigators are responsible for monitoring the safety of patients who have received any amount of study drug and for alerting ILEX™ to any event that seems unusual. See Section 3.9.2.1.1.

The investigator is responsible for appropriate medical care of study participants during the study in connection with protocol procedures.

After a study participant's completion of or discontinuation from the study, the investigator remains responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the study participant to discontinue before completing the study.

### 3.9.2.1. Clinical Adverse Events

The sponsor has standards for reporting adverse events that are to be followed, regardless of applicable regulatory requirements that are less stringent. For purposes of collecting and evaluating *all* information about Lilly drugs used in clinical trials, a clinical trial adverse event is any undesirable experience that occurs after the patient receives study drug. Lack of drug effect is not an adverse event in clinical trials, because the purpose of the clinical trial is to establish drug effect.

At the first visit, study site personnel will question each patient and will note the occurrence and nature of presenting condition(s) and any preexisting condition(s). At subsequent visits, site personnel will again question the patient and will note any change in the presenting condition(s), any change in the preexisting condition(s), and/or the occurrence and nature of any adverse events.

#### 3.9.2.1.1. Adverse Event Reporting Requirements

**All** adverse events must be reported to ILEX™ using the clinical report form (CRF).

Study site personnel must report to ILEX™ immediately, by telephone, any **serious** adverse event (see Section 3.9.2.1.2 below). Remember that **all** adverse events must be reported on the CRF even if a telephone report has been made.

If a patient's dosage is reduced or if a patient is discontinued from the study because of any significant laboratory abnormality, inadequate response to treatment, or any other reason, study site personnel must report and clearly document on the CRF the circumstances and data leading to any such dosage reduction or discontinuation.

#### *3.9.2.1.2. Serious Adverse Events*

Study site personnel must report to ILEX™ immediately, by telephone, any adverse event from this study that includes one of the following criteria:

- death
- initial or prolonged inpatient hospitalization
- is life-threatening
- severe or permanent disability

- cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer)
- congenital anomaly
- is significant for any other reason

Report all serious adverse events to:

MTA Project Director or designee
ILEX™ Oncology Inc
11550 IH 10 West, Suite 300
San Antonio, TX 78230
Telephone: (210) 949-8200
FAX: (800) 732-8499

Patients should be closely followed for adverse events while receiving study drug and for 30 days after the last dose of study drug in order to detect delayed toxicity. After this period, investigators should only report serious adverse events which are felt to be causally related to study drug therapy. All serious adverse events, including those for which a telephone report has been made, shall be promptly followed by a FAX form and also reported to ILEX™ using the CRF. See Protocol Attachment JMBQ.6 for the information required when reporting serious adverse events.

### 3.9.2.2. Clinical Laboratory Tests and Procedures

**Prestudy**

Prior to study enrollment each patient will have the following assessments (see Protocol Attachment JMBQ.4).

At 3 weeks prior to study enrollment (ie, day –21):

- Measurement of vitamin metabolites (all patients; see Protocol Attachment JMBQ.9). This measurement is required for study randomization and assignment of patients to treatment arms.

Within 3 weeks of study enrollment:

- Radiologic studies for baseline tumor measurements.
- Documentation of response to prior chemotherapy.

Within 2 weeks of study enrollment:

- Medical history and physical examination, including clinical measurement of palpable or visible tumor lesions.
- Measurements of height and weight.
- Vital signs (blood pressure, pulse rate, and temperature) and repeat as clinically indicated.
- Concomitant medication notation.

- Chest x-ray (PA and lateral) and repeated as clinically indicated.

Within 7 days of study enrollment:

- Hematology: hemoglobin, RBC, WBC, platelets, neutrophils, bands, lymphocytes, monocytes, eosinophils, and basophils.
- Blood chemistries: bilirubin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, uric acid, phosphorus, calcium, glucose, total protein, albumin, and electrolytes (sodium, potassium, bicarbonate, and chloride).
- Measurement of vitamin metabolites (all patients; see Protocol Attachment JMBQ.9).
- Evaluation of performance status (ECOG scale).
- Urinalysis: pH, protein, blood, and microscopic.
- Calculated creatinine clearance (see Protocol Attachment JMBQ.2).
- Serum pregnancy test, if applicable.

**During the Study**

The following tests and procedures will be performed at specific intervals during the study:

- Limited medical history and physical examination, including measurement of visible and palpable lesions prior to the start of each cycle.
- Measurement of vitamin metabolites immediately prior to the first dose of cytotoxic (all patients).
- Weight, performance status, and medical resource utilization interview (see Section 3.9.4 and Protocol Attachment JMBQ.8) at the start of each cycle.
- Concomitant medication notation, including number of units required for transfusions at the start of every cycle.
- Hematology weekly and within 4 days prior to each cycle.
- Blood chemistries weekly and within 4 days prior to each cycle.
- Calculated creatinine clearance within 4 days prior to the start of each cycle.
- Pharmacokinetic samples during cycles 1 and 3 of both the Phase 2 and Phase 3 portions of the study (MTA treatment groups only, see Protocol Attachment JMBQ.10).
- Toxicity rating prior to each cycle (see Protocol Attachment JMBQ.7) (Cancer Therapy Evaluation Program 1998).

**Every Other Cycle**

The following evaluations of tumor response will be performed every other cycle of therapy (every 6 weeks):

- Radiologic studies for tumor measurements.

**Note:** The central laboratory will perform the blood chemistries, calculated creatinine clearance, and urinalysis. Patients may be enrolled based on results of screening safety testing performed at a local laboratory. However, a specimen must be collected prior to the initiation of treatment and sent to the central laboratory for blood chemistries. These central laboratory results will be considered the baseline for subsequent safety analyses. The local laboratory will perform the hematology, pregnancy test, and baseline calculated creatinine clearance. Vitamin metabolite assays will be performed at Metabolite Laboratories Incorporated (see Protocol Attachment JMBQ.9). Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented on by the investigator by marking

"CS" (for clinically significant) or "NCS" (for not clinically significant) next to the values. Any clinically significant laboratory values that are outside a clinically acceptable range or differ importantly from a previous value should be further commented on in the CRF comments page. When multiple laboratory values are out of range but not clinically significant, "all labs NCS" may be written on the laboratory page in place of marking each individual laboratory value "NCS." However, all clinically significant laboratory values must be individually marked and explained on the comments page.

**Follow-Up**

Patients will be followed up every 3 months until death for disease progression, chemotherapy, surgery, and other treatments. Patients should be closely followed for adverse events while receiving study drug and for 30 days after the last dose of study drug in order to detect delayed toxicity. After this period, investigators should only report serious adverse events which are felt to be causally related to study drug therapy. If a patient discontinues prior to a response confirmation, an evaluation will occur 1 month after the patient discontinues from the study.

### *3.9.3. Safety Monitoring*

The ILEX™ clinical research physician will monitor safety data throughout the course of the study.

### *3.9.4. Medical Resource Utilization*

Medical resource utilization data will be collected at the beginning of each cycle (ie, every
3 weeks) and is largely derived from clinical data routinely collected through the case report forms and patient interviews. These data will be analyzed as defined in Protocol Attachment JMBQ.8.

### *3.9.5. Appropriateness and Consistency of Measurements*

All efficacy and safety assessments used in these studies are appropriate for an oncology study.

The EORTC QLQ-C30 is a cancer-specific quality of life (QoL) instrument and the QLQ-LC13 is a lung cancer-specific module. The QLQ-C30 and LC13 have been validated in multiple languages, including English, German, Dutch, Finnish, Swedish, Danish, Italian, and Spanish, and have been tested for reliability, sensitivity to change, and cross-cultural validation (Aaronson et al. 1993; Bergman et al. 1994). The SS14

symptom scale was constructed from the EORTC QLQ-C30 based on results of a Medical Research Council NSCLC trial using the Rotterdam index to identify the most frequently reported symptoms (Hopwood et al. 1995).

Collection of QoL data will not interfere with the routine collection of adverse event data reported by the patient, nor will the two sources of data be required to agree. These data will be analyzed with the same rigor as the study objectives relating to safety and efficacy. Only patients for which there is a validated translation will be required to complete QOL questionnaires.

### *3.9.6. Pharmacokinetics and Pharmacodynamics*

Pharmacokinetic concentrations of MTA and folic acid will be determined from samples obtained from patients treated with MTA. Details are given in Protocol Attachment JMBQ.10.

## 3.10. Patient Disposition Criteria

### *3.10.1. Discontinuations*

A patient will be discontinued from the study under the following circumstances.

- If there is evidence of progressive disease.
- If the attending physician thinks a change of therapy would be in the best interest of the patient.
- If the patient requests discontinuation.
- If the drug exhibits unacceptable toxicity.
- If a patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).
- If the patient is non-compliant with study procedures.
- If Lilly uses its discretion to discontinue the patient.

### *3.10.2. Qualifications for Analysis*

All patients who receive any amount of MTA or vinorelbine will be evaluated for safety. All enrolled patients meeting the criteria listed below will be evaluated for efficacy (tumor response). In addition, all randomized patients will be included for time to event efficacy analysis.

- Histologic or cytologic diagnosis of locally advanced or metastatic NSCLC.
- No concurrent systemic chemotherapy.
- Presence of bidimensionally measurable disease.
- Treatment with one dose of MTA or vinorelbine.

All patients who complete a baseline and at least one post-baseline EORTC QLQ-C30 and LC13 will be evaluated in the QoL and SS14 analyses.

- Patients must complete a questionnaire for Cycle 2 to be included in the 2-month SS14 analysis.

### *3.10.3. Study Extensions*

No extensions are planned in the study.

## 3.11. Compliance

MTA or vinorelbine will be administered intravenously only at the investigational sites. As a result, patient compliance monitoring is ensured.

## 3.12. Quality Assurance

To ensure accurate, complete, and reliable data, ILEX™ or its representatives will:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction in all sections of the protocol, the completion of the CRFs, and study procedures.
- Make periodic visits to the study site.
- Be available at all times for consultation and in contact with the study-site personnel by mail, telephone, and/or fax.
- Review and evaluate clinical report data and will use standard computer edits to detect errors in data collection.

To ensure accurate, complete, and reliable data, the investigator will do the following:

- Keep records of laboratory tests, clinical notes, and patient's medical records in the patient's files as original source documents for the study.
- Keep source documents for 15 years.

ILEX™ or its representatives may randomly check original source documents and clinical report forms at the study site. The study may be audited by Medical Quality Assurance (MQA) and/or regulatory agencies at any time. Investigators will be given notice before an MQA audit occurs.

ILEX™ or its representatives will randomly check original source documents and CRFs at the study site. The study may be audited by ILEX™ Quality Assurance and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

# 4. Data Analysis Methods

## 4.1. General Considerations

All statistical tests as well as confidence intervals for parameters to be estimated will be two-sided with a significance level of $\alpha$=0.05. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The interpretation of study results will be the responsibility of the Data Monitoring Board, ILEX™ Medical Affairs, and the biostatistician. ILEX™ Medical Affairs and the biostatistician will also be responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication.

## 4.2. Data to Be Analyzed

The efficacy and safety analyses will be performed on data from qualified patients as described in Section 3.10.2.

## 4.3. Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- A definition of patient qualification.
- A summary of data on patient discontinuation.
- A summary of data on overall qualification status of all patients.
- An account of all identified protocol violations.

All patients entered in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

## 4.4. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics.
- Baseline disease characteristics.
- Pre-existing conditions.
- Historical illness.
- Prior therapies.
- Concomitant drugs.

Other patient characteristics will be summarized as deemed appropriate.

## 4.5. Efficacy Analysis

All patients who meet the efficacy criteria for qualification will be evaluated for efficacy (Section 3.10.2). The efficacy analysis will include the following:

- A comparison of the treatment arms' tumor response rate including a 95% confidence interval, using Fisher's Exact Test. The estimate of the tumor response rate will be given by

$$\text{Response Rate} = \frac{\text{Number of CRs + PRs}}{\text{Number of patients qualified for tumor response efficacy analysis}}$$

- A comparison of Kaplan-Meier (Kaplan et al. 1958) curves and quartiles for duration of response, if a sufficient number of responders is observed.
- Comparisons of patient survival, time to progressive disease, and time to treatment failure between each MTA arm and the vinorelbine arm using the Wilcoxon test (for differences in early events) and the log-rank test (for differences in late events), utilizing PROC LIFETEST in Statistical Application Software® (SAS) (SAS Institute 1989). Other analyses will be done as necessary.
- Exploratory analysis relating survival, time to progressive disease, time to treatment failure, and duration of response to prognostic factors will be carried out using a variety of models, including the Cox proportional hazards model, the Cox model with time-dependent cofactors, the Anderson-Gill Multiplicative-Hazard Mode, the Wei-Lin-Weissfeld Marginal Model, and the Prentice-Williams-Peterson Conditional Model. The prognostic cofactors examined will include a number of visit-dependent lab, toxicity, as well as demographic and baseline disease characteristic measures (Andersen et al. 1982; Andersen et al. 1992; Cox 1972; Efron 1981; Le 1997; Lin 1984; Prentice et al. 1981; SAS Institute 1990,1997; Slud et al. 1982; Therneau et al. 1997; Wei et al. 1989).
- Comparison of changes from baseline EORTC QLQ-C30 and LC13 subscale mean scores.
  - Comparison of change in EORTC QLQ-C30 and LC13 symptom scale SS14 mean scores from baseline to 2 months.

## 4.6. Safety Analyses

All patients who are treated with MTA or vinorelbine will be evaluated for safety. Comparative safety analyses will include the following:

- Summaries of the number of blood transfusions required.
- Summaries of the adverse event rates and laboratory changes.
  - Listings and frequency tables categorizing laboratory and nonlaboratory adverse events by maximum CTC toxicity grade and relationship to study drug.

## 4.7. Interim Analyses

Any planned or unplanned interim analyses will be conducted under the auspices of an independent Data Monitoring Board assigned to this study. Only the Data Monitoring Board is authorized to review completely unblinded interim efficacy and safety analyses (and if necessary, to disseminate those results). The Data Monitoring Board will disseminate interim results in a manner that will minimize bias. Study sites will not receive information about interim results unless they need to know for the safety of their patients.

Six months after 50% of patients have been enrolled in Phase 3, an interim analysis will be performed on all patients in order to detect whether there are marked differences in survival time, response rate, duration on study, duration of response, time to progressive disease, or toxicity (see Sections 4.5 and 4.6). All significance tests will be performed at a level of 0.02, using the Slud-Wei sequential methodology (Slud et al. 1982). The final analysis will be performed at a significance level of 0.038, ensuring the overall significance level of .05.

### 4.8. Pharmacokinetic/Pharmacodynamic Analyses

The plasma concentration data for MTA and folic acid will be pooled and analyzed using a population pharmacokinetic approach. The appropriate pharmacokinetic parameters will be determined and the effects of demographic values (age, weight, gender, etc.) and habits (eg, smoking and alcohol) on the population pharmacokinetics will be examined. Assessments of creatinine clearance will also be included as an influential factor upon the clearance of MTA. Details can be found in Protocol Attachment JMBQ.10.

## 5. Informed Consent, Institutional Review, and Regulatory Considerations

### 5.1. Informed Consent

The informed consent document will be used to explain in simple terms, before the patient is entered into the study, the risks and benefits to the patient. The informed consent document must contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time.

The investigator is responsible to see that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent and/or assent given by subjects, patients, or their legal representatives.

### 5.2. Institutional Review

The appropriate institutional review board(s) must approve the protocol and informed consent document, and if appropriate, agree to monitor the conduct of the study and agree to review it periodically. The investigator will provide ILEX™ with documentation that the institutional review board has approved the study before the study may begin.

In addition, the investigator must provide the following documentation.

- The institutional review board's annual reapproval of the protocol.
- The institutional review board's approvals of any revisions to the informed consent document or amendments to the protocol.

## 5.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to an ILEX™ representative (see Protocol Attachment JMBQ.11).

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**Protocol Attachment JMBQ.1**
**Performance Status Scale**

## Protocol Attachment JMBQ.1
## ECOG Performance Status

| Activity Status | Description |
|---|---|
| 0 | Asymptomatic, fully active, and able to carry on all predisease performance without restrictions. |
| 1 | Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature, eg, light housework, office work. |
| 2 | Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; in bed less than 50% of day. |
| 3 | Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bedridden. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally bedridden. |
| 5 | Dead. |

**Protocol Attachment JMBQ.2**
**Calculated Creatinine Clearance**

**Protocol Attachment JMBQ.2**
**Calculated Creatinine Clearance**
**Modified Cockcroft and Gault**

Weight in kg (W)

Height in cm (H)

Age in years (A)

Serum creatinine in mg/dL (C)

**Lean Body Weight (LBW) Males**

0.32810 x (W) = _____
0.33929 x (H) = + _____
- 29.5336
LBW = _____

**Lean Body Weight (LBW) Females**

0.29569 x (W) = _____
0.41813 x (H) = + _____
- 43.2933
LBW = _____

**Calculated Creatinine Clearance**

$\frac{[140 - (A)] \times (LBW)}{71 \times (C)}$ = mL/min

**Serum Creatinine Conversion**

µmol/L x 0.0113 = mg/dL

**Protocol Attachment JMBQ.3**
**American Joint Committee on Cancer**
**Staging Criteria**

## Protocol Attachment JMBQ.3
## American Joint Committee on Cancer Staging Criteria for Lung Cancer

### Stage Grouping – TNM Subsets[a]

| Stage | TNM Subset | | |
|---|---|---|---|
| Stage 0 | Carcinoma in situ | | |
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T1 | N1 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| Stage IIIB | Any T | N3 | M0 |
| | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

a Staging is not relevant for occult carcinoma, designated TXN0M0.

## Protocol Attachment JMBQ.3 (continued)
## American Joint Committee on Cancer Staging Criteria for Lung Cancer

### Primary Tumor (T):

| | |
|---|---|
| TX | Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |
| T1 | Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus[a] (ie, not in the main bronchus) |
| T2 | Tumor with any of the following features of size or extent:<br>More than 3 cm in greatest dimension<br>Involving main bronchus, 2 cm or more distal to the carina<br>Invading the visceral pleura<br>Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung |
| T3 | Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, or parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung |
| T4 | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with malignant pleural or pericardial effusion,[b] or with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung |

[a] The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to main bronchus, is also classified as T1.

[b] Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged as T1, T2, or T3. Pericardial effusion is classified according to the same rules.

## Protocol Attachment JMBQ.3 (concluded)
## American Joint Committee on Cancer Staging Criteria for Lung Cancer

### Regional Lymph Nodes (N):

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph node(s), and intrapulmonary nodes involved by direct extension of the primary tumor |
| N2 | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) |
| N3 | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) |

### Distant Metastasis (M):

| | |
|---|---|
| MX | Presence of distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis present [a] |

[a] Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified as M1.

**Protocol Attachment JMBQ.4**
**Schedule of Events**

## Protocol Attachment JMBQ.4
## MTA Schedule of Events

| Cycle | 0 | 1 | | | | 2 | | | | 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relative Day Within a Cycle | | 1 | 8 | 15 | 21 | 1 | 8 | 15 | 21 | 1 | 8 | 15 | 21 |
| Visit (for CRF use only) | 0 | 1 | | | | 2 | | | | 3 | | | |
| Relative Day | Base-line[a] | 1 | 8 | 15 | 21 | 22 | 29 | 36 | 42 | 43 | 50 | 57 | 62 |
| Activity | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | |
| MTA therapy and dexamethasone | | X | | | | X | | | | X | | | |
| Vitamin supplementation[b] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | | | | | X | | | | X | | | |
| Medical history | X | | | | | X | | | | X | | | |
| Weight | X | | | | | X | | | | X | | | |
| Height | X | | | | | | | | | | | | |
| Tumor measurement (visual or palpable) | X | | | | | X | | | | X | | | |
| Performance status (ECOG) | X | | | | | X | | | | X | | | |
| Chest x-ray | X[d] | | | | | | | | | | | | |
| Radiologic tests for tumor measurement | X | | | | | | | | X[c] | | | | |
| Document response to prior chemotherapy | X | | | | | | | | | | | | |
| Vital signs | X[d] | | | | | | | | | | | | |
| Vitamin metabolite assay | X | X[a] | | | | X[f] | | | | X[f] | | | |
| Chemistry | X | | X | X | | X[f] | X | X | | X[f] | X | X | |
| CBC w/dif, platelets | X | | X | X | | X[f] | X | X | | X[f] | X | X | |
| Serum pregnancy test if applicable | X | | | | | | | | | | | | |
| Urinalysis | X | | | | | | | | | | | | |
| Calculated creatinine clearance | X[g] | | | | | X[f,g] | | | | X[f,g] | | | |
| Toxicity rating | | | | | | X | | | | X | | | |
| EORTC QLQ-C30 & LC13 | | X[c] | | | | X[c] | | | | X[c] | | | |
| Medical resource utilization interview | | X[c] | | | | X[c] | | | | X[c] | | | |
| Concomitant meds notation | X | | | | | X | | | | X | | | |
| Pharmacokinetic samples | | X[h] | | | | | | | | X[h] | | | |

a - For timing of baseline activities, please see Sections 3.9.1.1 and 3.9.2.2.

b - For patients randomized to MTA with vitamin supplementation only. See Protocol Section 3.6.2.

c - Questionnaires to be administered **prior to all other assessments and treatments**.

d - Repeat as clinically indicated.

e - Repeat every 6 weeks prior to every other cycle; after documentation of response, confirm with studies 4 weeks later.

f - Obtain within 4 days prior to the start of each cycle.

g - Calculated creatinine clearance must be measured at local and central labs at baseline. During the study, central labs may be used. Dose adjustments may be based on the local creatinine clearance.

h - Cycles 1 and 3: PK samples should be drawn according to the schedule provided in Protocol Attachment JMBQ.10.

## Vinorelbine Schedule of Events

| Cycle | 0 | 1 | | | | 2 | | | | 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relative Day Within a Cycle | | 1 | 8 | 15 | 21 | 1 | 8 | 15 | 21 | 1 | 8 | 15 | 21 |
| Visit (for CRF use only) | 0 | 1 | | | | 2 | | | | 3 | | | |
| Relative Day | Baseline[a] | 1 | 8 | 15 | 21 | 22 | 29 | 36 | 42 | 43 | 50 | 57 | 62 |
| Activity | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | |
| Vinorelbine therapy | | X | X | X | | X | X | X | | X | X | X | |
| Physical examination | X | | | | | X | | | | X | | | |
| Medical history | X | | | | | X | | | | X | | | |
| Weight | X | | | | | X | | | | X | | | |
| Height | X | | | | | | | | | | | | |
| Tumor measurement (visual or palpable) | X | | | | | X | | | | X | | | |
| Performance status (ECOG) | X | | | | | X | | | | X | | | |
| Chest x-ray | X[c] | | | | | | | | | | | | |
| Radiologic tests for tumor measurement | X | | | | | | | | X[d] | | | | |
| Document response to prior chemotherapy | X | | | | | | | | | | | | |
| Vital signs | X[c] | | | | | | | | | | | | |
| Vitamin metabolite assay | X | X[a] | | | | X[e] | | | | X[e] | | | |
| Chemistry | X | | X | X | | X[e] | X | X | | X[e] | X | X | |
| CBC w/dif, platelets | X | | X | X | | X[e] | X | X | | X[e] | X | X | |
| Serum pregnancy test if applicable | X | | | | | | | | | | | | |
| Urinalysis | X | | | | | | | | | | | | |
| Calculated creatinine clearance | X[f] | | | | | X[e,f] | | | | X[e,f] | | | |
| Toxicity rating | | | | | | X | | | | X | | | |
| EORTC QLQ-C30 & LC13 | | X[b] | | | | X[b] | | | | X[b] | | | |
| Medical resource utilization interview | | X[b] | | | | X[b] | | | | X[b] | | | |
| Concomitant meds notation | X | | | | | X | | | | X | | | |

a - For timing of baseline activities, please see Sections 3.9.1.1 and 3.9.2.2.

b - Questionnaires to be administered **prior to all other assessments and treatments**.

c - Repeat as clinically indicated.

d - Repeat prior to every other cycle; after documentation of response, confirm with studies 4 weeks later.

e - Obtain within 4 days prior to start of each cycle.

f - Calculated creatinine clearance must be measured at local and central labs at baseline. During the study, central labs will be used.

**Protocol Attachment JMBQ.5**
**Quality of Life Questionnaire**
**(EORTC QLQ-C30 & LC13)**

## Attachment JMBQ.5
## EORTC QLQ-C30 & LC13 (Version 2.0)

**EORTC QLQ-C30**

**Patient Initials** ___ ___ ___

**Date Patient Completed Questionnaire** __/__/__

DD/MM/YY

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

| | | No | Yes |
|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 |
| 2. | Do you have trouble taking a **long** walk? | 1 | 2 |
| 3. | Do you have any trouble taking a **short** walk outside of the house? | 1 | 2 |
| 4. | Do you stay in bed or a chair for most of the day? | 1 | 2 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 |

**Attachment JMBQ.5 (continued)**
**EORTC QLQ-C30 & LC13**

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |

## Attachment JMBQ.5 (continued)
## EORTC QLQ-C30 & LC13

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |
| 17. | Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. | Were you tired? | 1 | 2 | 3 | 4 |
| 19. | Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. | Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. | Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. | Did you worry? | 1 | 2 | 3 | 4 |
| 23. | Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. | Did you feel depressed? | 1 | 2 | 3 | 4 |

**Attachment JMBQ.5 (continued)**
**EORTC QLQ-C30 & LC13**

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| 25. | Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. | Has your physical condition or medical treatment interfered with your **family** life? | 1 | 2 | 3 | 4 |
| 27. | Has your physical condition or medical treatment interfered with your **social** activities? | 1 | 2 | 3 | 4 |
| 28. | Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**Attachment JMBQ.5 (continued)**
**EORTC QLQ-C30 & LC13**

**For the following questions please circle the number between 1 and 7 that best applies to you.**

29. How would you rate your overall **health** during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very Poor | | | | | | Excellent |

30. How would you rate your overall **quality of life** during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very Poor | | | | | | Excellent |

## Attachment JMBQ.5 (continued)
## EORTC QLQ-C30 & LC13

**EORTC QLQ-LC13**

**Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.**

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| 31. | How much did you cough? | 1 | 2 | 3 | 4 |
| 32. | Did you cough blood? | 1 | 2 | 3 | 4 |
| 33. | Were you short of breath when you rested? | 1 | 2 | 3 | 4 |
| | 34. Were you short of breath when you walked? | 1 | 2 | 3 | 4 |
| 34. | Were you short of breath when you climbed stairs? | 1 | 2 | 3 | 4 |
| 35. | Have you had a sore mouth or tongue? | 1 | 2 | 3 | 4 |
| 37. | Have you had trouble swallowing? | 1 | 2 | 3 | 4 |
| 38. | Have you had tingling hands or feet? | 1 | 2 | 3 | 4 |

## Attachment JMBQ.5 (continued)
## EORTC QLQ-C30 & LC13

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| 39. | Have you had hair loss? | 1 | 2 | 3 | 4 |
| 40. | Have you had pain in your chest? | 1 | 2 | 3 | 4 |
| 41. | Have you had pain in your arm or shoulder? | 1 | 2 | 3 | 4 |
| *42.* | *a. Have you had pain in other parts of your body?* | 1 | 2 | 3 | 4 |
| | b. If yes, where? | | | | |
| 43. | a. Did you take any medicine for pain? | Yes | No | | |

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| b. | If yes, did it help? | 1 | 2 | 3 | 4 |

**Protocol Attachment JMBQ.5a**
**EORTC QLQ-C30 & LC13**
**Symptom Scale (SS14)**

## Protocol Attachment JMBQ.5a
## EORTC QLQ-C30 & LC13
## Symptom Scale (SS14)

| Original number in QLQ-C30 & LC13 | New subset number | Question | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 31 | 1 | How much did you cough? | 1 | 2 | 3 | 4 |
| 32 | 2 | Did you cough blood? | 1 | 2 | 3 | 4 |
| 33 | 3 | Were you short of breath when you rested? | 1 | 2 | 3 | 4 |
| 34 | 4 | Were you short of breath when you walked? | 1 | 2 | 3 | 4 |
| 35 | 5 | Were you short of breath when you climbed stairs? | 1 | 2 | 3 | 4 |
| 40 | 6 | Have you had pain in your chest? | 1 | 2 | 3 | 4 |
| 41 | 7 | Have you had pain in your arm or shoulder? | 1 | 2 | 3 | 4 |
| 42 | 8 | Have you had pains in other parts of your body? | 1 | 2 | 3 | 4 |
| 12 | 9 | Have you felt weak? | 1 | 2 | 3 | 4 |
| 18 | 10 | Were you tired? | 1 | 2 | 3 | 4 |
| 11 | 11 | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 22 | 12 | Did you worry? | 1 | 2 | 3 | 4 |
| 13 | 13 | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 16 | 14 | Have you been constipated? | 1 | 2 | 3 | 4 |

This index was based on the 10 most frequently reported symptoms from a Medical Research Council NSCLC trial using the Rotterdam Symptom Checklist, reported moderate or severe (in order): shortness of breath, cough, lack of energy, tiredness, decreased sexual interest, difficulty, sleeping, worrying, lack of appetite, chest pain, and constipation. The only question not included was decreased sexual interest, since this was not asked on the full EORTC QLQ-C30.

## Protocol Attachment JMBQ.6
## Recommendations for Reporting of Serious Adverse Events

## Protocol Attachment JMBQ.6
## Recommendations for Reporting of Serious Adverse Events

When telephoning the ILEX™ office to report a serious adverse event, please have the following information available:

Patient Demographics
- patient identification (number)
- sex
- date of birth
- race

Study Identification
- protocol number
- investigator's name

Test Drug
- drug code or drug name
- unit dose
- total daily dose
- frequency
- route
- start dose

Adverse Event
- description
- date of onset
- severity
- treatment (including hospitalization)
- action taken with respect to test drug
- clinical significance
- test results (if applicable)

Relationship to Test Drug

Concomitant Drug Therapy
- indication
- total daily dose
- duration of treatment

In Case of Death
- cause
- autopsy findings (if available)

**Protocol Attachment JMBQ.7**
**Common Toxicity Criteria**

## Protocol Attachment JMBQ.7
## Common Toxicity Criteria

See attached pages.

**Protocol Attachment JMBQ.8**
**Medical Resource Utilization**

## Protocol Attachment JMBQ.8
## Medical Resource Utilization

**Objective**

The objective of this health economic evaluation is to assess the resource utilization and corresponding costs of providing cancer services for MTA versus vinorelbine in NSCLC.

**Investigational Plan**

The target population includes all patients entered into the trial, and the time horizon is calculated from the date the patient enters the trial until the end of treatment. The following principal high cost resources will be collected for each patient:

Hospitalization (including length of stay).
Location of administration of chemotherapy (inpatient, outpatient).
Health care professional visits.
Medical procedures.
Transfusions.
Concomitant medications.
Distance from home to clinic.

At each visit, resources will be collected by a research coordinator, who will interview the patient and note the resources consumed.

The data analysis will include:

Comparison of the resources consumed.
Sensitivity analysis of the totals to different resource drivers.

The perspective for the trial will be community care.

**References**

1. Evans WK. Rationale for the treatment of non-small cell lung cancer. Lung Cancer. 1993;9(suppl 2):S5-S14.

2. Jaakimainen L, Goodwin PJ, Pater J. Counting the costs of chemotherapy in the National Cancer Institute of Canada randomized study of non-small cell lung cancer. J Clin Oncol. 1990;8:1301-1309.

**Protocol Attachment JMBQ.9**
**Vitamin Metabolite Assay**

## Protocol Attachment JMBQ.9
## Vitamin Metabolite Assay

**Purpose:** Blood will be drawn in order to assess the influence of folate status as assessed by amino acid metabolism at baseline and within 4 days prior to the start of each cycle.

The following metabolites will be quantified:

- homocysteine
- cystathionine
- methylmalonic acid
- methylcitrate - total, plus:
  - methylcitrate I (2S, 3R and 2R, 3S enantiomers)
  - methylcitrate II (2S, 3S and 2R, 3R)

and others as deemed necessary.

**Protocol Attachment JMBQ.10**
**Blood Sampling Schedule for Pharmacokinetics**

## Protocol Attachment JMBQ.10
## Pharmacokinetic Sampling Schedule

### PK SAMPLING SCHEDULE

Blood samples for the analysis of MTA in plasma should be collected in the MTA arm of the study. Blood samples for analysis of MTA and folic acid in plasma should be collected in the MTA + vitamin supplementation arm of the study. Blood samples should be collected in Cycles 1 and 3. The schedule for blood sampling times is provided in the following table. An additional predose blood sample prior to Cycle 3 should also be collected. Blood samples should be drawn as closely as possible to these times. **It is very important that the actual date and clock time relative to the start of the MTA infusion be documented.**

**Cycle 1**

| Sample # | Time | Relative to MTA Administration |
|---|---|---|
| 1 | 9.5 min | Immediately prior to end of MTA infusion |
| 2 | 1-4 hours | 1-2 hours after start of MTA infusion |
| 3 | 8-12 hours | 8-12 hours after start of MTA infusion |

**Cycle 3**

| Sample # | Time | Relative to MTA Administration |
|---|---|---|
| 1 | predose | Prior to administration |
| 2 | 9.5 min | Immediately prior to end of MTA infusion |
| 3 | 1-4 hours | 1-2 hours after start of MTA infusion |
| 4 | 8-12 hours | 8-12 hours after start of MTA infusion |

The following is a randomization schedule for blood sample times (#2 and #3) for the up to 275 patients who will receive MTA in this study.

| Patient Number | Blood Sample #2 (Cycle 1) #3 (Cycle 3) | Blood Sample #3 (Cycle 1) #4 (Cycle3) |
|---|---|---|
| 1 | 1hr 30 min | 9 hr 30 min |
| 2 | 4 hr | 12 hr |
| 3 | 2 hr 15 min | 11 hr 30 min |
| 4 | 1 hr 45 min | 10 hr |
| 5 | 3 hr 45 min | 11 hr 30 min |
| 6 | 4 hr | 12 hr |
| 7 | 2 hr 45 min | 8 hr |
| 8 | 2 hr 30 min | 8 hr |
| 9 | 1 hr | 8 hr |
| 10 | 1 hr | 8 hr 30 min |
| 11 | 3 hr 30 min | 10 hr 30 min |
| 12 | 2 hr 30 min | 8 hr |
| 13 | 3 hr 45 min | 11 hr |
| 14 | 1 hr | 8 hr 30 min |
| 15 | 4 hr | 12 hr |
| 16 | 1 hr 45 min | 10 hr 30 min |
| 17 | 1 hr 45 min | 10 hr |
| 18 | 3 hr | 9 hr 30 min |
| 19 | 4 hr | 12 hr |
| 20 | 1 hr 30 min | 10 hr |
| 21 | 3 hr | 9 hr 30 min |
| 22 | 2 hr 15 min | 11 hr 30 min |
| 23 | 2 hr 45 min | 8 hr 30 min |
| 24 | 1 hr 45 min | 10 hr 30 min |
| 25 | 2 hr 30 min | 12 hr |
| 26 | 3 hr 30 min | 11 hr |
| 27 | 3 hr | 9 hr |
| 28 | 2 hr 45 min | 8 hr 30 min |
| 29 | 2 hr 45 min | 8 hr 30 min |
| 30 | 2 hr | 11 hr |
| 31 | 3 hr 15 min | 10 hr |
| 32 | 2 hr 30 min | 8 hr |
| 33 | 4 hr | 11 hr 30 min |
| 34 | 4 hr | 11 hr 30 min |
| 35 | 2 hr 45 min | 8 hr 30 min |
| 36 | 1 hr 45 min | 10 hr 30 min |
| 37 | 2 hr 15 min | 11 hr 30 min |
| 38 | 2 hr 30 min | 12 hr |
| 39 | 3 hr | 9 hr 30 min |
| 40 | 1 hr 30 min | 9 hr 30 min |
| 41 | 1 hr 30 min | 9 hr |
| 42 | 3 hr 45min | 11 hr |
| 43 | 1 hr 45 min | 10 hr 30 min |
| 44 | 4 hr | 11 hr 30 min |
| 45 | 3 hr 45 min | 11 hr 30 min |
| 46 | 2 hr 45 min | 8 hr 30 min |

| Patient Number | Blood Sample #2 (Cycle 1) #3 (Cycle 3) | Blood Sample #3 (Cycle 1) #4 (Cycle3) |
|---|---|---|
| 47 | 1 hr | 8 hr |
| 48 | 1 hr 15 min | 9 hr |
| 49 | 2 hr 30 min | 8 hr |
| 50 | 2 hr 15 min | 11 hr 30 min |
| 51 | 1 hr 30 min | 9 hr 30 min |
| 52 | 3 hr | 9 hr |
| 53 | 2 hr 15 min | 11 hr 30 min |
| 54 | 1 hr 15 min | 9 hr |
| 55 | 2 hr 15 min | 12 hr |
| 56 | 1 hr 30 min | 9 hr 30 min |
| 57 | 2 hr 45 min | 8 hr 30 min |
| 58 | 3 hr 15 min | 10 hr |
| 59 | 2 hr 15 min | 11 hr 30 min |
| 60 | 1 hr | 8 hr |
| 61 | 2 hr 30 min | 8 hr |
| 62 | 2 hr | 11 hr |
| 63 | 1 hr | 8 hr |
| 64 | 3 hr 15 min | 9 hr 30 min |
| 65 | 4 hr | 11 hr 30 min |
| 66 | 2 hr 15 min | 12 hr |
| 67 | 4 hr | 12 hr |
| 68 | 3 hr 15 min | 9 hr 30 min |
| 69 | 1 hr 15 min | 8 hr 30 min |
| 70 | 1 hr 30 min | 9 hr 30 min |
| 71 | 1 hr 45 min | 10 hr |
| 72 | 2 hr 45 min | 9 hr |
| 73 | 2 hr 15 min | 11 hr 30 min |
| 74 | 1 hr | 8 hr 30 min |
| 75 | 2 hr | 11 hr |
| 76 | 3 hr 15 min | 9 hr 30 min |
| 77 | 1 hr 30 min | 9 hr 30 min |
| 78 | 1 hr 15 min | 9 hr |
| 79 | 2 hr 45 min | 8 hr 30 min |
| 80 | 1 hr 45 min | 10 hr |
| 81 | 2 hr | 10 hr 30 min |
| 82 | 2 hr 45 min | 8 hr 30 min |
| 83 | 1 hr | 8 hr |
| 84 | 2 hr 15 min | 11 hr 30 min |
| 85 | 3 hr 45 min | 11 hr 30 min |
| 86 | 2 hr 30 min | 8 hr |
| 87 | 3 hr 15 min | 10 hr |
| 88 | 3 hr 45 min | 11 hr 30 min |
| 89 | 2 hr 45 min | 8 hr 30 min |
| 90 | 1 hr 30 min | 9 hr 30 min |
| 91 | 2 hr | 10 hr 30 min |
| 92 | 3 hr 15 min | 9 hr 30 min |

| Patient Number | Blood Sample #2 (Cycle 1) #3 (Cycle 3) | Blood Sample #3 (Cycle 1) #4 (Cycle3) |
|---|---|---|
| 93 | 1 hr 15 min | 9 hr |
| 94 | 1 hr 15 min | 9 hr 30 |
| 95 | 1 hr 45 min | 10 hr |
| 96 | 3 hr | 9 hr |
| 97 | 2 hr 15 min | 11 hr 30 min |
| 98 | 1 hr | 8 hr |
| 99 | 1 hr 45 min | 10 hr |
| 100 | 2 hr 15 min | 11 hr 30 min |
| 101 | 3 hr 30 min | 10 hr 30 min |
| 102 | 3 hr 30 min | 11 hr |
| 103 | 3 hr 45 min | 11 hr |
| 104 | 1 hr 45 min | 10 hr |
| 105 | 1 hr 45 min | 10 hr 30 min |
| 106 | 2 hr 15 min | 11 hr 30 min |
| 107 | 2 hr | 11 hr |
| 108 | 3 hr 15 min | 10 hr |
| 109 | 2 hr 45 min | 8 hr |
| 110 | 2 hr 45 min | 9 hr |
| 111 | 2 hr 45 min | 8 hr |
| 112 | 3 hr 15 min | 10 hr |
| 113 | 2 hr | 11 hr |
| 114 | 3 hr | 9 hr |
| 115 | 2 hr 45 min | 8 hr 30 min |
| 116 | 3 hr 45 min | 11 hr |
| 117 | 2 hr 45 min | 8 hr 30 min |
| 118 | 3 hr 15 min | 10 hr |
| 119 | 1 hr 15 min | 9 hr |
| 120 | 1 hr | 8 hr |
| 121 | 3 hr 30 min | 10 hr 30 min |
| 122 | 3 hr | 9 hr |
| 123 | 1 hr | 8 hr |
| 124 | 3 hr 45 min | 11 hr |
| 125 | 2 hr | 11 hr |
| 126 | 2 hr | 11 hr |
| 127 | 2 hr 30 min | 8 hr |
| 128 | 3 hr 15 min | 9 hr 30 min |
| 129 | 2 hr | 11 hr |
| 130 | 1 hr 30 min | 10 hr |
| 131 | 3 hr | 9 hr 30 min |
| 132 | 2 hr 45 min | 8 hr |
| 133 | 2 hr 45 min | 8 hr 30 min |
| 134 | 1 hr 30 min | 9 hr 30 min |
| 135 | 1 hr | 8 hr |
| 136 | 3 hr | 9 hr |
| 137 | 3 hr | 9 hr |
| 138 | 1 hr 15 min | 8 hr 30 min |

| Patient Number | Blood Sample #2 (Cycle 1) #3 (Cycle 3) | Blood Sample #3 (Cycle 1) #4 (Cycle3) |
|---|---|---|
| 139 | 3 hr | 9 hr |
| 140 | 1 hr 15 min | 8 hr 30 min |
| 141 | 3 hr | 9 hr 30 min |
| 142 | 1 hr 30 min | 9 hr 30 min |
| 143 | 3 hr | 9 hr |
| 144 | 1 hr 30 min | 9 hr 30 min |
| 145 | 1 hr 45 min | 10 hr 30 min |
| 146 | 3 hr | 9 hr |
| 147 | 2 hr 15 min | 11 hr |
| 148 | 3 hr | 9 hr 30 min |
| 149 | 2 hr 30 min | 12 hr |
| 150 | 3 hr 30 min | 10 hr 30 min |
| 151 | 1 hr | 8 hr |
| 152 | 1 hr 30 min | 9 hr 30 min |
| 153 | 1 hr 15 min | 8 hr 30 min |
| 154 | 1 hr 15 min | 9 hr |
| 155 | 1 hr 30 min | 10 hr |
| 156 | 2 hr | 11 hr |
| 157 | 3 hr 15 min | 9 hr 30 min |
| 158 | 2 hr 30 min | 12 hr |
| 159 | 3 hr | 9 hr |
| 160 | 3 hr 45 min | 11 hr 30 min |
| 161 | 1 hr 45 min | 10 hr 30 min |
| 162 | 4 hr | 11 hr 30 min |
| 163 | 2 hr 15 min | 11 hr 30 min |
| 164 | 2 hr 45 min | 8 hr 30 min |
| 165 | 3 hr 30 min | 10 hr 30 min |
| 166 | 2 hr 15 min | 11 hr 30 min |
| 167 | 1 hr 15 min | 9 hr |
| 168 | 3 hr 15 min | 10 hr |
| 169 | 1 hr 30 min | 9 hr 30 min |
| 170 | 3 hr 30 min | 10 hr 30 min |
| 171 | 1 hr 15 min | 8 hr 30 min |
| 172 | 1 hr 30 min | 9 hr 30 min |
| 173 | 2 hr | 10 hr 30 min |
| 174 | 3 hr 15 min | 9 hr 30 min |
| 175 | 4 hr | 11 hr 30 min |
| 176 | 1 hr 45 min | 10 hr 30 min |
| 177 | 1 hr 30 min | 10 hr |
| 178 | 1 hr 15 min | 9 hr |
| 179 | 2 hr 45 min | 8 hr 30 min |
| 180 | 2 hr 30 min | 12 hr |
| 181 | 2 hr 15 min | 11 hr 30 min |
| 182 | 1 hr 45 min | 10 hr |
| 183 | 1 hr 30 min | 10 hr |
| 184 | 1 hr 15 min | 8 hr 30 min |

| Patient Number | Blood Sample #2 (Cycle 1) #3 (Cycle 3) | Blood Sample #3 (Cycle 1) #4 (Cycle3) |
|---|---|---|
| 185 | 2 hr 15 min | 11 hr 30 min |
| 186 | 3 hr | 9 hr 30 min |
| 187 | 2 hr 15 min | 11 hr 30 min |
| 188 | 2 hr 30 min | 12 hr |
| 189 | 3 hr 45 min | 11 hr |
| 190 | 2 hr 45 min | 8 hr 30 min |
| 191 | 2 hr 30 min | 8 hr |
| 192 | 2 hr 45 min | 8 hr 30 min |
| 193 | 1 hr | 8 hr |
| 194 | 2 hr 30 min | 8 hr |
| 195 | 3 hr | 9 hr 30 min |
| 196 | 2 hr 15 min | 12 hr |
| 197 | 3 hr 30 min | 11 hr |
| 198 | 1 hr 45 min | 10 hr 30 min |
| 199 | 2 hr 15 min | 11 hr 30 min |
| 200 | 4 hr | 12 hr |
| 201 | 2 hr 15 min | 11 hr 30 min |
| 202 | 3 hr 30 min | 10 hr 30 min |
| 203 | 2 hr | 10 hr 30 min |
| 204 | 1 hr 30 min | 9 hr 30 min |
| 205 | 3 hr 45 min | 11 hr 30 min |
| 206 | 1 hr 45 min | 10 hr |
| 207 | 4 hr | 12 hr |
| 208 | 1 hr 15 min | 9 hr |
| 209 | 1 hr 45 min | 10 hr |
| 210 | 2 hr 45 min | 8 hr 30 min |
| 211 | 3 hr | 9 hr |
| 212 | 3 hr | 9 hr 30 min |
| 213 | 1 hr | 8 hr |
| 214 | 3 hr 15 min | 10 hr |
| 215 | 2 hr 45 min | 8 hr 30 min |
| 216 | 2 hr 30 min | 8 hr |
| 217 | 1 hr | 8 hr |
| 218 | 3 hr | 9 hr |
| 219 | 4 hr | 12 hr |
| 220 | 1 hr 30 min | 9 hr 30 min |
| 221 | 2 hr 45 min | 8 hr 30 min |
| 222 | 4 hr | 12 hr |
| 223 | 2 hr | 11 hr |
| 224 | 1 hr 15 min | 9 hr |
| 225 | 3 hr | 9 hr |
| 226 | 1 hr | 8 hr 30 min |
| 227 | 2 hr 45 min | 8 hr 30 min |
| 228 | 3 hr 15 min | 9 hr 30 min |
| 229 | 2 hr 15 min | 11 hr 30 min |
| 230 | 1 hr | 8 hr |

| Patient Number | Blood Sample #2 (Cycle 1) #3 (Cycle 3) | Blood Sample #3 (Cycle 1) #4 (Cycle3) |
|---|---|---|
| 231 | 2 hr 30 min | 12 hr |
| 232 | 4 hr | 11 hr 30 min |
| 233 | 3 hr | 9 hr |
| 234 | 2 hr 30 min | 8 hr |
| 235 | 3 hr | 9 hr |
| 236 | 1 hr 45 min | 10 hr 30 min |
| 237 | 1 hr 30 min | 9 hr 30 min |
| 238 | 2 hr 45 min | 8 hr 30 min |
| 239 | 2 hr 45 min | 8 hr 30 min |
| 240 | 2 hr 45 min | 8 hr 30 min |
| 241 | 1 hr | 8 hr |
| 242 | 3 hr 30 min | 10 hr 30 min |
| 243 | 2 hr 15 min | 11 hr |
| 244 | 3 hr 30 min | 10 hr 30 min |
| 245 | 1 hr 45 min | 10 hr |
| 246 | 1 hr 30 min | 9 hr 30 min |
| 247 | 3 hr 15 min | 10 hr |
| 248 | 2 hr 15 min | 12 hr |
| 249 | 2 hr | 11 hr |
| 250 | 2 hr 15 min | 11 hr 30 min |
| 251 | 3 hr 30 min | 10 hr 30 min |
| 252 | 1 hr 45 min | 10 hr 30 min |
| 253 | 3 hr 45 min | 11 hr 30 min |
| 254 | 1 hr 45 min | 10 hr 30 min |
| 255 | 3 hr | 9 hr |
| 256 | 3 hr 15 min | 10 hr |
| 257 | 2 hr 30 min | 8 hr |
| 258 | 2 hr 15 min | 11 hr 30 min |
| 259 | 3 hr 15 min | 10 hr |
| 260 | 4 hr | 12 hr |
| 261 | 2 hr 45 min | 8 hr 30 min |
| 262 | 3 hr 30 min | 10 hr 30 min |
| 263 | 2 hr 30 min | 8 hr |
| 264 | 1 hr 30 min | 9 hr 30 min |
| 265 | 4 hr | 12 hr |
| 266 | 3 hr 30 min | 10 hr 30 min |
| 267 | 1 hr 45 min | 10 hr 30 min |
| 268 | 2 hr | 10 hr 30 min |
| 269 | 2 hr 30 min | 8 hr |
| 270 | 3 hr 30 min | 10 hr 30 min |
| 271 | 2 hr 30 min | 8 hr |
| 272 | 4 hr | 12 hr |
| 273 | 2 hr 30 min | 12 hr |
| 274 | 4 hr | 12 hr |
| 275 | 3 hr | 9 hr |

## Protocol Attachment JMBQ.11
## Protocol Signatures

# Protocol Signatures
# Protocol H3E-MC-JMBQ(a)

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with ILEX™.

Instructions to the investigator: Please SIGN and DATE both copies of this signature page and PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the completed, signed copies to ILEX™.

_____ _____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility
(City, State (if applicable), Country)

_____ _____

Signature of Representative of ILEX™ Date
Thomas Williams, MD
Director of Medical Affairs
ILEX™ Oncology Inc.

# Protocol Signatures
# Protocol H3E-MC-JMBQ(a)

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with ILEX™.

Instructions to the investigator: Please SIGN and DATE both copies of this signature page and PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the completed, signed copies to ILEX™.

Signature of Investigator _____ Date _____

Investigator Name _____

Investigator Title _____

Name of Facility _____

Location of Facility
(City, State (if applicable), Country) _____

Signature of Representative of ILEX™ _____ Date _____
Thomas Williams, MD
Director of Medical Affairs
ILEX™ Oncology Inc.

Appendix 7

# Appendix 7
# Protocol H3E-MC-JMCH



## MTA (LY231514)

## Protocol H3E-MC-JMCH

## A Randomized Phase 3 Trial of MTA plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma

## "EMPHACIS"
(**E**valuation of **M**TA in Mesothelioma in a **Ph**ase 3 Study with **Cis**platin)

Protocol Approved by Lilly: 16 July 1998

# A Randomized Phase 3 Trial of MTA plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma

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# A Randomized Phase 3 Trial of MTA plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma

## 1. Introduction

### 1.1. Malignant Mesothelioma

Malignant mesothelioma is a rare, seldom curable tumor of the pleura or the peritoneum whose origin has generally been linked to asbestos exposure. Survival of untreated patients is dismal with a median survival of less than 12 months. Prognosis can be predicted by a number of factors including histologic subtype, performance status, disease extent at baseline, presence of chest pain, gender, and white blood cell count, among others (Curran et al 1998). In pleural disease, the tumor usually grows in the space between the visceral and parietal pleura, and forms a hardened rind which encases the lung. This tumor is commonly accompanied by pleural effusions, which complicate interpretation of radiologic imaging. For these reasons, mesothelioma presents a particular challenge with respect to obtaining two-dimensional tumor measurements.

Malignant mesothelioma is a notoriously refractory tumor to treat: neither surgery nor radiotherapy results in increased survival (DeVita et al. 1997). Various chemotherapeutic agents have been tested, with doxorubicin, cisplatin, and ifosfamide each showing modest activity. Antimetabolites such as methotrexate and edatrexate also have single agent activity (Solheim et al. 1992; Belani et al. 1994). Gemcitabine has also shown promising results (Millard et al. 1997). The EORTC Lung Cancer Cooperative Group (LCCG) has conducted sequential Phase 2 studies in malignant mesothelioma with mitoxantrone, epirubicin, etoposide and paclitaxel (van Breukelen et al 1991; Mattson et al 1992; Sahmoud et al 1997; van Meerbeeck et al 1996). None of these drugs has obtained a greater than 20% response rate.

### 1.2. MTA

#### *1.2.1 Background and Phase 1 Results*

Inhibition of the enzyme thymidylate synthase (TS) is the primary mechanism of action of MTA, a folate antimetabolite (Lilly Research Laboratories 1997; Shih et al. 1992; Grindey et al. 1992). Thymidylate synthase, a folate-dependent enzyme, catalyzes the transformation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Inhibition of TS results in decreased thymidine necessary for DNA synthesis (Grem 1990; Schilsky 1992).

MTA also inhibits dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT), a folate-dependent enzyme that is involved in purine synthesis (Shih et al. 1996). These targets are related to the cytotoxicity of MTA since both thymidine and hypoxanthine are required to circumvent cellular death caused by MTA (Schultz et al. 1996). MTA gains entry to the cell via the reduced folate carrier and once localized is an excellent substrate for folypolyglutamate synthase (FPGS). The pentaglutamate form of MTA is the predominant intracellular form and is >60-fold more potent in its inhibition of TS than the monoglutamate (Chen et al. 1996).

MTA exhibits highly cytotoxic *in vitro* activity against the CCRF-CEM human leukemia cell line and has shown significant antitumor activity against thymidine-and hypoxanthine-deficient murine tumor cell lines as well as two human colon xenografts resistant to methotrexate. Several dose schedules were studied in dogs with the predominant toxicities being gastrointestinal and hematological. Marked schedule dependency was noted, with a 34-fold increase in dose intensity found using a once weekly compared to daily dosing. Folinic acid treatment initiated 24 hours after a potentially fatal dose prevented lethality, suggesting a role for folinic acid in the treatment of severe, drug-induced toxicity (Lilly Research Laboratories 1997).

Two studies were conducted to evaluate potential rescue agents (leucovorin and thymidine) for treatment of severe toxicity due to MTA administration. Two intravenous doses of 50 mg MTA/kg, 3 days apart, were used to produce toxicity. In the leucovorin rescue study, both clinical signs of toxicity and hematological alterations were reversed by co-administration of leucovorin, a reduced form of folate. In the thymidine, rescue study, subsequent (24 hours after last MTA dose) administration of thymidine, the end product of thymidilate synthase, as a continuous infusion for 3 days was successful in rescuing dogs from life-threatening toxicity associated with MTA.

Given the schedule dependency observed in animal models, Phase 1 studies were conducted exploring three treatment schedules: daily times 5 every 3 weeks (H3E BP-001); weekly times 4 every 6 weeks (H3E-MC- JMAB); and once every 3 weeks (H3E-MC-JMAA).

Thirty-eight patients were treated at doses ranging from 0.2 to 5.2 mg/m$^2$ daily times 5 every 3 weeks in Study BP-001 (McDonald et al. 1996). The maximum tolerated dose (MTD) was 4 mg/m$^2$/day, with dose limiting toxicities (DLTs) on this schedule of reversible neutropenia and liver enzyme disturbance. Other toxicities included mucositis, diarrhea, rash, fatigue, and elevated transaminases. Minor responses were observed in 2 patients with colorectal and non-small cell lung cancer (NSCLC).

In Study JMAB, 24 patients were treated with a 10-minute infusion of MTA once a week for 4 weeks, with cycles repeated every 6 weeks (Rinaldi et al. 1995). Doses ranged from 10 to 40 mg/m$^2$/week. The DLT was myelosuppression, particularly leukopenia and granulocytopenia. Neutropenia prevented weekly dosing in some patients. Nonhematologic toxicities included mild fatigue, anorexia, and nausea. DLT was

observed at 40 mg/m2/week, and the recommended dose for Phase 2 evaluation was 30 mg/m2/week. The weekly schedule was not pursued in Phase 2 trials.

In Study JMAA, MTA was administered to 37 patients as a 10-minute infusion once every 3 weeks at doses ranging from 50 to 700 mg/m2 (Rinaldi et al. 1996). The DLTs on this schedule were neutropenia, thrombocytopenia, and fatigue. Of the 20 patients treated at 600 mg/m2, Common Toxicity Criteria (CTC) Grade 4 neutropenia and CTC Grade 4 thrombocytopenia occurred in 4 and 1 patients, respectively, during the first cycle. CTC Grade 2 toxicities at that dose level included rash, mucositis, nausea, vomiting, fatigue, anorexia, and elevations of liver transaminases. Ten patients who developed rashes received dexamethasone 4 mg twice daily for 3 days starting 1 day prior to treatment with MTA which improved or prevented the rash during subsequent cycles of therapy. There was evidence of cumulative toxicities of neutropenia, thrombocytopenia, and mucositis which may have been due to the prolonged intracellular half-life of the polyglutamate of MTA and decreasing renal function over time with decreased renal drug clearance. Based on this study, the recommended dose for Phase 2 studies was 600 mg/m2. Partial responses were observed in two patients with pancreatic cancer and two patients with advanced colorectal cancer. Three of the 4 patients with partial responses had failed previous treatment with thymidylate synthase inhibitors including either 5-FU, FUDR, or raltitrexed.

Two patients experienced severe toxicity during Cycle 1 in Study JMAS, which is an MTA plus folic acid Phase 1 study. One of these patients was on stable doses of naproxen (500 mg twice per day) concurrent with MTA at 800 mg/m2. The other patient was on stable doses of a long acting NSAID concurrent with MTA at 900 mg/m2. It is anticipated that a 3- to 4-fold higher MTA concentration would be achieved at these doses in relation to the dose received by Patient 4407 in Study JMAA. At these higher concentrations, it is more likely that MTA may compete with aspirin or other NSAIDs for renal tubular secretion. Until the pharmacokinetic parameters have been calculated for these 2 patients, the possibility that concurrent NSAID therapy decreased MTA clearance (predisposing these patients to severe toxicity) cannot be ruled out. Additional considerations include the potential renal toxicity of chronic NSAID therapy and the nutritional and folate status of these patients.

The pharmacokinetics of MTA have been determined in three Phase 1 studies, with dosing given once a week for 3 consecutive weeks and also once every 3 weeks (Rinaldi et al. 1995, 1996). Doses were given as 10-minute infusions in all studies. Doses ranged from 10 to 40 mg/m2 weekly for 3 weeks in the first study, 50 to 700 mg/m2 as a single administration every 3 weeks in the second study, and 0.2 to 6.0 mg/m2 given daily for 5 consecutive days, every 3 weeks in the third study.

Pharmacokinetic determinations were made in 20 patients with various cancers (primarily colorectal cancer) at the MTD dose (600 mg/m2). A mean maximum concentration of 137 μg/mL was attained, with a mean half-life of 3.1 hours (range, 2.2 to 7.2 hours). Mean respective clearance and steady-state volume of distribution values of 40

mL/min/m$^2$ and 7.0 L/m$^2$ were also measured. This mean clearance value is similar to that of creatinine clearance in the age range of the patients enrolled (approximately 45 to 55 mL/min/m$^2$), and the volume of distribution reflects limited distribution outside the bloodstream.

Samples collected after the first dose in each course of therapy showed the disposition of MTA to be linear over the entire dose range (0.2 to 700 mg/m$^2$). The clearance of the compound is primarily renal, with 80% or greater of the dose recovered unchanged in the urine during the first 24 hours after dosing. No accumulation appears to occur with multiple courses, and the disposition of MTA does not change after multiple doses. MTA clearance does appear to decrease with age, although this decrease is most likely related to decreasing renal function associated with aging.

### *1.2.2. Phase 2 Results*

Two Phase 2 studies in colorectal cancer, one in pancreas cancer, two in NSCLC and one in breast cancer began in late 1995. These studies were designed to include patients with advanced disease who were either chemonaive or had received limited prior chemotherapy in the metastatic setting, with a starting dose of 600 mg/m$^2$ once every 21 days. Results from these studies are preliminary.

Clinical activity of MTA in metastatic colorectal carcinoma has been demonstrated in two multicenter trials performed in Canada and the US (Cripps et al 1997; John et al. 1997). Prior adjuvant chemotherapy was allowed if completed at least 1 year prior to study entry. In the Canadian study, the starting dose of 600 mg/m$^2$ was reduced to 500 mg/m$^2$ after dose reductions were required in 5 of the first 8 patients. Toxicities leading to these reductions included rash, mucositis, neutropenia, and febrile neutropenia. Responses were seen at this reduced dose in 5 patients for an overall response rate of 17% (95% CI: 6 to 36%) (Cripps et al. 1997). In the US colorectal study, objective tumor responses were seen in 6 of 40 patients for an overall response rate of 15% (95% CI: 6 to 31%) (John et al. 1997).

Two responses, one complete and one partial, were observed in 35 evaluable patients in the pancreatic cancer Phase 2 study for an overall response rate of 6% (Miller et al. 1997). Importantly, there were 13 additional patients with stable disease lasting for over 6 months of treatment, suggesting a clinical benefit not immediately apparent from objective tumor measurements.

A Phase 2 study in patients with locally advanced and/or metastatic breast cancer is ongoing and includes patients who have received prior adjuvant chemotherapy as well as one prior therapy for metastatic disease. Twenty-eight of 36 patients had received prior chemotherapy, 16 as adjuvant treatment, 12 for metastatic disease, and 5 patients who received both. Of the 36 patients evaluable for response, one complete and 10 partial responses have been documented for an overall response rate of 31%. Responses have been seen in pulmonary and hepatic metastases. Three responding patients had received

recent prior therapy with paclitaxel, docetaxel or an anthracycline for metastatic disease (Smith et al. 1997).

One multi-institutional study in NSCLC has been completed in Canada (Rusthoven et al. 1997) and an additional study is ongoing in Australia and South Africa (Clarke et al. 1997). All patients were chemonaive. The majority of patients on the Canadian study used the lower starting dose of 500 mg/m$^2$, which was reduced from 600 mg/m$^2$ during the course of the study after 1 of the first 3 patients experienced CTC Grade 3 mucositis and Grade 4 vomiting and myalgia. Seven partial responses have been observed in 30 evaluable patients for an overall response rate of 23.3% (95% CI 9.9 to 42.3%) (Rusthoven et al. 1997). All responding patients were treated at the 500 mg/m$^2$ dose level.

The second NSCLC study, which is being carried out jointly between Australia and South Africa, has enrolled 21 patients to date, with 20 evaluable for response. All patients are receiving 600 mg/m$^2$ every 3 weeks in this study. Five partial responses have been noted for an overall response rate of 25% (Clarke et al. 1997). The initial Phase 2 experience is summarized in Table JMCH.1.

**Table JMCH.1. Phase 2 Experience**

| Study | JMAC | JMAD | JMAN | JMAO | JMAG | JMAL |
|---|---|---|---|---|---|---|
| Site | US | US | Canada | Canada | UK | Aus/S Africa |
| Tumor site | colorectal | pancreas | NSCLC | Colorectal | breast | NSCLC |
| No. evaluable patients | 41 | 35 | 30 | 29 | 36 | 42 |
| Median cycles | 4 | 2 | 3 | 3 | 4 | 4 |
| (Range) | (1 -12) | (1-12) | (1-8) | (1-8) | (1-9) | (1-9) |
| CR | 1 | 1 | 0 | 0 | 1 | 0 |
| PR | 5 | 1 | 7 | 5 | 10 | 7 |
| Overall RR (%) | 15 | 6 | 23 | 17 | 31 | 17 |
| (95% CI, %) | | | (9.9-42.3) | (8-39.7) | | |

A total of 209 patients have been treated on the once every 3 weeks schedule in the Phase 2 setting at 600 mg/m$^2$ and are evaluable for safety analysis. The most frequent, serious toxicity has been hematologic in nature. CTC Grade 3 and 4 hematologic toxicity included neutropenia (24% and 24%, respectively) and thrombocytopenia (6% and 9%, respectively). Although severe neutropenia is common, the frequency of serious infection has been low (CTC Grade 4 infection 2%). Likewise, thrombocytopenia has been apparent, and yet serious episodes of bleeding have been rare (<1%). While 11% of patients experienced CTC Grade 3 (5% with Grade 4) skin rash, prophylactic dexamethasone is reported to ameliorate or prevent the rash in subsequent cycles. Other Grade 3 and 4 nonhematologic toxicities included stomatitis, diarrhea, vomiting, and infection. As seen in clinical studies of other antifolates, transient Grade 3 and 4 elevation of liver transaminases are common but not dose-limiting. There have been no

cases of persistent transaminase elevation. Tables JMCH.2 and JMCH.3 summarize the laboratory and non-laboratory toxicity data from the Phase 2 studies conducted at a starting dose of 600 mg/m$^2$.

Toxicity at 600 mg/m$^2$ has recently been compared to that at 500 mg/m$^2$. For hematologic parameters there appears to be no difference between the incidence of Grade 3 and 4 toxicity or Grade 4 toxicity alone. For nonhematologic parameters there is also no difference except for rash, fatigue, and stomatitis, which appear to be less severe at 600 mg/m$^2$. Of note, patients who were administered MTA 500 mg/m$^2$ in previous trials received concomitant dexamethasone after the onset of toxicity, whereas patients at the 600 mg/m$^2$ dose level were given dexamethasone prophylactically. The reduced toxicity profile at the 600 mg/m$^2$ dose level is thus likely a result of concomitant corticosteroid administration, and is not considered a dose response effect of MTA treatment.

**Table JMCH.2. Laboratory Toxicity (n=209)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| ANC | 9 | 21 | 24 | 24 |
| Leukocytes | 14 | 28 | 35 | 10 |
| Platelets | 31 | 6 | 6 | 9 |
| Hb | 34 | 43 | 12 | 2 |
| ALT | 33 | 26 | 22 | 0 |
| AST | 42 | 30 | 10 | 0 |
| Bilirubin | 0 | 18 | 7.3 | 2 |
| Creatinine | 13 | 5 | 0 | 0 |
| Alk phos | 49 | 13 | 4 | 0 |

**Table JMCH.3. Non-laboratory Toxicity (n=209)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Cutaneous | 19 | 39 | 11 | 5 |
| Diarrhea | 17 | 11 | 4 | 3 |
| Infection | 13 | 8 | 2 | 2 |
| Nausea | 33 | 30 | 9 | 0.5 |
| Fatigue | 13 | 11 | 6 | 0 |
| Pulmonary | 0.5 | 7 | 2 | 2 |
| Stomatitis | 23 | 16 | 6 | 1 |
| Vomiting | 13 | 30 | 2 | 3 |

A recent multivariate analysis of potential prognostic factors has been undertaken in an attempt to identify factors which might identify patients at risk of developing serious toxicity (Niyikiza et al, 1998). Of a total of 300 patients in Phase 2 trials treated with MTA (600 mg/m$^2$ intravenously over 10 minutes once every 21 days), 139 Phase 2 patients with tumors of the colon, breast, pancreas, and esophagus had homocysteine

(Hcys), cystathionine, and methylmalonic acid measured at baseline and once each cycle thereafter. Stepwise regression modeling was used to help trim out models to predict the toxicity, with a careful review of correlation between various prognostic to avoid issues of colinearity. Prognostic factors retained (p-value <0.15) were then used in a standard least square regression model fitting to confirm their correlation with the toxicity. Threshold values were tested using chi-square test. A multivariate fitting using MANOVA with the identity matrix as the response design matrix was implemented with the final selected predictors. These selected predictor variables were used in a multivariate discriminant analysis to predict patients who will develop toxicity. Prognostic factors considered were age, gender, baseline performance status, baseline albumin, liver enzymes, creatinine clearance, prior treatment with a myelosuppressive agent, ANC, platelets, vitamin metabolites (ie, homocysteine, cystathionine, and methylmalonic acid), and AUC.

Following one course of therapy with MTA, statistically significant predictors of Grade 4 neutropenia (n=21 patients) were baseline albumin ($p<0.0001$) and baseline Hcys ($p=0.002$), while Grade 4 thrombocytopenia (n=8 patients) was predicted by baseline Hcys ($p<0.0001$) and baseline albumin ($p=0.0237$). Baseline Hcys was also found to be the only statistically significant ($p=0.0014$) prognostic factor for Grade 3/4 mucositis, diarrhea, rash, or fatigue after one cycle of treatment. A threshold baseline homocysteine value of 10 μmol/L for Grade 4 neutropenia after Cycle 1 was identified ($\chi^2=6.2$, $p=0.01$). Hcys levels did not change from baseline ($p=0.77$) during MTA therapy. Hcys ≥10 μM predicted Grade 4 neutropenia in cycle one 75% of the time. Grade 4 neutropenia was predicted by Hcys alone in 71% of cases. Hcys ≥10 μM predicted Grade 4 thrombocytopenia in Cycle 1 87.5% of the time.

Statistically significant predictors of Grade 4 neutropenia at any time during MTA therapy (n=32 patients) were again found to be albumin ($p=0.0021$) and Hcys ($p=0.0065$), while Grade 4 thrombocytopenia at any time during MTA therapy (n=16 patients) was predicted by Hcys ($p=0.0014$). Hcys ≥10 μM predicted Grade 4 neutropenia at any time during MTA therapy 66% of the time. Grade 4 thrombocytopenia at any time during MTA therapy was predicted by Hcys alone in 81% of cases. While AUC was not found to be a predictor of toxicity, little variability was observed in AUC. Maximum values were still below AUC values related to hematologic toxicity in Phase 1 studies.

In conclusion, toxicities resulting from therapy with MTA appear to be predictable from pre-therapy homocysteine levels. Elevated baseline homocysteine levels (≥10 μM) highly correlate with severe hematologic and nonhematologic toxicities following therapy with MTA. Homocysteine was found to be better than albumin at predicting hematologic toxicity. Homocysteine levels were not changed during the course of MTA therapy, making it an ideal marker for use in screening patients at risk of hematologic and nonhematologic toxicities prior to therapy with MTA. These results apply to the tumor types studied. Further studies are underway in patients with renal impairment or patients who received prior cisplatin.

## 1.3. Phase 1 Experience with MTA plus Cisplatin

A Phase 1 trial of MTA in combination with cisplatin has recently completed patient accrual. In this study, patients with solid tumors were enrolled into one of two cohorts. The first cohort received both MTA and cisplatin on Day 1 of a 21-day cycle, and the second cohort received MTA on Day 1 and cisplatin on Day 2 of a 21-day cycle. Forty patients were enrolled into the first cohort; the MTD was reached at 600 mg/m$^2$ MTA and 100 mg/m$^2$ cisplatin, with dose-limiting toxicities of thrombocytopenia and febrile neutropenia. Eleven patients were enrolled into the second cohort. The degree of toxicity seen using this split schedule, which has included two therapy-related deaths, has led to the conclusion that the second schedule is clinically inferior. Partial responses were seen in 1 of 6 patients with NSCLC, 2 of 4 patients with colorectal cancer (one of these on the split schedule), 3 of 9 patients with head and neck cancer, 1 of 2 patients with melanoma, 1 patient with cancer of unknown primary, and in particular, 5 of 13 patients with pleural mesothelioma. Four of these mesothelioma patients received the same day schedule and 1 patient received the split schedule. While patients with pleural effusions were not formally excluded from participation in this study, a brief analysis of toxicity data has shown that patients with mesothelioma experienced toxicities which were no worse than those experienced by the general study population.

## 1.4. Cisplatin

Currently, there is no standard chemotherapeutic treatment regimen for patients with malignant pleural mesothelioma. While many oncolytics, including anthracyclines, antifolates, and platinum-containing compounds have been investigated as single-agents, none has demonstrated distinctly superior response rates over any other. Additionally, reported response rates must be viewed with an appreciation and understanding of the difficulties in obtaining valid measurements of this tumor.

The single agent response rates for cisplatin in malignant mesothelioma have been reported to be roughly 14% (Dabouis et al 1977, Daboys et al 1979, Glatstein et al 1977, Hays et al 1977, Mintzen et al 1984, Rossoff et al 1972, Samson et al 1979). Because we have seen promising response rates in patients with mesothelioma who have received the combination of MTA plus cisplatin, and because comparing this regimen to single-agent cisplatin will allow us to isolate the value of MTA in the combination, we have chosen to utilize single-agent cisplatin as the comparator in this randomized trial.

The major toxicities of cisplatin include peripheral neuropathy, nausea/vomiting (both acute and delayed), nephrotoxicity, manifesting as an increase in blood urea nitrogen and serum creatinine, often with electrolyte disturbances, ototoxicity, myelosuppression, and occasional anaphylactic-like reactions. Nephrotoxicity is greater in patients who receive other potentially nephrotoxic drugs, especially aminoglycosides. The peripheral neuropathy is associated with cumulative doses greater than 300 mg/m$^2$. Ototoxicity is

often manifested as high-frequency hearing loss. Myelosuppression is typically mild with nadirs occurring at 14 to 21 days.

### 1.5. Rationale

MTA is a novel multitargeted antifolate which inhibits thymidylate synthase, dihyrofolate reductase and glycinamide formyltransferase. Single agent antitumor activity has been seen several Phase 2 clinical trials. As previously mentioned, a Phase 1 trial of MTA in combination with cisplatin has recently completed patient accrual, and has shown an encouraging level of activity in mesothelioma with manageable accompanying toxicity. These results suggest an encouraging response rate in this refractory tumor for which there is no proven treatment option. The current study aims to compare the objective response rate in patients with advanced malignant pleural mesothelioma who receive MTA plus cisplatin to the response rate in patients who receive cisplatin alone.

All patients in this study will receive vitamin supplementation with $B_6$, $B_{12}$, and folic acid, in amounts similar to those which would be found in a standard daily multivitamin. This level of supplementation, when given over 2 days, has been shown in previous studies to normalize homocysteine, which when elevated, is a strong predictor for severe neutropenia associated with MTA treatment. We therefore feel that vitamin supplementation may serve to reduce toxicity and aid in patient management. There exists a theoretical concern that because MTA is an antifolate, adding folic acid to the treatment protocol will result in reduced efficacy. The proposed level of supplementation is similar to that found in multivitamin tablets. There is no data from preclinical models that would suggest that this level of supplementation would reduce efficacy. Because palliation is a major goal of treatment in this tumor type, we feel that an attempt to reduce toxicity through vitamin supplementation is desirable and appropriate.

## 2. Objectives

### 2.1. Primary Objective

The primary objective of this study is to compare the tumor response in patients with advanced pleural mesothelioma when treated with MTA plus cisplatin combination therapy to the tumor response in the same patient population when treated with cisplatin alone.

### 2.2. Secondary Objectives

The secondary objectives of this study are:

- The comparison between the two treatment arms of time to event efficacy measures such as:

  -duration of response for responding patients

-time to progressive disease

-time to treatment failure

-survival time.

- The comparison of changes in disease related symptom (pain, analgesic consumption, dyspnea, weight, and performance status) between the two treatment arms.

- The comparison of the relative toxicities encountered when this patient population is treated with cisplatin alone versus the combination of cisplatin and MTA.
  - To assess pharmacokinetics (cytotoxics and folate) in all patients.
  - To collect information regarding vitamin metabolite status in this patient population.

# 3. Investigational Plan

## 3.1. Summary of Study Design

This is a randomized, Phase 3 study of cisplatin monotherapy versus the combination of cisplatin and MTA in patients with pleural mesothelioma who have received no prior chemotherapeutic regimens. Approximately 150 patients will be enrolled in this study and will be randomized to either Treatment A or Treatment B, defined as follows:

A. MTA, 500 mg/m$^2$, administered intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/m$^2$, administered intravenously over approximately 2 hours on Day 1 of each 21-day cycle. Because pharmacokinetic samples will be collected every patient, all infusion start and stop times must be accurately recorded. Patients will be pre- and post-hydrated according to local practice. Patients will also receive concomitant vitamin supplementation which will consist of two tablets orally, each containing 12.5 mg vitamin $B_6$, 1 mg vitamin $B_{12}$, and 0.5 mg folic acid, administered daily starting 7 days prior to the first dose of MTA (ie, 1-week lead-in period). The vitamin dosages will be halved (ie, to one tablet) starting on the first day of MTA therapy and will continue daily for as long as the patients remain on study.

B. Cisplatin, 75 mg/m$^2$, administered intravenously over approximately 2 hours on Day 1 of each 21-day cycle. Because pharmacokinetic samples will be collected every patient, all infusion start and stop times must be accurately recorded. Patients will be pre- and post-hydrated according to local practice. Patients will also receive concomitant vitamin supplementation which will consist of two tablets orally, each containing 12.5 mg vitamin $B_6$, 1 mg vitamin $B_{12}$, and 0.5 mg folic acid, administered daily starting 7 days prior to the first dose of cisplatin (ie, 1-week lead-in period). The vitamin dosages will be halved (ie, to one tablet) starting on the first day of cisplatin therapy and will continue daily for as long as the patients remain on study.

Patient randomization to treatment arms will be balanced for the following baseline prognostic factors: performance status, homocysteine levels, gender, degree of measurability of disease, white blood cell count, and histological subtype.

Cycles will be repeated until there is evidence of disease progression, unacceptable toxicity, the patient requests therapy be discontinued, if the investigator feels that it is not in the patient's best interest, or if Lilly, after consultation with the investigator, decides to discontinue the patient. Seventy-five qualified patients will be enrolled into each arm of the study.

## 3.2. Discussion of Design and Control

This is a randomized, controlled Phase 3 study of MTA plus cisplatin versus cisplatin alone in patients with pleural mesothelioma. According to data examined in a multivariate analysis across a variety of Phase 2 MTA studies, elevated baseline homocysteine levels (≥10 μM) strongly correlated with severe hematologic and nonhematologic toxicities following treatment with MTA (Niyikiza et al. 1998). Because of these correlations, this study will provide for balancing the numbers of patients with baseline homocysteine levels ≤10 μM or >10 μM equally across all treatment groups. Additional prognostic factors to be balanced include performance status, histological subtype, white blood cell count, and gender (Curran et al. 1998). Because both unidimensionally and bidimensionally measurable disease will be permitted, treatment arms will also be balanced for degree of measurability of disease.

## 3.3. Investigator Information

The names, titles, and institutions of the investigators are listed in the Contacts for Protocol H3E-MC-JMCH provided with this protocol.

If investigators are added after the study has been approved by Lilly, an ethical review board, or a regulatory agency, these additions will not be considered changes to the protocol, but the Contacts for Protocol H3E-MC-JMCH will be updated to provide this information.

### 3.3.1. Final Report Signature

The final report coordinating investigator will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The investigator with the most patients assigned to treatment groups will serve as the final report coordinating investigator.

## 3.4. Study Population

### 3.4.1. Entry Procedures

An informed consent will be obtained from each patient after the nature of the study is explained.

### 3.4.2. Criteria for Enrollment

**Enter** The act of obtaining informed consent for participation in a clinical study from individuals deemed potentially eligible to participate in the clinical study. Individuals *entered* into a study are those for whom informed consent documents for the study have been signed by the potential study participants or their legal representatives.

**Enroll** The act of assigning an individual to a treatment group. Individuals who are *enrolled* in the study are those who have been assigned to a treatment group.

A person who has been *entered* into the study is potentially eligible to be *enrolled* in the study, but must meet *all* criteria for enrollment specified in the protocol before being *enrolled* (assigned to a treatment group). Individuals who are *entered* into the study but fail to meet the criteria for enrollment are *not* eligible to participate in the study and will not be *enrolled*.

Adverse events are reported for all individuals who receive study drug. For the purposes of this study, "study drug" will be defined as any of the following: MTA, cisplatin, or vitamin supplementation or dexamethasone administered as described in the protocol.

#### 3.4.2.1. Inclusion Criteria

Patients may be included in the study only if they meet **all** of the following criteria:

[1] Histologically proven diagnosis of mesothelioma of the pleura in patients not candidates for surgery. Patients will be clinically staged using the IMIG TNM staging criteria (see Protocol Attachment JMCH.1). Patients may be entered and randomized based on local pathology; however, independent centralized review of pathology slides will be carried out on all patients.

[2] Disease status must be that of measurable or evaluable disease defined as:

*Measurable disease.* Bidimensionally measurable lesions with clearly defined margins by computerized tomography (CT). Examples of measurable disease would include a mediastinal or hilar node, or a discrete pleural mass. A CT scan will also be required for any palpable masses. For metastatic disease, this would include a clearly defined mass on CT.

*Evaluable disease.* Lesions apparent on CT which do not fit the criteria for bidimensionally measurable disease, such as unidimensionally measurable circumferential pleural thickening of the primary tumor. The thickening should be measurable on at least two contiguous sections of the CT scan.

**NOTE**: Pleural effusions are considered neither measurable nor evaluable.

[3] Patients may have undergone pleurodesis. If the original CT scan and pleurodesis occurred more than one week prior to the start of therapy, an additional CT scan is required, which will then be considered the baseline scan.

[4] Performance status of 70 or higher on the Karnofsky Scale (after any palliative measures including pleural drainage have occurred). See Protocol Attachment JMCH.2.

[5] Estimated life expectancy of at least 12 weeks.

[6] Patient compliance and geographic proximity that allow adequate follow-up.

[7] Adequate organ function including the following:

Adequate bone marrow reserve: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin $\geq 9$ g/dL.

Hepatic: bilirubin $\leq 1.5$ times the upper limit of normal, alkaline phosphatase, aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 3.0$ times normal (alkaline phosphatase, AST, ALT $\leq 5$ times normal is acceptable if liver has tumor involvement).

Albumin $\geq 2.5$ g/dL.

Renal: calculated creatinine clearance $\geq 45$ mL/min (see Protocol Attachment JMCH.3). NOTE: This is the formula for lean body mass.

[8] Signed informed consent from patient.

[9] Males or females at least 18 years of age.

[10] Male and female patients with reproductive potential must use an approved contraceptive method (eg, intrauterine device [IUD], birth control pills, or barrier device) during and for 3 months after the study.

### 3.4.2.2. Exclusion Criteria

Patients will be excluded from the study for **any** of the following reasons:

[11] Prior systemic chemotherapy. Prior intracavitary cytotoxic drugs or immunomodulators are not permitted, unless given for the purpose of pleurodesis.

[12] Prior radiation therapy to the target lesion, unless the lesion is clearly progressing and the interval between the most recent radiation therapy and enrollment is at least 4 weeks.

[13] Active infection (at the discretion of the investigator). Patients previously treated with a nephrotoxic antibiotic are at risk of further toxicity due to cisplatin and should be very carefully monitored.

[14] Pregnancy or breast feeding.

[15] Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator).

[16] Second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or other malignancy treated at least 5 years previously with no evidence of recurrence).

[17] Use of any investigational agent within 4 weeks before enrollment into the study.

[18] Inability to interrupt aspirin or other nonsteriodal anti-inflammatory agents 2 days before, the day of, and 2 days after the dose of MTA (5 days prior for long-acting agents such as piroxicam).

#### 3.4.2.3. Violation of Criteria for Enrollment

The criteria for enrollment must be followed explicitly. If there is inadvertent enrollment of individuals who do not meet enrollment criteria, these individuals should be discontinued from the study. Such individuals can remain in the study only if there are ethical reasons to have them continue. In these cases, the investigator must obtain approval from the Lilly clinical research physician for the study participant to continue in the study.

### *3.4.3. Disease Diagnostic Criteria*

Patients must have a histologic diagnosis of pleural mesothelioma. Study entry will not be restricted to patients with a particular stage of disease, but for the purposes of analysis, all patients must be staged prior to enrollment according to the International Mesothelioma Interest Group staging criteria (Protocol Attachment JMCH.1).

### *3.4.4. Sample Size*

A total of 75 patients will be randomized to each treatment arm. This sample size will give at least an 81% chance of detecting a difference between a treatment arm having a true tumor response rate of 0.35 and a treatment arm with a true response rate of 0.15. In

addition, this sample size gives the study a 5% chance of concluding falsely that there is a difference between the treatment arms if there is in fact no difference.

## 3.5. Patient Assignment

This is a competitive enrollment study. All patients will be randomized to receive the specified regimen of either MTA plus cisplatin or cisplatin alone. Randomization will be controlled by a computerized voice response unit at a central location for all study sites. Each patient's treatment assignment will be unknown until time of randomization. Randomization will be stratified as to investigational site, as well as to six baseline prognostic factors: performance status, degree of measurability of disease, histologic subtype, gender, baseline homocysteine levels, and baseline white blood cell count. For each prognostic factor, the following stratification will be performed:

- Performance status will have two strata:

  High: Baseline score = 90 or 100

  Low: Baseline score = 70 or 80
- Degree of measurability of disease will have two strata:

  Bidimensionally measurable disease

  Unidimensionally measurable disease
- Histological subtype will have two strata:

  Epithelial

  All others
- Baseline white blood cell count will have two strata:

  High: WBC $\geq 8.3 \times 10^9$/L

  Low: WBC $< 8.3 \times 10^9$/L
- Baseline homocysteine will have two strata:

  High: Baseline homocysteine >10μM/mL

  Low: Baseline homocysteine ≤10μM/mL
- Treatment arms will be stratified for gender.
- Each investigational site will be a stratum.

Patients will be balanced with respect to the study drug in each stratum for each prognostic factor, using the algorithm outlined in Pocok and Simon (Pocok et al 1975). This algorithm is discussed in detail in Protocol Attachment JMCH.4. The randomization probablility parameter P will be set at 0.75.

## 3.6. Dosage and Administration

### *3.6.1. Materials and Supplies*

#### 3.6.1.1. MTA

The drug product is composed of a 40 mg/mL aqueous solution of MTA and contains 2 mg/mL of the antioxidant monothioglycerol, which protects the MTA from air oxidation during processing and storage. Sodium hydroxide and/or hydrochloride acid solution may have been added during processing to adjust pH. Each vial contains MTA disodium equivalent to 200 mg, or 1000 mg of the base compound, MTA. The vials contain 0.3 mL/vial and 0.6 mL/vial excess to facilitate the withdrawal of the label amount 200 mg or 1000 mg, respectively. The drug product is stored at room temperature.

For purposes of clinical administration, the appropriate quantity of the contents of the vial(s) may be added to an intravenous bag or bottle containing sodium chloride for injection. The diluted formulation should be used within 24 hours. The vials of MTA contain no preservative, and as such are single use vials. Any unused portion of a vial may not be stored for future use and must be discarded.

#### 3.6.1.2. Cisplatin

Cisplatin is supplied as a 1 mg/mL solution in 10-mL or 50-mL vials. The total dose of cisplatin will be diluted to a volume of 1000 mL with 0.9% sodium chloride prior to infusion. The cisplatin solution should not be refrigerated. Prior to the administration of cisplatin the patient will be adequately hydrated.

### *3.6.2. Dosage Selection and Administration Procedures*

Each patient's body surface area should be recalculated based on height and weight prior to each cycle.

Patients will be randomized into either Treatment Arm A (combination of MTA and cisplatin) or Treatment Arm B (cisplatin alone). Patients will be prehydrated according to local practice prior to administration of either study drug.

All patients will also receive concomitant vitamin supplementation which will consist of two tablets orally, each containing 12.5 mg vitamin $B_6$, 1 mg vitamin $B_{12}$, and 0.5 mg folic acid, administered daily starting 7 days prior to the first dose of MTA or cisplatin (ie, 1-week lead-in period). The vitamin dosages will be halved (ie, to one tablet) starting on the first day of MTA therapy and will continue daily for as long as the patients remain on study.

Cycles will be repeated until there is evidence of disease progression, unacceptable toxicity, the patient requests therapy be discontinued, if the investigator feels that it is not in the patient's best interest, or if Lilly, after consultation with the investigator, decides to discontinue the patient.

**Treatment Arm A:**

MTA will be given as an intravenous infusion over approximately 10 minutes. A starting dose of 500 mg/m$^2$ will be administered every 21 days. Dexamethasone 4 mg, or equivalent should be taken orally twice per day on the day before, the day of, and the day after each dose of MTA.

Cisplatin will be given on Day 1 of each 21-day cycle beginning approximately 30 minutes after the end of administration of MTA. Patients will receive 75 mg/m$^2$ cisplatin as an infusion, over approximately 2 hours. Pre-hydration for cisplatin should occur prior to administration of either drug, and pre- and post-hydration should be administered according to local practice. However, a guideline is supplied in Protocol Attachment JMCH.5.

Because pharmacokinetic samples will be collected every patient, all infusion start and stop times must be accurately recorded.

**Treatment Arm B:**

Cisplatin will be given on Day 1 of each 21-day cycle. Patients will receive 75 mg/m$^2$ cisplatin as an infusion, over approximately 2 hours. Pre- and post-hydration for cisplatin should be administered according to local practice. However, a guideline is supplied in Protocol Attachment JMCH.5.

Because pharmacokinetic samples will be collected every patient, all infusion start and stop times must be accurately recorded.

### 3.6.2.1. Dose Adjustments for Subsequent Doses

**Treatment Arm A only:**

For Treatment Arm A only, dose adjustments at the start of a subsequent course of therapy will be based on nadir counts or maximal nonhematologic toxicity from the preceding cycle of therapy. ANC must be $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L prior to the start of any cycle. Treatment may be delayed to allow sufficient time for recovery. Upon recovery patients should be retreated using the guidelines in Tables JMCH.4.

**Table JMCH.4. Dose Adjustments for MTA and Cisplatin Based on Nadir Hematologic Values for Preceding Cycle – Treatment Arm A**

| Percent of Full Dose (both drugs) | ANC ($\times 10^9$/L) Nadir | | Platelets ($\times 10^9$/L) Nadir |
|---|---|---|---|
| 100% | ≥0.5 | and | ≥50 |
| 75% | <0.5 | and | ≥50 |
| 50% | <0.5 | and | <50 |
| Discontinue patient from study | | | Recurrence of Grade 3 or 4 after 2 dose reductions |

**Treatment Arm A and Treatment Arm B:**

Tables JMCH.5 and JMCH.6 document the relevant dose adjustments in case of neurosensory toxicity or mucositis for both Treatment Arm A and Treatment Arm B.

**Table JMCH.5. Neurosensory Toxicity**

| CTC Grade | Dose for Cisplatin (mg/m$^2$) | Dose for MTA (mg/m$^2$) |
|---|---|---|
| 0 - 1 | 100% of previous dose | 100% of previous dose |
| 2 | 50% of previous dose | 100% of previous dose |
| 3 | Omit Dose | Omit Dose |

**Table JMCH.6. Dose Modifications for Mucositis**

| CTC Grade | Dose for Next Cycle | |
|---|---|---|
| | MTA | cisplatin |
| Grade 0-2 | 100% of previous dose | 100% of previous dose |
| Grade 3 | 75% of previous dose | 100% of previous dose |
| Grade 4 | 50% of previous dose | 100% of previous dose |
| Recurrence of Grade 3 or 4 after treatment at 2 dose reductions | Discontinue patient from study | Discontinue patient from study |

In the event of diarrhea requiring hospitalization, the drug should be held until resolution to baseline before proceeding. Treatment should be restarted at a 25% dose reduction. For other nonhematologic effects greater than or equal to Grade 3 (with the exception of Grade 3 nausea/vomiting or transaminase elevations), the drug should be held until resolution to less than or equal to the patient's baseline value before proceeding. Treatment should restart at a 25% dose reduction if deemed appropriate by the treating physician.

In case of tinnitus or significant clinical hearing loss, cisplatin therapy should be reduced or stopped.

Once a dose reduction of either drug has been made, the patient will not be eligible for any dose escalations for the remainder of the protocol. A patient who cannot be administered the study drug for 42 days from time of last treatment must be discontinued from the study unless continuation is approved by Lilly.

#### 3.6.2.2. Cycle Delay for Subsequent Doses

If a patient develops a calculated creatinine clearance <45 mL/min, then the next cycle will not begin until the calculated creatinine clearance value is ≥45 mL/min. Re-testing is recommended at weekly intervals but will be conducted at the investigator's discretion. If a patient's calculated creatinine clearance has not returned to ≥45 mL/min within 42 days, the patient must be discontinued from the study unless continuation is approved by Lilly.

All patients must have baseline local and central creatinine clearance. If results from the central laboratory are not available for treatment decisions, patients may be treated based on calculated creatinine clearance using local serum creatinine and the formula in Protocol Attachment JMCH.3.

A patient who cannot be administered the study drug for 42 days from time of last treatment for any reason must be discontinued from the study unless approved by Lilly.

## 3.7. Blinding

This is an open-label, randomized study with the identity of the treatment known to the investigator, patient, and Eli Lilly and Company (Lilly).

## 3.8. Concomitant Therapy

Patients are allowed to receive full supportive care therapies concomitantly during the study. No other chemotherapy, immunotherapy, hormonal cancer therapy, radiation therapy, or experimental medications will be permitted while the patients are participating in this study. Any disease progression requiring other forms of specific antitumor therapy will be cause for early discontinuation in this study. The following concomitant therapies warrant special attention.

### *3.8.1. Colony Stimulating Factors*

Routine use of granulocyte colony stimulating factors (G-CSFs) is not permitted during this study. Patients should not receive G-CSFs prophylactically in any cycle. G-CSFs may be used only for patients who have AGC $<0.5 \times 10^9$/L for at least 5 days, neutropenic fever, or documented infections while neutropenic. G-CSFs must be discontinued at least 24 hours prior to the start of the next cycle of chemotherapy.

### 3.8.2. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Patients taking NSAIDs or salicylates will not take the NSAID 2 days before, the day of, or 2 days after receiving MTA. If a patient is taking a NSAID or salicylate with a long half-life (eg, naproxen, piroxicam, diflunisal, or nabumetone), it should not be taken 5 days before, the day of, or 2 days after receiving MTA.

### 3.8.3. Leucovorin

Leucovorin rescue is allowed for CTC Grade 4 leukopenia, CTC Grade 4 neutropenia lasting greater than 5 days, or CTC Grade 4 thrombocytopenia. Leucovorin should be started for CTC Grade 4 myelosuppression lasting 5 days or more beginning on the fifth day of CTC Grade 4 myelosuppression. Leucovorin should be started immediately if a patient develops CTC Grade 3 or 4 mucositis. The following doses and schedules are **recommended**:

- Leucovorin 100 mg/m$^2$ intravenously times one; then
- Leucovorin 50 mg/m$^2$ intravenously every 6 hours for 8 days.

**Note:** The primary mode of cytotoxicity of MTA is proposed to be inhibition of thymidylate synthase and it may be more appropriate to provide the end product of TS inhibition as a rescue agent, namely thymidine. Thymidine has been proposed as a reversal agent for severe toxicity from either 5-fluorouracil (5-FU) or methotrexate, but overall the clinical experience is limited (Abelson et al. 1983; Grem et al. 1991). Thymidine has been reported to reverse the severe toxicity associated with 5-FU in a patient with dihydropyrimidine dehydrogenase deficiency (Takimoto et al. 1996). Reversal of methotrexate toxicity has also been reported in patients with normal as well as impaired renal function (Widemann et al. 1997). Recently, one patient treated with MTA has received thymidine after developing severe toxicity. This patient developed severe myelosuppression as well as somnolence on Day 5 following MTA. Myelosuppression is an expected toxicity of MTA, but severe neurotoxicity is not a common toxicity. Leucovorin was administered for 24 hours, beginning on Day 6. Since the leucovorin did not appear to resolve the toxic effects, thymidine was administered for 3 days by continuous infusion at a dose of 8 g/m$^2$/day (Takimoto et al. 1996). Partial resolution of the neurotoxicity was noted after the first day of infusion and by the third day the patient had fully recovered.

### 3.8.4. Therapy for Diarrhea

In the event of CTC Grade 3 or 4 diarrhea, patients should receive hydration and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration), or associated with fever or severe neutropenia (Grade 3 or 4), broad spectrum antibiotics should be administered. Patients with severe diarrhea (requiring intravenous rehydration) with severe nausea or

vomiting must be hospitalized for intravenous hydration and correction of electrolyte imbalances.

### *3.8.5. Therapy for Febrile Neutropenia*

Patients experiencing febrile neutropenia, with or without diarrhea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

## 3.9. Efficacy and Safety Evaluations

See the schedule of events (Protocol Attachment JMCH.6), and Sections 3.9.1.1 and 3.9.2.2.

### *3.9.1. Efficacy*

#### 3.9.1.1. Efficacy Measures

Within 4 weeks of study enrollment each patient will have been assessed by computerized tomography of the chest and upper abdomen. Contrast medium should be used consistently throughout the study unless clinically contraindicated. The thickness of sections should be 10 mm and the spacing should be 10 mm. Scans should include the apex through the base of the lung. This method will be used consistently for tumor assessment and will be repeated every 6 weeks (prior to every other cycle). For each patient, every CT image will be compared to the corresponding image from the previous examination. To ensure identical localization of CT images, anatomical landmarks in vertebrae, ribs or the central bronchial tree will be used during the CT scanning procedure. The thickness of the tumorous parietal, visceral, diaphragmatic, and mediastinal pleura will be measured together with any enlarged lymph nodes in the mediastinum, rectrocural space or axillae.

**Within 2 weeks** of study enrollment the disease status of each patient will be assessed with the following procedures:

- Medical history and physical examination, including measurements of height and weight (in gown, without shoes, using a consistent scale)
- Evaluation of performance status (Karnofsky scale)
    - Dyspnea recorded using the dyspnea symptom scale (see Protocol Attachment JMCH.7)

**Seven days prior to the start of therapy with MTA or cisplatin,** patients will begin completing daily:

- Analgesic consumption documented in patient diary.

- Pain assessed by patient using a 100 mm visual analog scale (VAS) with endpoints labeled "no pain" and "worst possible pain".

At the stated intervals during the study, efficacy will be assessed in each patient by the following evaluations:

- Prior to each cycle of treatment:
  - Weight measurements (in gown, without shoes, using a consistent scale).
  - Performance status evaluation.
  - Limited medical history and physical examination.
  - Dyspnea symptom scale administered prior to consultation with physician and other procedures.
- Prior to every other treatment cycle:
  - CT scan for tumor measurement. After first documentation of response, the studies must be repeated 4 weeks later to confirm the response.

**Post Study Follow-Up**

For the purposes of follow-up for tumor response and time to event variables, the following assessments will take place at the stated intervals:

- One month after a responding patient has discontinued from the study:
  - CT scan for the purposes of response confirmation (for those patients who have experienced a partial or complete response which has been documented by lesion measurements).
- Every 3 months after the patient has discontinued from the study:
  - Information will be collected regarding date of disease progression or death, and any post study chemotherapy, radiotherapy, or surgical intervention.

### 3.9.1.2. Efficacy Criteria

The response status of each patient will be reviewed by a panel of independent investigators and may be reviewed by Eli Lilly and Company (Lilly). The measurability of a tumor is defined as follows (Green 1992):

**Disease Status**

- Measurable disease: Bidimensionally measurable lesions with clearly defined margins by 1) medical photograph (skin or oral lesions) or plain x-ray, with at least one diameter 0.5 cm or greater (bone lesions not included) or 2) CT, MRI, or other imaging scan, with both diameters greater than the distance between cuts of the imaging study or 3) palpation, with both diameters 2 cm or greater.
- Evaluable disease: Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease.
- Nonevaluable disease: Pleural effusions, ascites, disease documented by indirect evidence only (eg, by lab values).

All documented lesions are to be followed. If an organ has too many lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be documented and considered evaluable for the purpose of objective status determination. Included in the evaluations are the following standard criteria:

**Objective status** (to be recorded at each evaluation)

- Complete response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No disease-related symptoms. No evidence of nonevaluable disease, including normalization of markers and other abnormal lab values. All measurable, evaluable, and nonevaluable lesions and sites must be assessed using the same technique as baseline. Refers to clinical CR. When restaging surgery is required, a separate pathologic response variable is incorporated in the response data.
- Partial response (PR): Applies only to patients with at least one measurable lesion. Greater than or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. Nonmeasurable lesions must remain stable or regress for this category. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.
- Partial response in nonmeasurable disease (PRNM): Greater than 50% decrease in estimated area of evaluable, but nonmeasurable, tumor mass, as agreed upon by two independent observers, not to include pleural effusions. (Note: Response in patients with these specific types of evaluable disease and no measurable disease will be reported separately. Patients with both measurable and evaluable disease will be assessed for response according to the above criteria for partial response.)
- Stable/No response: Does not qualify for CR, PR, or progression. All measurable and evaluable sites must be assessed using the same techniques as baseline.
- Progression: 50% increase or an increase of 10 $cm^2$ (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR reappearance of any lesion which had disappeared, OR appearance of any new lesion/site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). For 'scan-only' bone disease, increased uptake does not constitute clear worsening. Worsening of existing nonevaluable disease does not constitute progression.
  Exceptions: In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond 4 weeks or there must be additional evidence of progression. Lesions which appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
- Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

**Notes**

1) Nonevaluable disease does not affect objective status except in determination of CR (all disease must be absent -- a patient who otherwise has a CR, but who has nonevaluable disease present or not assessed, will be classified as having a PR) and in determination of progression (if new sites of nonevaluable disease develop). Patients with only nonevaluable disease cannot be assessed for response.

2) For evaluable disease other than types specified in partial response in nonmeasurable disease, the only objective statuses which apply are CR, stable/no response, progression, and unknown.

3) Objective statuses must stay the same or improve over time until progression (unknown excepted).

4) PR and PRNM cannot apply to the same patient.

**Best Response**

Best response is determined from the sequence of objective statuses. Initial response will be based on baseline tumor measurements. Once a response is noted, this measurement becomes the new baseline. Subsequent responses will be compared to the new baseline.

- Disease assessment every 3 to 6 weeks: Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of PRNM or better before progression, but not qualifying for CR, are required for PRNM. Two determinations of stable/no response or better before progression, but not qualifying as CR, PR, or PRNM, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) will have a best response of increasing disease. Best response is unknown if the patient does not qualify for a best response of increasing disease and if all objective statuses after the first determination and before progression are unknown. **For CR, PR, or PRNM, response must be confirmed; a second assessment should be scheduled for 4 weeks after the first documentation of response.**

### 3.9.1.3. Definition of Efficacy Measures

A responder will be defined as any patient who exhibits a CR or PR. The duration of a CR or PR is defined as the time from first objective status assessment of CR or PR to the first time of progression or death due to any cause. Time-to-treatment failure is defined as the time from study entry to the first observation of disease progression, death due to any cause, or early discontinuation of treatment. Survival is defined as the time from study enrollment to time of death due to any cause.

All responses must be documented using appropriate diagnostic tests which must be repeated every 6 weeks to continue evaluation. **The same assessment method used to determine disease status at baseline will be used consistently for efficacy evaluation throughout the study.**

## *3.9.2. Safety*

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly to any event that seems unusual. See Section 3.9.2.1.1.

The investigator is responsible for appropriate medical care of study participants during the study in connection with protocol procedures.

After a study participant's completion of or discontinuation from the study, the investigator remains responsible to follow, through an appropriate health care option,

adverse events that are serious or that caused the study participant to discontinue before completing the study.

### 3.9.2.1. Clinical Adverse Events

Lilly has standards for reporting adverse events that are to be followed, regardless of applicable regulatory requirements that are less stringent. For purposes of collecting and evaluating *all* information about Lilly drugs used in clinical trials, a clinical trial adverse event is any undesirable experience that occurs after the patient has received the first dose of study drug without regard to the possibility of a causal relationship, without regard to treatment group assignment. Lack of drug effect is not an adverse event in clinical trials, because the purpose of the clinical trial is to establish drug effect.

At the first visit, study site personnel will question each patient and will note the occurrence and nature of presenting condition(s) and any pre-existing condition(s). At subsequent visits, site personnel will again question the patient and will note any change in the presenting condition(s), any change in the pre-existing condition(s), and/or the occurrence and nature of any adverse events.

Patients should be closely followed for adverse events while receiving study drug and for 30 days after the last dose of study drug (MTA, cisplatin, or vitamin) in order to detect delayed toxicity. After this period, investigators should only report serious adverse events which are felt to be causally related to study drug therapy.

#### *3.9.2.1.1. Adverse Event Reporting Requirements*

**All** adverse events must be reported to Lilly by clinical report form (CRF).

Study site personnel must report to Lilly immediately, by telephone, any **serious** adverse event (see Section 3.9.2.1.2 below). Remember that **all** adverse events must be reported by CRF, even if a telephone or fax report has been made. See Protocol Attachment JMCH.8 for information required when reporting serious adverse events.

If a patient's dosage is reduced or if a patient is discontinued from the study because of any significant laboratory abnormality, inadequate response to treatment, or any other reason, study site personnel must report and clearly document the circumstances and data leading to any such dosage reduction or discontinuation, using the designated clinical report form.

#### *3.9.2.1.2. Serious Adverse Events*

Study site personnel must report to Lilly immediately, by telephone, any adverse event from this study that includes one of the following criteria:

- death

- initial or prolonged inpatient hospitalization
- is life-threatening
- severe or permanent disability
- cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer)
- congenital anomaly
- is significant for other reason.

### 3.9.2.2. Clinical Laboratory Tests and Procedures

**Prestudy**

Prior to study enrollment each patient will have the following assessments (see Protocol Attachment JMCH.6).

Within 3 weeks of study enrollment:

- Vitamin metabolites: homocysteine, cystathionine, methylmalonic acid, methylcitrate (total, I and II). This blood sample will be drawn before vitamin supplementation is initiated.

Within 2 weeks of study enrollment:

- Vital signs (blood pressure, pulse rate, and temperature).
- Concomitant medication notation.

Within 7 days of study enrollment:

- Hematology: hemoglobin, red blood cells, WBC, platelets, neutrophils, bands, lymphocytes, monocytes, eosinophils, and basophils.
- Blood chemistries: bilirubin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, calcium, glucose, total protein, albumin, and electrolytes (sodium, potassium, magnesium, bicarbonate, and chloride).
- Urinalysis: protein, blood, bilirubin, specific gravity, and microscopic.
- Calculated creatinine clearance (see Protocol Attachment JMCH.3).

**During the Study**

The following tests and procedures will be performed at specific intervals during the study:

- Measurement of vital signs should be repeated as clinically indicated.
- Concomitant medication notation at every cycle.
- Number of units required for transfusions at every cycle.

- Hematology weekly (±3 days) and up to 4 days prior to each cycle.
- Blood chemistries on Day 8 (±3 days) and up to 4 days prior to each cycle
- Measurement of vitamin metabolites prior to receiving MTA or cisplatin on Day 1 of Cycle 1.
- Measurement of vitamin metabolites up to 4 days prior to the start of each cycle subsequent to the first cycle.
- Calculated creatinine clearance up to 4 days prior to the start of each cycle.
- Toxicity rating using the NCI CTC scale prior to each cycle (see the CTC Investigator Guide, Version 1.0, supplied with the clinical report form) (Cancer Therapy Evaluation Program 1998).
- Pharmacokinetic sampling from each patient during every other cycle beginning with Cycle 1.

**Note:** The central laboratory will perform the blood chemistries, calculated creatinine clearance, and urinalysis. Patients may be enrolled based on results of screening safety testing performed at a local laboratory. However, a specimen must be collected prior to the initiation of treatment and sent to the central laboratory for blood chemistries. These central laboratory results will be considered the baseline for subsequent safety analyses. The local laboratory will perform the hematology and baseline calculated creatinine clearance. Vitamin metabolite assays will be performed at Metabolite Laboratories Incorporated.

Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated by the investigator. Any clinically significant laboratory values that are outside a clinically acceptable range or differ importantly from a previous value should be further commented on in the CRF comments page.

**Follow-Up**

After each patient discontinues the study, the investigator should make every effort to continue to evaluate the patient for delayed toxicity by clinical and laboratory evaluations as clinically indicated. Every attempt should be made to obtain hematology, chemistry, and urinalysis 30 days post last dose. The patient must be followed every 30 days until toxicity resolves.

### *3.9.3. Safety Monitoring*

The Lilly clinical research physician will monitor safety data throughout the course of the study.

### 3.9.4. Appropriateness and Consistency of Measurements

Currently, there are no self-administered instruments for measuring dyspnea which have been validated for patients with mesothelioma. The EORTC QLQ-C30 and LC-13 is a validated, lung cancer-specific quality of life instrument which includes a dyspnea symptom scale (Aaronson et al 1993, Bergman et al 1994). Since not all the other items included in the QLQ-C30 and LC13 are relevant to mesothelioma, only the items which contribute to the dyspnea symptom scale will be included in the patient questionnaire (Protocol Attachment JMCH.7). The QLQ-C30 and LC13 have been validated in English, Danish, Dutch, Finnish, French, German, Greek, Hebrew, Hungarian, Italian, Japanese, Norwegian, Russian, Spanish, and Swedish. Only patients for which there is a validated translation will complete the dyspnea symptom scale.

Collection of dyspnea and pain data will not interfere with the routine collection of adverse event data reported by the patient nor will the sources of data be required to agree.

### 3.9.5. Pharmacokinetics and Pharmacodynamics

Blood samples will be collected for the analysis of MTA, folic acid, and total platinum (MTA plus cisplatin arm) and for total platinum (cisplatin alone arm) in plasma. In the MTA plus cisplatin arm, 5 blood samples will be collected every alternate cycle (1, 3, 5, etc.) for pharmacokinetic analysis of MTA, folic acid, and total platinum. Six blood samples will be collected every alternate cycle for pharmacokinetic analysis of cisplatin in the single agent cisplatin arm. Blood samples will be collected according to the schedule presented in Protocol Attachment JMCH.9. Some of the blood samples will be collected at random times to provide a more complete characterization of the MTA and cisplatin concentration-time profiles. Pharmacokinetic analysis will be performed by mixed-effect modeling methods using the NONMEM program. Total plasma clearance values for each patient will be used to calculate the area under the plasma concentration-time curve (AUC). Patient specific AUC values will be used as a measure of drug exposure in a multivariate analysis.

## 3.10. Patient Disposition Criteria

### 3.10.1. Discontinuations

A patient will be discontinued from the study under the following circumstances.

- If there is evidence of progressive disease.
- If the attending physician thinks a change of therapy would be in the best interest of the patient.
- If the patient requests discontinuation.

- If the patient experiences unacceptable toxicity due to study drug administration.
- If a patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).
- If the patient is noncompliant with study procedures, at the discretion of the investigator.
- If, in consultation with the investigator, Lilly uses its discretion as the sponsor to discontinue the patient.

### *3.10.2. Qualifications for Analysis*

All patients who receive at least one dose of MTA or cisplatin (Treatment Arm A) or one dose of cisplatin (Treatment Arm B) will be evaluated for safety.

All enrolled patients meeting the following criteria will be evaluated for efficacy:

- Histologic diagnosis of malignant pleural mesothelioma.
- No prior chemotherapy.
- No concurrent systemic chemotherapy or radiotherapy.
- Presence of unidimensionally or bidimensionally measurable disease.
- Treatment with at least one dose of both MTA and cisplatin (Treatment Arm A) or one dose of cisplatin (Treatment Arm B). A patient who discontinues from the study due to unacceptable drug toxicity prior to receiving one complete cycle of therapy will be included in the efficacy analysis.
- Each patient who has a baseline observation and at least one post-baseline observation will be included in the analysis of disease-related symptoms.

### *3.10.3. Study Extensions*

No extensions are planned in the study.

### *3.10.4. Post Study Follow Up*

## 3.11. Compliance

MTA and cisplatin will be intravenously administered only at the investigational sites. As a result, patient compliance monitoring is ensured. Patients who return for subsequent on-drug study visits will receive study drug unless they are encountering toxicity

problems or their disease has progressed. All patients who are discontinued from the study will receive a follow up visit 1 month after the study ends.

### 3.12. Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction in all sections of the protocol, the completion of the CRFs, and study procedures.
- Make periodic visits to the study site.
- Be available at all times for consultation and in contact with the study-site personnel by mail, telephone, and/or fax.
- Review and evaluate clinical report data and will use standard computer edits to detect errors in data collection.

To ensure accurate, complete, and reliable data, the investigator will do the following:

- Keep records of laboratory tests, clinical notes, and patient's medical records in the patient's files as original source documents for the study.
- Keep source documents for 15 years.

Lilly or its representatives may randomly check original source documents and clinical report forms at the study site. The study may be audited by Medical Quality Assurance (MQA) and/or regulatory agencies at any time. Investigators will be given notice before an MQA audit occurs.

Lilly or its representatives will randomly check original source documents and CRFs at the study site. The study may be audited by Lilly Quality Assurance and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

## 4. Data Analysis Methods

### 4.1. General Considerations

All confidence intervals for parameters to be estimated will be constructed with a significance level of $\alpha$=0.05 (ie, a 95% confidence interval). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The interpretation of study results will be the responsibility of the Lilly clinical research physician and the statistician. The Lilly clinical research physician and the statistician will also be responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication.

### 4.2. Data to Be Analyzed

The efficacy and safety analyses will be performed on data from qualified patients as described in Section 3.10.2.

## 4.3. Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- A definition of patient qualification.
- A summary of data on patient discontinuation.
- A summary of data on overall qualification status of all patients.
- An account of all identified protocol violations.

All patients entered in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

## 4.4. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics.
- Baseline disease characteristics.
- Baseline disease-related symptoms.
- Pre-existing conditions.
- Historical illness.
- Prior therapies.
- Concomitant drugs.

Other patient characteristics will be summarized as deemed appropriate.

## 4.5. Efficacy Analysis

All patients who meet the efficacy criteria for qualification will be evaluated for efficacy (Section 3.10.2).

The primary efficacy analysis will include a comparison of the objective tumor response rates between the cisplatin treatment arm and the MTA plus cisplatin treatment arm using Fisher's Exact test. The objective tumor response rate (for each arm) is define by:

$$\text{Response Rate} = \frac{\text{Number of CRs + PRs}}{\text{Number of patients qualified for efficacy analysis}}$$

Let:

$P_C$ = True tumor response rate on cisplatin monotherapy, and

$P_{MTA+C}$ = True tumor response rate on MTA plus cisplatin combination therapy.

A binomial test of the null hypothesis $H_0$ against the alternative hypothesis $H_1$ will be performed:

$H_0: P_{MTA+C} - P_C \leq 0.2$

$H_1: P_{MTA+C} - P_C > 0.2$

Secondary efficacy analyses will also be done regarding time to event efficacy measures and symptom improvement and will include the following:

- A comparison of patient survival between the two treatment arms using the Kaplan-Meier techniques. Kaplan-Meier analysis will also be performed for time to progressive disease, time to treatment failure, including quartiles for each variable in each treatment arm. Differences in these time to event efficacy variables will be compared using the log rank test to account for late events and the Wilcoxon test to account for early events. Kaplan-Meier analysis will be done using the PROC LIFETEST in Statistical Application Software® (SAS Institute 1989).
- Kaplan-Meier curves and quartiles for duration of response, if a sufficient number of responders is observed.
- Exploratory analysis relating survival, time to progressive disease, time to treatment failure, and duration of response to prognostic factors will be carried out using a variety of models, including the Cox proportional hazards model, the Cox model with time-dependent cofactors, the Anderson-Gill Multiplicative-Hazard Mode, the Wei-Lin-Weissfeld Marginal Model, and the Prentice-Williams-Peterson Conditional Model. The prognostic cofactors examined will include a number of visit-dependent lab, toxicity, as well as demographic and baseline disease characteristic measures (Andersen et al. 1982; Andersen et al. 1992; Cox 1972; Efron 1981; Le 1997; Lin 1994; Prentice et al. 1981; SAS Institute 1997; Slud et al. 1982; Therneau et al. 1997; Wei et al. 1989).
- A comparison of changes in performance status from baseline.
- A comparison of changes in weight from baseline.
- A comparison of changes in dyspnea symptom scale scores from baseline.
- A comparison of changes in pain and analgesic consumption from baseline.

## 4.6. Safety Analyses

All patients who are treated with at least one dose of study drug will be evaluated for safety. Safety analyses will include the following:

- Summaries of the number of blood transfusions required.
- Summaries of the adverse event rates and laboratory changes.
- Listings and frequency tables categorizing laboratory and nonlaboratory adverse events by maximum CTC toxicity grade and relationship to study drug.

## 4.7. Interim Analyses

No interim analyses are planned for this study.

# 5. Informed Consent, Ethical Review, and Regulatory Considerations

## 5.1. Informed Consent

The informed consent document will be used to explain in simple terms, before the patient is entered into the study, the risks and benefits to the patient. The informed consent document must contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time.

The investigator is responsible to see that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent and/or assent given by subjects, patients, or their legal representatives.

## 5.2. Institutional Review

The appropriate institutional review board(s) must approve the protocol and informed consent document, and if appropriate, agree to monitor the conduct of the study and agree to review it periodically. The investigator will provide Lilly with documentation that the institutional review board has approved the study before the study may begin.

In addition, the investigator must provide the following documentation.

- The institutional review board's annual reapproval of the protocol.
- The institutional review board's approvals of any revisions to the informed consent document or amendments to the protocol.

## 5.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to an Lilly representative (see Protocol Attachment JMCH.10).

# 6. References

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**Protocol Attachment JMCH.1**
**International Mesothelioma Interest Group**
**Staging Criteria for Mesothelioma**

# Protocol Attachment JMCH.1
# International Mesothelioma Interest Group Staging Criteria for Mesothelioma

## Primary Tumor (T):

| | | |
|---|---|---|
| **T1** | T1a | Tumor limited to the ipsilateral parietal including mediastinal and diaphragmatic pleura, no involvement of the visceral pleura |
| | T1b | Tumor involving the ipsilateral parietal including mediastinal and diaphragmatic pleura, scattered foci of tumor also involving the visceral pleura |
| **T2** | | Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: involvement of diaphragmatic muscle; confluent visceral pleural tumor (including the fissures), or extension of tumor from visceral pleura into the underlying plumonary parenchyma |
| **T3** | | Describes locally advanced but potentially resectable tumor: tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: involvement of the endothoracic fascia; extension into the mediastinal fat; solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall; non-transmural involvement of the pericardium |
| **T4** | | Describes locally advanced tecnically unresectable turmor: tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features: diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction; direct transdiaphragmatic extension of tumor to the peritoneum; direct extension of tumor to the contralateral pleura; direct extension of tumor to one or more mediastinal organs; direct extension of tumor into the spine; tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium |

## Lymph Nodes (N):

| | |
|---|---|
| **NX** | Regional Lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastases |
| **N1** | Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes |
| **N2** | Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary nodes |
| **N3** | Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes |

## Protocol Attachment JMCH.1
## International Mesothelioma Interest Group Staging Criteria for Mesothelioma, concluded

### Metastases (M):

| | |
|---|---|
| **MX** | Presence of distant metastases cannot be assessed |
| **M0** | No distant metastasis |
| **M1** | Distant Metastasis present |

### Staging:

| | |
|---|---|
| **Stage Ia** | $T_{1a}N_0M_0$ |
| **Stage Ib** | $T_{1b}N_0M_0$ |
| **Stage II** | $T_2N_0M_0$ |
| **Stage III** | Any $T_3M_0$, Any $N_1M_0$, Any $N_2M_0$ |
| **Stage IV** | Any $T_4$, Any $N_3$, Any $M_1$ |

**Protocol Attachment JMCH.2**
**Karnofsky Performance Status Scale**

## Protocol Attachment JMCH.2
## Karnofsky Performance Status Scale

| Activity Status | Point | Description |
|---|---|---|
| Normal Activity | 100 | Normal, with no complaints or evidence of disease |
| | 90 | Able to carry on normal activity but with minor signs or symptoms of disease present |
| | 80 | Normal activity but requiring effort; signs and symptoms of disease more prominent |
| Self-Care | 70 | Able to care for self, but unable to work or carry on other normal activities |
| | 60 | Able to care for most needs but requires occasional assistance |
| | 50 | Considerable assistance required, along with frequent medical care; some self-care still possible |
| Incapacitated | 40 | Disabled and requiring special care and assistance |
| | 30 | Severely disabled; hospitalization required but death from disease not imminent |
| | 20 | Extremely ill, supportive treatment, hospitalized care required |
| | 10 | Imminent death |
| | 0 | Dead |

**Protocol Attachment JMCH.3**
**Calculated Creatinine Clearance**

**Protocol Attachment JMCH.3**
**Calculated Creatinine Clearance**
**Modified Cockcroft and Gault**

Weight in kg (W)

Height in cm (H)

Age in years (A)

Serum creatinine in mg/dL (C)

**Lean Body Weight (LBW) Males**

0.32810 × (W) = _____
0.33929 × (H) = + _____
- 29.5336
LBW = _____

**Lean Body Weight (LBW) Females**

0.29569 × (W) = _____
0.41813 × (H) = + _____
- 43.2933
LBW = _____

**Calculated creatinine clearance**

$\frac{[140 - (A)] \times (LBW)}{71 \times (C)}$ = mL/min

**Serum creatinine conversion**

µmol/L × 0.0113 = mg/dL

**Protocol Attachment JMCH.4**
**Discussion of Randomization and Stratification**

## Protocol Attachment JMCH.4
## Discussion of Randomization and Stratification

**Randomization and Stratification:**

It is desired to avoid imbalance on the following prognostic variables: baseline performance status, baseline homocysteine, degree of measurability of the disease, histology, baseline WBC, gender, and investigator site. The methodology to be used follows the design as outlined in Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial by Pocok and Simon. The methodology will be described here in the context of an example, using the prognostic variables in the current protocol.

**Setup**

In this example, it is assumed that there are eight centers. Levels of the different prognostic variables are as follows:

| Stratification Variable | Abbreviation | Levels |
|---|---|---|
| Baseline Performance Status | KPS | Low (70-80) and High (90-100) |
| Baseline Homocysteine | Hcys | Low (<10μM/mL) and High (≥10μM/mL) |
| Disease Measurability | DM | Bidimensional and Unidimensional |
| Histology Subtype | HS | Epithelial and Others |
| Baseline WBC | WBC | Low (<8.3x10$^9$/L) and High (≥8.3x10$^9$/L) |
| Gender | Gender | M and F |
| Investigation Center | IC | C1, C2, C3, C4, C5, C6, C7, and C8 |

A new patient is eligible for randomization. This patient is at center C6, and has the following baseline prognostic factor information: KPS=90 (high), DM=Bidimensional, HS=Epithelial, WBC=Low, Hcys=16 (High), Gender=F. The current database is as follows:

## Protocol Attachment JMCH.4 (continued)
## Discussion of Randomization and Stratification

### Current Database

| IC | MTA+Cis | Cis |
|---|---|---|
| C1 | 1 | 2 |
| C2 | 5 | 3 |
| C3 | 3 | 1 |
| C4 | 1 | 0 |
| C5 | 2 | 2 |
| C6 | 3 | 4 |
| C7 | 1 | 0 |
| C8 | 2 | 0 |
| **Total** | 18 | 12 |

| DM | MTA+Cis | Cis |
|---|---|---|
| Bidim | 16 | 9 |
| Unidim | 2 | 3 |
| **Total** | 18 | 12 |

| KPS | MTA+Cis | Cis |
|---|---|---|
| Low (70-80) | 7 | 3 |
| High (90-100) | 11 | 9 |
| **Total** | 18 | 12 |

| HS | MTA+Cis | Cis |
|---|---|---|
| Epithelial | 15 | 11 |
| Others | 3 | 1 |
| **Total** | 18 | 12 |

| Hcys | MTA+Cis | Cis |
|---|---|---|
| High(≥10μM/mL) | 3 | 1 |
| Low(<10μM/mL) | 15 | 11 |
| **Total** | 18 | 12 |

| Gender | MTA+Cis | Cis |
|---|---|---|
| Female | 5 | 5 |
| Male | 13 | 7 |
| **Total** | 18 | 12 |

| WBC | MTA+Cis | Cis |
|---|---|---|
| Low (<8.3x10$^9$/L) | 4 | 4 |
| High (≥8.3x10$^9$/L) | 14 | 8 |
| **Total** | 18 | 12 |

The amount of imbalance among the levels for the 31st patient in baseline prognostic variables can be measured by summing the ranges between MTA + cisplatin and cisplatin for each prognostic variable.

| | MTA+cis | Cis | Range |
|---|---|---|---|
| Center C6 | 3 | 4 | 1 |
| High KPS | 11 | 9 | 2 |
| High homocysteine | 3 | 1 | 2 |
| Bidimensional disease | 14 | 9 | 5 |
| Epithelial disease | 15 | 11 | 4 |
| Female | 5 | 5 | 0 |
| Low WBC | 4 | 4 | 0 |
| **Total** | | | **14** |

## Protocol Attachment JMCH.4 (concluded)
## Discussion of Randomization and Stratification

**Implications of the Allocation**

If the 31st patient is allocated to MTA + cisplatin, the overall measure of imbalance would increase:

| | MTA+cis | Cis | Range |
|---|---|---|---|
| Center C6 | 4 | 4 | 0 |
| High KPS | 12 | 9 | 3 |
| High homocysteine | 4 | 1 | 3 |
| Bidimensional disease | 15 | 9 | 6 |
| Epithelial disease | 16 | 11 | 5 |
| Female | 6 | 5 | 1 |
| Low WBC | 5 | 4 | 1 |
| **Total** | | | **19** |

If the 31st patient is allocated to cisplatin, the overall measure of imbalance would decrease:

| | MTA+cis | Cis | Range |
|---|---|---|---|
| Center C6 | 3 | 5 | 2 |
| High KPS | 11 | 10 | 1 |
| High homocysteine | 3 | 2 | 1 |
| Bidimensional disease | 14 | 10 | 4 |
| Epithelial disease | 15 | 12 | 3 |
| Female | 5 | 6 | 1 |
| Low WBC | 4 | 5 | 1 |
| **Total** | | | **13** |

**Allocation Rule**

The treatment allocation which results in a smaller overall measure of imbalance is allocated with probability P = 0.75. In this case, it is cisplatin. Therefore, the 31st patient receives cisplatin with probability P = 0.75. If the measures of imbalance are equal for both groups, then the probability of allocation to both groups equals probability P = 0.50.

**Protocol Attachment JMCH.5**
**Guideline for Pre- and Post-Hydration for Cisplatin**

## Protocol Attachment JMCH.5
## Guideline for Pre- and Post-Hydration for Cisplatin

This is only a guideline, pre- and post-hydration for cisplatin administration should be administered according to local practice.

Prior to cisplatin administration there will be pre-hydration with 1500 mL of dextrose saline over 3 hours, with 10 mEq of potassium chloride (KCl) and 750 mg of magnesium sulfate added to each 500 mL. A 250 mL ampule of 10% mannitol will be administered prior to and after each cisplatin infusion.

After the cisplatin infusion, there will be a 3-hour infusion of 1500 mL of dextrose saline together with 10 mEq KCl and 750 mg of magnesium sulfate per 500 mL dextrose saline.

**Protocol Attachment JMCH.6**
**Schedule of Events**

## Protocol Attachment JMCH.6
## Schedule of Events

| Cycle/Visit | 0 | 1 | | | 2 | | | 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Relative Day Within a Cycle | | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 |
| Relative Day | baseline | 1 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 57 |
| Informed consent | X | | | | | | | | | |
| **Treatment Arm A** | | | | | | | | | | |
| MTA/cisplatin therapy | | X | | | X | | | X | | |
| **Treatment Arm B** | | | | | | | | | | |
| cisplatin therapy | | X | | | X | | | X | | |
| **All patients** | | | | | | | | | | |
| Physical examination[a] | X | | | | X | | | X | | |
| Medical history[a] | X | | | | X | | | X | | |
| Weight[a] | X | | | | X | | | X | | |
| Height | X | | | | | | | | | |
| Karnofsky performance status | X | | | | X | | | X | | |
| CT scan for tumor measurement[a,b] | X | | | | | | | X | | |
| Dyspnea Symptom Scale[c] | X | | | | X | | | X | | |
| Analgesic Consumption[d] | X | | X | X | X | X | X | X | X | X |
| Pain Assessment[d] | X | | X | X | X | X | X | X | X | X |
| Vital signs[e] | X | | | | | | | | | |
| Concomitant meds notation | X | | | | X | | | X | | |
| Chemistry[f] | X | | X | | X | X | | X | X | |
| Hematology[f] | X | | X | X | X | X | X | X | X | X |
| Urinalysis[e] | X | | | | | | | | | |
| Calculated creatinine clearance[f] | X | | | | X | | | X | | |
| Vitamin metabolites[f] | X | X | | | X | | | X | | |
| Pharmacokinetic samplings[g] | | X | | | | | | X | | |
| Toxicity rating[a] | | | | | X | | | X | | |

a - Obtain prior to infusion.

b - Repeat prior to every other cycle; after documentation of response; confirm with studies 4 weeks later.

c - To be administered prior to consultation with physician or other assessments.

d - Will be documented daily by each patient; investigational site will record weekly averages.

e - Repeat as clinically indicated.

f - Obtain up to 4 days prior to each cycle.

g - Pharmacokinetic samples will be collected from each patient in every other cycle beginning with Cycle 1. See sampling schedule in Protocol Attachment JMCH.9.

**Protocol Attachment JMCH.7**
**Dyspnea Symptom Scale**

## Protocol Attachment JMCH.7
## Dyspnea Symptom Scale

Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

**Today's date** __/__/__
DD/MM/YY

| During the Past Week: | Not At All | A Little | Quite A Bit | Very Much |
|---|---|---|---|---|
| 1. Were you short of breath? | 1 | 2 | 3 | 4 |
| 2. Were you short of breath when you rested? | 1 | 2 | 3 | 4 |
| 3. Were you short of breath when you walked? | 1 | 2 | 3 | 4 |
| 4. Were you short of breath when you climbed stairs? | 1 | 2 | 3 | 4 |

**Protocol Attachment JMCH.8**
**Recommendations for Reporting of Serious Adverse Events**

## Protocol Attachment JMCH.8
## Recommendations for Reporting of Serious Adverse Events

When telephoning the Lilly office to report a serious adverse event, please have the following information available:

Patient Demographics
- patient identification (number)
- sex
- date of birth
- race

Study Identification
- protocol number
- investigator's name

Test Drug
- drug code or drug name
- unit dose
- total daily dose
- frequency
- route
- start dose

Adverse Event
- description
- date of onset
- severity
- treatment (including hospitalization)
- action taken with respect to test drug
- clinical significance
- test results (if applicable)

Relationship to Test Drug

Concomitant Drug Therapy
- indication
- total daily dose
- duration of treatment

In Case of Death
- cause
- autopsy findings (if available)

## Protocol Attachment JMCH.9
## Pharmacokinetic Sampling Instructions

## Protocol Attachment JMCH.9
## Pharmacokinetic Sampling Instructions

### PK SAMPLING SCHEDULE

Blood samples for the analysis of MTA, folic acid, and total platinum in plasma should be collected for the cisplatin and MTA arm. Blood samples for the analysis of total platinum in plasma should be collected for the single agent cisplatin arm. Blood samples should be collected every other cycle starting with the first cycle (Cycle 1). The schedule for blood sampling times is provided in the following tables. Blood samples should be drawn as closely as possible to these times. **It is very important that the actual date and clock time of the start and end of infusion and of all blood samples be documented.**

**Blood Sampling Scheme for MTA + Cisplatin**

| # | Time | Sample | LY231514 (MTA) | Folic Acid | Cisplatin |
|---|---|---|---|---|---|
| 1 | 0 | Predose Sample | x | x | x |
| 2 | 9.5 min | Prior to End of MTA infusion | x | x | - |
| 3 | 2 hr 40 min | Prior to end of cisplatin infusion | x | x | x |
| 4 | 4 - 12 hr | Random sample collected between 4 and 12 hours | x | x | x |
| 5 | 24 hr | 24 hours after start of MTA | x | x | x |
| 6 | 168 hr | 168 hours after start of MTA | - | - | x |

## Randomization table for blood sample #4

| Patient # | Blood Sample #4 |
|---|---|
| 1 | 5 hr |
| 2 | 12 hr |
| 3 | 7 hr |
| 4 | 6 hr |
| 5 | 12 hr |
| 6 | 12 hr |
| 7 | 8 hr |
| 8 | 8 hr |
| 9 | 4 hr |
| 10 | 4 hr |
| 11 | 11 hr |
| 12 | 8 hr |
| 13 | 11 hr |
| 14 | 4 hr |
| 15 | 12 hr |
| 16 | 6 hr |
| 17 | 6 hr |
| 18 | 10 hr |
| 19 | 12 hr |
| 20 | 6 hr |
| 21 | 10 hr |
| 22 | 7 hr |
| 23 | 9 hr |
| 24 | 6 hr |
| 25 | 8 hr |
| 26 | 11 hr |
| 27 | 9 hr |
| 28 | 9 hr |
| 29 | 9 hr |
| 30 | 7 hr |
| 31 | 10 hr |
| 32 | 8 hr |
| 33 | 12 hr |
| 34 | 12 hr |
| 35 | 9 hr |
| 36 | 6 hr |
| 37 | 7 hr |
| 38 | 8 hr |
| 39 | 10 hr |
| 40 | 5 hr |
| 41 | 5 hr |
| 42 | 11 hr |

| | |
|---|---|
| 43 | 6 hr |
| 44 | 12 hr |
| 45 | 12 hr |
| 46 | 9 hr |
| 47 | 4 hr |
| 48 | 5 hr |
| 49 | 8 hr |
| 50 | 7 hr |
| 51 | 5 hr |
| 52 | 9 hr |
| 53 | 7 hr |
| 54 | 5 hr |
| 55 | 8 hr |
| 56 | 5 hr |
| 57 | 9 hr |
| 58 | 10 hr |
| 59 | 7 hr |
| 60 | 4 hr |
| 61 | 8 hr |
| 62 | 7 hr |
| 63 | 4 hr |
| 64 | 10 hr |
| 65 | 12 hr |
| 66 | 8 hr |
| 67 | 12 hr |
| 68 | 10 hr |
| 69 | 4 hr |
| 70 | 5 hr |
| 71 | 6 hr |
| 72 | 9 hr |
| 73 | 7 hr |
| 74 | 4 hr |
| 75 | 7 hr |

## Blood Sampling Scheme for Cisplatin

| # | Time | Sample |
|---|---|---|
| 1 | 0 | Predose Sample |
| 2 | 2 hr | Prior to end of Cisplatin infusion |
| 3 | 3 - 5 hr | Random sample collected between 2 and 4 hours |
| 4 | 6 - 12 hr | Random sample collected between 6 and 12 hours |
| 5 | 24 hr | 24 hours after start of Cisplatin |
| 6 | 168 hr | 168 hours after start of Cisplatin |

## Randomization table for blood samples #3 and #4

| Patient # | Blood Sample #3 | Blood Sample #4 |
|---|---|---|
| 1 | 3 hr 15 min | 7 hr |
| 2 | 5 hr | 12 hr |
| 3 | 3 hr 45 min | 8 hr |
| 4 | 3 hr 30 min | 7 hr |
| 5 | 5 hr | 12 hr |
| 6 | 5 hr | 12 hr |
| 7 | 4 hr | 9 hr |
| 8 | 4 hr | 9 hr |
| 9 | 3 hr | 6 hr |
| 10 | 3 hr | 6 hr |
| 11 | 4 hr 45 min | 11 hr |
| 12 | 4 hr | 9 hr |
| 13 | 4 hr 45 min | 11 hr |
| 14 | 3 hr | 6 hr |
| 15 | 5 hr | 12 hr |
| 16 | 3 hr 30 min | 8 hr |
| 17 | 3 hr 30 min | 7 hr |
| 18 | 4 hr 30 min | 10 hr |
| 19 | 5 hr | 12 hr |
| 20 | 3 hr 30 min | 7 hr |
| 21 | 4 hr 30 min | 10 hr |
| 22 | 3 hr 45 min | 8 hr |
| 23 | 4 hr 15 min | 9 hr |
| 24 | 3 hr 30 min | 8 hr |
| 25 | 4 hr | 9 hr |
| 26 | 4 hr 45 min | 11 hr |
| 27 | 4 hr 15 min | 10 hr |
| 28 | 4 hr 15 min | 10 hr |
| 29 | 4 hr 15 min | 10 hr |
| 30 | 3 hr 45 min | 8 hr |
| 31 | 4 hr 30 min | 11 hr |
| 32 | 4 hr | 9 hr |
| 33 | 5 hr | 12 hr |
| 34 | 5 hr | 12 hr |
| 35 | 4 hr 15 min | 10 hr |
| 36 | 3 hr 30 min | 8 hr |
| 37 | 3 hr 45 min | 8 hr |
| 38 | 4 hr | 9 hr |
| 39 | 4 hr 30 min | 10 hr |
| 40 | 3 hr 15 min | 7 hr |
| 41 | 3 hr 15 min | 7 hr |
| 42 | 4 hr 45 min | 12 hr |

| | | |
|---|---|---|
| 43 | 3 hr 30 min | 8 hr |
| 44 | 5 hr | 12 hr |
| 45 | 5 hr | 12 hr |
| 46 | 4 hr 15 min | 9 hr |
| 47 | 3 hr | 6 hr |
| 48 | 3 hr 15 min | 6 hr |
| 49 | 4 hr | 9 hr |
| 50 | 3 hr 45 min | 9 hr |
| 51 | 3 hr 15 min | 7 hr |
| 52 | 4 hr 15 min | 10 hr |
| 53 | 3 hr 45 min | 8 hr |
| 54 | 3 hr 15 min | 6 hr |
| 55 | 4 hr | 9 hr |
| 56 | 3 hr 15 min | 7 hr |
| 57 | 4 hr 15 min | 10 hr |
| 58 | 4 hr 30 min | 11 hr |
| 59 | 3 hr 45 min | 9 hr |
| 60 | 3 hr | 6 hr |
| 61 | 4 hr | 9 hr |
| 62 | 3 hr 45 min | 8 hr |
| 63 | 3 hr | 6 hr |
| 64 | 4 hr 30 min | 10 hr |
| 65 | 5 hr | 12 hr |
| 66 | 4 hr | 9 hr |
| 67 | 5 hr | 12 hr |
| 68 | 4 hr 30 min | 10 hr |
| 69 | 3 hr | 6 hr |
| 70 | 3 hr 15 min | 7 hr |
| 71 | 3 hr 30 min | 7 hr |
| 72 | 4 hr 15 min | 10 hr |
| 73 | 3 hr 45 min | 8 hr |
| 74 | 3 hr | 6 hr |
| 75 | 3 hr 45 min | 8 hr |

## Protocol Attachment JMCH.10
## Protocol Signatures

# Protocol Signatures
# Protocol H3E-MC-JMCH

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with Eli Lilly and Company (or subsidiary).

Instructions to the investigator: Please SIGN and DATE both copies of this signature page and PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the completed, signed copies to Lilly.

_____ _____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility
(City, State (if applicable), Country)

_____ _____

Signature of Representative of
Eli Lilly and Company (or Subsidiary)
David Seitz, MD PhD
Medical Advisor
Lilly Research Laboratories

Date

# Protocol Signatures
# Protocol H3E-MC-JMCH

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with Eli Lilly and Company (or subsidiary).

Instructions to the investigator: Please SIGN and DATE both copies of this signature page and PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the completed, signed copies to Lilly.

_____ _____

Signature of Investigator Date

_____

Investigator Name

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility
(City, State (if applicable), Country)

_____ _____

Signature of Representative of
Eli Lilly and Company (or Subsidiary)
David Seitz, MD PhD
Medical Advisor
Lilly Research Laboratories

Date

Appendix 8

# Appendix 8
# List of Completed, Ongoing, and Planned Studies

## Summary of Clinical Trials - Completed

| Study Investigator / Coordinating center / Number of center(s) / Report number | Design | Number of Patients With Age and Sex | Diagnosis Plus Criteria for Inclusion | Test Product / Dosage / Regimen / Route of Administration | Criteria for Evaluation |
|---|---|---|---|---|---|
| H3E-MC-JMAB<br>Dr. Daniel D. VonHoff<br>University of TX Health Science Center at San Antonio<br>4 Centers | Phase I, Open label, Dose-escalating | N=24 | Metastatic or advanced cancer; solid tumor refractory to standard therapy | MTA IV once every 7 days for 4 weeks, followed by 2 weeks of rest; dose-escalating: 10mg/m$^2$ to 1000mg/m$^2$ by MCR method<br>MTD 30 mg/m$^2$/wk | Received 1 dose of MTA |
| H3E-MC-JMAA<br>Dr. Daniel D. VonHoff<br>University of TX Health Science Center at San Antonio<br>4 Centers | Phase I, Open label, Dose-escalating | N=37<br>18+ years of age<br>Male and female | Metastatic or advanced cancer; solid tumor refractory to standard therapy | MTA IV (10 minute infusion) every 21 days; dose- escalating: 50 mg/m$^2$ to 900 mg/m$^2$ by MCR method<br>MTD 600 mg/m$^2$ | Received 1 dose of MTA |
| H3E-BP-001<br>Dr. J. Cassidy & Prof. S. Kaye<br>Beatson Oncology Center-Glasgow<br>Prof. A. H. Calvert<br>Regional Radiotherapy Center - New Castle<br>UK - 2 Center | Phase I, Open label, Dose-Escalating | N=38<br>18-75 years of age<br>Male and female | Metastatic or advanced cancer; solid tumor refractory to standard therapy. | MTA IV daily for 5 days every 21 days; dose-escalating: starting at 0.2mg/m$^2$.<br>MTD 4 mg/m$^2$/day | Completed 1 course of MTA |

## Summary of Clinical Trials - Completed

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMAC<br>Dr. Patrick Loehrer Indiana University Medical Center<br>7 Centers | Phase 2<br>Open-label<br>Non-random | N=39<br>18+ years of age<br>Male and female | Metastatic colorectal cancer not amenable to curative surgery or radiation | MTA IV (10 minute infusion) every 21 days;<br>dose of 600 mg/m$^2$ | Received 2 doses of MTA |

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMAD<br>Dr. Patrick Loehrer Indiana University Medical Center<br>7 Centers | Phase 2<br>Open-label<br>Non-random | N=35<br>18+ years of age<br>Male and female | Unresectable adenocarcinoma of the exocrine pancreas, Stage II-IV, no prior chemotherapy, not amenable to curative surgery or radiation | MTA IV (10 minute infusion) every 21 days;<br>dose of 600 mg/m$^2$ | Received 2 doses of MTA |
| H3E-MC-JMAG<br>Dr. Coleman<br>Western Park Hospital - Sheffield<br>Dr. Lind<br>Newcastle General Hosp. - Newcastle<br>Dr. Miles<br>Guys Hospital - London<br>Dr. I. E. Smith<br>Roayal Marsden Hosp. - London<br>UK - 4 Centers | Phase II,<br>Open-Label,<br>Non-Randomized | N=36<br>18+ years of age<br>Female | Histologic or cytologic diagnosis of locally advanced or metastatic breast cancer, not amenable to surgery or radiation. No more than one prior chemotherapy regimen for metastatic disease | MTA (approximately 10 minute infusion) every 21 days; Dose 600mg/m$^2$ | Received 2 doses of MTA |
| H3E-MC-JMAH<br>Dr. Carmichael<br>Nottingham City Hosp. - Nottingham<br>Dr. Harper<br>Guys Hospital<br>Dr. Geddes<br>Groote Schuur Hospital - Cape Town<br>Dr. Goedhals<br>National Hospital - Bloemfontein<br>4 Sites, 2 UK, 2 South Africa | Phase II,<br>Open-Label,<br>Non-Randomized | N=35<br>18+ years of age<br>Male and female | Inoperable, locally advanced recurrent or metastatic esophageal cancer. No prior chemotherapy. | MTA IV (over approximately 10 minutes) every 21 days; dose 600mg/m$^2$ | Received 2 doses of MTA. |

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMAL<br>Dr. Millward, Peter MacCallum Cancer Inst.-East Melbourne, Australia<br>Dr. Ackland, Newcastle Mater Hosp., Waratah Australia<br>Dr. Clark, Royal Prince Alfred Hospital, Camoerdon, Australia<br>Dr. Abratt, Groote Schur Hospital, Cape Town, South Africa<br>Dr. Goedhals, National Hospital, Bloenfontein South Africa<br>5 sites; 3 Australia, 2 South Africa | Phase II<br>Open-Label, Non-Randomized | N=53<br>18+ years of age<br>Male and female | Inoperable locally advanced recurrent or metastatic NSCLC.<br>No prior chemotherapy | MTA IV (over approximately 10 minutes) every 21 days; dose 600 mg/m$^2$ | Received 2 doses of MTA |
| H3E-MC-JMAN<br>Multi-Site, Multi-Investigator<br>NCIC | Phase II,<br>Open-Label, Non-Randomized | N=33<br>16+ years of age<br>Male and female | Locally advanced or metastatic NSCLC not eligible for curative radiotherapy or surgery | MTA IV (over approximately 10 minutes) every 21 days; dose 500mg/m$^2$ | Received 2 doses of MTA |
| H3E-MC-JMAO<br>Multi-Site, Multi-Investigator<br>NCIC | Phase II,<br>Open-Label, Non-Randomized | N=32<br>16+ years of age<br>Male and female | Locally advanced or metastatic colorectal cancer | MTA IV (over approximately 10 minutes) every 21 days; dose 500mg/m$^2$ | Received 2 doses of MTA |
| H3E-MC-JMAP<br>Dr. A. R. Hanauske<br>Klinikum Rechts Der Isar<br>I.Medizin. Klinik Und Poliklinik<br>Abt. F. Haematologie U. Onkologie<br>Ismaninger Str. 22<br>Muenchen D-81675<br>GERMANY<br>1 Site - Germany | Phase I,<br>Open-Label, Dose-Escalating | N=50<br>18+ years of age<br>Male and female | Locally advanced or metastatic cancer. Solid tumor refractory to standard therapy. | MTA IV (over approximately 10 minutes) on Day 1 every 21 days. Cis-platin 30 minutes following (over approximately 120 minutes). MTA starting dose 300mg/m$^2$ to 900mg/m$^2$ and Cisplatin starting dose 60mg/m$^2$ to 100mg/m$^2$ using MCR method. Study extension with Cisplatin being given 24 hours after MTA. | Received 1 dose of MTA and Cisplatin |

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMBB<br>CRO: IPI<br>14785 Omicron<br>Suite 101<br>San Antonio, TX 78245-3201 | Phase 2,<br>open label<br>non-random | N=75<br>18+ years of age<br>Male and female | 5-FU AND Irinotecan refractory colorectal cancer | MTA<br>500mg/m$^2$<br>over approximately 10 minutes every 21 days IV.<br>4mg/m$^2$ Dexamethasone 2x day before, of and after MTA infusion | Received 1 dose of MTA |
| H3E-MC-JMAY<br>This study is being conducted in Germany and Austria | Phase 2,<br>open label<br>non-random | N=35<br>19+ years of age<br>Male and female | Stage IIIb or IV NSCLC,<br>chemonaive, | MTA, 500 mg/m$^2$, IV, over 10 minutes every 21 days. Beginning 30 minutes after the end of MTA administration, Cisplatin, 75 mg/m$^2$, IV according to local practice. Dexamethasone 4mg PO twice a day on the day before, day of and day after MTA | Received 1 dose of MTA or Cisplatin |

## Summary of Clinical Trials - Ongoing

| Study Investigator / Coordinating center / Number of center(s) / Report number | Design | Number of Patients With Age and Sex | Diagnosis Plus Criteria for Inclusion | Test Product / Dosage / Regimen / Route of Administration | Criteria for Evaluation |
|---|---|---|---|---|---|
| H3E-MC-JMAF<br>Professor E. Baietta, et al.<br>Oncologia Medica B<br>Istituto Nazionale Tumori<br>Via Venezian, 1<br>20100 MILANO<br>7 centers | Phase 2,<br>Open label<br>Non-random | N=35<br>18+ years of age<br>Male and female | Locally advanced or metastatic gastric cancer with no prior chemotherapy | MTA 500mg/m$^2$ IV over 10 minutes every 21 days | Received 2 doses of MTA |
| H3E-MC-JMAI<br>Dr. Weissbach<br>Dr. Hanauske<br>Dr. Berdel<br>Dr. Jakse<br>4 Sites - Germany | Phase II,<br>Open-Label,<br>Non-Randomized | N=35<br>18+ years of age<br>Male and female | Metastatic renal cell cancer, no prior chemotherapy, not amenable to surgery. | MTA IV (over approximately 10 minutes) every 21 days; dose 600mg/m$^2$ | Received 2 doses of MTA. |
| H3E-MC-JMAJ<br>Dr. J. P. Armand, et al.<br>Institut Gustave Roussy<br>39 rue Camille Desmoulins<br>94805 VILLEJUIF CEDEX<br>4 centers | Phase 2,<br>Open label<br>Non-random | N=35<br>18+ years of age<br>Male and female | Locally advanced or metastatic head and neck cancer | MTA<br>500mg/m$^2$<br>over 10 minutes every 21 days<br>IV | Received 1 dose of MTA |

## Summary of Clinical Trials - Ongoing

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMAK<br>Dr. Moyano<br>Dr. Tabernero<br>Dr. Rifa<br>Dr. Sanchez<br>Dr. Cortes Funes De Castro<br>5 Sites - Spain | Phase II<br>Open-Label,<br>Non-Randomized | N=35<br>18+ years of age<br>Male and female | Inoperable metastatic or locally advanced bladder cancer, no prior chemotherpay | MTA IV (over approximately 10 minutes) every 21 days; dose 600 mg/m$^2$.<br>Dose reduced to 500 mg/m$^2$ in amendment. | Received 2 doses of MTA |
| H3E-MC-JMAM<br>Dr. Goedhals, National Hospital<br>Bloenfontein, South Africa<br>Dr. Van Wiik, Groote Schuur Hosp.<br>Cape Town, South Africa<br>2 Sites - South Africa | Phase II,<br>Open-Label,<br>Non-Randomized | N=35<br>18+ years of age<br>Female | Inoperable, locally advanced, recurrent or metastatic cervical cancer. No prior chemotherapy. | MTA IV (over approximately 10 minutes) every 21 days; dose 500mg/m$^2$ | Received 2 doses of MTA. |
| H3E-MC-JMAQ<br>Dr. Alex A. Adjei<br>Mayo Clinic<br>Rochester, MN 55905<br>USA<br>1 center | Phase 1,<br>Open label<br>Non-random | N=36<br>18+ years of age<br>Male and female | Locally advanced or metastatic cancer for which no other therapy exists. | Dose ranging Gemcitabine (over 30 minutes) Day 1 and 8 every 21 days (dose range 750-1250 mg/m$^2$)<br>MTA Day 1 (over 10 minutes) 90 minutes after Gemcitabine. (MTA dose range 200-500 mg/m$^2$) | Received 1 dose of MTA and Gemcitabine combination therapy |
| H3E-MC-JMAR<br>Dr. T. R. Johnson<br>Brooke Army Medical Center<br>MCHE MDH<br>Building 3600<br>3851 Roger Brooke Drive<br>Fort Sam<br>Houston, TX 78234-6200<br>USA<br>1 center | Phase 1,<br>Open label<br>Non-random | N=40<br>18+ years of age<br>Male and female | Locally advanced or metastatic cancer | Dose ranging MTA (300-500 mg/m$^2$) on Day 1 (over 10 minutes) followed by 5-FU (250-500 mg/m$^2$) which will be a bolus infusion given on days 1-5. This will be repeated every 21 days | Received 1 dose of MTA and 5-FU combination therapy |

## Summary of Clinical Trials - Ongoing

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMAS<br>Dr. L. A. Hammond<br>Cancer Therapy and Research Center<br>8122 Datapoint Drive<br>Suite 650<br>San Antonio, TX 78229<br>Hammond<br>1 center | Phase 1,<br>Open label<br>Non-random | N=30<br>18+ years of age<br>Male and female | Locally advanced or metastatic cancers | Dose ranging MTA (600-1400 mg/m$^2$) Day 1 every 21 days over 10 minutes.<br>Folic acid 5 mg PO 2 days before and on Day 1, 2 and 3 of the cycle | Received 1 dose of MTA and folic acid supplementation |
| H3E-MC-JMAX<br>CRO: IPI<br>14785 Omicron<br>Suite 101<br>San Antonio, TX 78245-3201 | Phase 1,<br>Open label<br>Non-random | N=42<br>18+ years of age<br>Male and female | Locally advanced or metastatic cancer | Dose ranging MTA (300-600 mg/m$^2$) IV over 10 minutes followed by Irinotecan (175-350 mg/m$^2$) IV over 90 minutes. Repeat cycle every 21 days. | Received 1 dose of MTA or Irinotecan |
| H3E-MC-JMBM<br>CRO: IPI<br>14785 Omicron<br>Suite 101<br>San Antonio, TX 78245-3201 | Phase 2,<br>open label<br>non-random | N=75<br>18+ years of age<br>Male and female | 5-FU refractory colorectal cancer | MTA<br>500mg/m$^2$<br>over 10 minutes every 21 days<br>IV<br>4mg/m$^2$ Dexamethasone 2x day before, of and after MTA infusion | Received 1 dose of MTA |
| H3E-MC-JMBN<br>CRO: IPI<br>14785 Omicron<br>Suite 101<br>San Antonio, TX 78245-3201 | Phase 2,<br>open label<br>non-random | N=105<br>18+ years of age<br>Male and female | 5-FU refractory or 5-FU and Irinotecan refractory or chemonaive colorectal cancer | MTA<br>4mg/m$^2$<br>over 10 minutes daily for 5 days every 21 days<br>IV | Received 1 dose of MTA |
| H3E-MC-JMAW<br>CRO: IPI<br>14785 Omicron<br>Suite 101<br>San Antonio, TX 78245-3201 | Phase 1,<br>open labe<br>dose-finding | N=50<br>18+years of age<br>Male and female | Advance cancer, varying degrees of renal function | Dose ranging MTA (150-600 mg/m$^2$) over 10 minutes every 21-days IV. Dexamethasone 4 mg PO twice a day the day before, day of and day after MTA | Received 1 dose of MTA |

## Summary of Clinical Trials - Ongoing

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMBP<br>This study is being conducted in the United Kingdom, Spain and Austria | Phase 2, open label non-random | N=70<br>18+ years of age<br>Female | Metastatic breast cancer, previously treated with an anthracycline or anthracenedione agent in the locally advanced or metastatic setting. | MTA, 500 mg/m$^2$, IV over approximately 10 minutes every 21 days. Dexamethasone 4 mg PO twice a day on the day before, day of and day after MTA | Received 1 dose of MTA |
| H3E-MC-JMBR<br>This study is being conducted in Germany and Austria | Phase 2 open label non-random | N=70<br>18+ years of age<br>Male and female | Patients with Stage IIIb or IV NSCLC who have failed first-line chemotherapy. | MTA, 500 mg/m$^2$ IV over approximately 10 minutes every 21 days. Dexamethasone 4 mg PO twice a day the day before, day of and day after MTA. | Received 1 dose of MTA |
| H3E-MC-JMBS<br>This study is being conducted in Belgium | Phase 1, dose finding open label | N=51<br>18+ years of age<br>Male and female | Solid malignant tumor for which no other treatment option is available. | MTA (400-600 mg/m$^2$), IV, over 10 minutes, every 21 days. Paclitaxel (135-225 mg/m$^2$), IV, over 3 hours every 21 days. | Received 1 dose of MTA and paclitaxel |
| H3E-MC-JMBU<br>This study is being conducted in the US and UK | Phase 1 dose-finding open label | N=40<br>18+ years of age<br>Male and female | Locally advanced or metastatic cancer. Up to 2 prior chemotherapeutic regimen in the adjuvant or metastatic setting. | MTA (300-600 mg/m$^2$), IV, over 10 minutes every 21 days. Docetaxel (75-100 mg/m$^2$), IV, over 1 hour, every 21 days, approximately 20 minutes after MTA infusion. Dexamethasone 8 mg PO twice a day the day before, day of and day after MTA | Received 1 dose of MTA and docetaxel. |
| H3E-MC-JMBZ | Phase 2 | N=40<br>18+ years of age<br>Male and Female | NSCLC | MTA plus Cisplatin | |

## Summary of Clinical Trials - Planned

| Study Investigator / Coordinating center / Number of center(s) / Report number | Design | Number of Patients With Age and Sex | Diagnosis Plus Criteria for Inclusion | Test Product / Dosage / Regimen / Route of Administration | Criteria for Evaluation |
|---|---|---|---|---|---|
| H3E-MC-JMAU<br>This study will be conducted in the United Kingdom | Phase 1, dose finding open label | N=40<br>18= years of age<br>Male and female | Locally advanced or metastatic cancer. Up to one prior chemotherapeutic regimen for metastatic disease. | MTA (300-600 mg/m$^2$) , IV, over 10 minutes, every 21 days. Carboplatin (4-5 mg/ml/min AUC) , IV over 30 minutes approximately 30 minutes after the end of MTA infusion. Dexamethasone 4 mg PO twice a day the day before, day of and day after MTA | Received 1 dose of MTA and Carboplatin |
| H3E-MC-JMBT<br>5 sites in the U.S. | Phase 2 open label non-random | N=50<br>18+ years of age<br>Female | Locally advanced or metastatic breast cancer. Previous treatment with either combination therapy with a taxane plus an anthracycline or anthracendione, or sequential therapy with an anthracycline or anthracenedione containing regimen followed by a taxane. | MTA, 500 mg/m$^2$, IV, over approximately 10 minutes every 21 days. | Received 1 dose of MTA |
| H3E-MC-JMCD<br>Study to be conducted in the U.S. | Phase 2 open label non-random | N=35-50<br>18+ years of age<br>Male and female | Locally advanced or metastatic NSCLC. No previous treatment. | Gemcitabine, IV, over 30 minutes on days 1 and 8 of each 21-day cycle. MTA, IV, over approximately 10 minutes every 21 days. | Received 1 dose of MTA and gemcitabine |

## Summary of Clinical Trials - Planned

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMCE<br>Study to be conducted in France. | Phase 2<br>open label<br>non-random | N=35-50<br>18+ years of age<br>Male and female | Locally advanced or metastatic NSCLC.<br>No previous treatment. | Gemcitabine, IV, over 30 minutes on days 1 and 8 of each 21-day cycle. MTA, IV, over approximately 10 minutes every 21 days. | Received 1 dose of MTA and gemcitabine |
| H3E-MC-JMBQ<br>CRO: IPI<br>14785 Omicron<br>Suite 101<br>San Antonio, TX 78245-3201 | Phase 2/3<br>randomized, active-controlled, open-label | N=440<br>18+ years of age<br>Male and female | Patients with Stage IIIb or IV NSCLC who have failed first line therapy with taxane + platinum regimen | MTA, 500 mg/m$^2$ IV over approximately 10 minutes every 21 days during Phase 2 and 3.<br>Dexamethasone 4 mg PO twice a day the day before, day of and day after MTA.<br>Vinorelbine, IV, 30 mg/m$^2$, weekly for three weeks during Phase 3.<br>Vitamin supplements of 25 mg $B_6$, 2 mg of $B_{12}$ and 1 mg of folic acid daily one week before MTA and continued throughout study. | Received 1 dose of MTA or vinorelbine with or without vitamins. |
| H3E-MC-JMAV | Phase 1<br>dose finding<br>open label | N=30<br>18+ years of age<br>Male and female | Histologic or cytologic diagnosis of solid tumor. Up to 2 prior chemotherapeutic regmens in the adjuvant or metastatic setting are allowed. | MTA, IV, over 10 minutes every 21 days and radiation therapy. | |

## Summary of Clinical Trials - Planned

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JMBV<br>Study to be conducted in France | Phase 1 dose finding open label | N=50<br>18+ years of age<br>Male and famale | Locally advanced or metastatic disease not amenable to curative therapy | MTA (300-500 mg/m$^2$) IV over 10 minutes on day one of 21.<br>Oxaliplatin (70-120 mg/m$^2$) IV over 2 hours 30 minutes after MTA.<br>Dexamethasone 4 mg PO twice a day the day before, day of and day after MTA. | Received one dose of MTA and Oxaliplatin |
| H3E-MC-JMAT<br>This study will be conducted in Australia | Phase 1<br>Dose finding<br>Open label | N=30<br>18+ years of age<br>Male and female | Locally advanced or metastatic disease not amenable to curative therapy | MTA and Navalbine | |
| H3E-MC-JMCB | Phase 1<br>Dose finding<br>Open label | N=30<br>18+ years of age<br>Male and female | Locally advanced or metastatic disease not amenable to curative therapy | MTA and Taxol weekly | |
| H3E-MC-JMCI | Phase 1 and 2 dose finding open label non randomized | N=30<br>18+ years of age<br>Male and Female | Locally advanced or metastatic disease not amenable to curative therapy | MTA plus adriamycin | |
| H3E-MC-JMCF<br>This study will be done in the US | Phase 2 | N=35-50<br>18+ years of age<br>Female | Second line Breast cancer | MTA and Gemzar | |
| H3E-MC-JMCH | Phase 2<br>Randomized | N=120<br>18+ year of age<br>Male or female | Mesothelioma previously untreated | MTA | |
| H3E-MC-JM20 | | N=100<br>18+ years of age<br>Male and Female | Head and Neck cancer | MTA versus MTA plus vitamins | |

| | | | | | |
|---|---|---|---|---|---|
| H3E-MC-JML1 | Phase 1<br>Open label | N=120<br>18+ years of age<br>Male and Female | Head and Neck cancer with Cisplatin and 5-FU failures. | MTA | |

Appendix 9

# Appendix 9
# Bibliography

# Bibliography

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AUG 05 1998

dmm

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21, CODE OF FEDERAL REGULATIONS (CRF) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date:* December 31, 1999
*See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
ELI LILLY AND COMPANY

2. DATE OF SUBMISSION
August 5, 1998

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, IN 46285

4. TELEPHONE NUMBER *(Include Area Code)*
(317) 276-2000

5. NAME(S) OF DRUG *(include all available names: Trade, Generic, Chemical, Code)*
Compound LY231514 Disodium (MTA)

6. IND NUMBER *(If previously assigned*
IND 40,061

7. INDICATION(S) *(Covered by this submission)*
Cancer

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER NA *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.
NA

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submission should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
127

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
■ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

**CHECK ONLY IF APPLICABLE**

**JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.**

**☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)**

**FOR FDA USE ONLY**

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | IND NUMBER ASSIGNED: |
|---|---|---|
| | | DIVISION ASSIGNMENT: |

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 [21 CFR 312.23(a)(1)]
- ☐ 2. Table of Contents [21 CFR 312.23(a)(2)]
- ☐ 3. Introductory statement [21 CFR 312.23(a)(3)]
- ☐ 4. General investigational plan [21 CFR 312.23(a)(3)]
- ☐ 5. Investigator's brochure [21 CFR 312.23(a)(5)]
- ☐ 6. Protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ a. Study protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ b. Investigator data [21CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)]
- ☐ [illegible]nmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
- ☐ [illegible]gy and toxicology data ]21 CFR 312.23(a)(8)]
- ☐ [illegible]man experience [21 CFR 312.23(a)(9)]
- ☐ 10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

NA

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Steven J. Nicol, M.D.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Same as #14 Above

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

| 16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | 17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | |
|---|---|---|
| Gregory T. Brophy, Ph.D., Director<br>U.S. Regulatory Affairs | | |
| 18. ADDRESS *(Number, Street, City, State and Zip Code)* | 19. TELEPHONE NUMBER *(Include Area Code)* | 20. DATE |
| Eli Lilly and Company<br>Lilly Corporate Center<br>Indianapolis, IN 46285 | (317) 277-3799 | 8/4/98 |

**(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)**

**Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:**

**DHHS Reports Clearance Officer**
**Paperwork Reduction Project 0910-0014**
**Hubert H. Humphrey Building, Room 531-H**
**200 Independence Avenue, S.W.**
**Washington, DC 20201**

**"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."**

**Please DO NOT RETURN this application to this address.**

IND 40,061 - Compound LY231514, Thymidylate Synthase Inhibitor
August 5, 1998
Serial No. 127

**CONTENTS OF SUBMISSION**

**Information Amendment: Chemistry/Microbiology**

Page 7027 - Clinical Trial Labels

P06113 10 vials
VIAL LY231514 Disodium For Injection
Equiv. to 100 mg LY231514
H3E-MC-JMBR For I.V. Use Only

Each vial contains: LY231514 Disodium, equiv. to 100 mg LY231514; Mannitol, USP, 100 mg. Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust pH. To reconstitute, add 2 to 10 mL of 0.9% sodium chloride injection, USP, (without preservatives) to make a solution containing 10 mg/mL to 50 mg/mL LY231514. Use solution within 24 hours. Discard unused portion. Store at controlled room temperature 59° to 86° F (15° to 30° C). Protect from light. For clinical trial use only. Keep out of the reach of children. Caution: New drug - Limited by Federal law to investigational use.

Exp. Date: 09 1999
CT10725

ZK 0187 CTX
ELI LILLY AND COMPANY Lilly Indianapolis, IN 46285, U.S.A.

P06113
VIAL
LY231514
Disodium
For Injection
Equiv. to
100 mg LY231514
H3E-MC-JMBR
For I.V. Use Only

Each vial contains: LY231514 Disodium, equiv. to 100 mg LY231514; Mannitol, USP, 100 mg. Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust pH. To reconstitute, add 2 to 10 mL of 0.9% sodium chloride injection, USP, (without preservatives) to make a solution containing 10 mg/mL to 50 mg/mL LY231514. Use solution within 24 hours. Discard unused portion. Store at controlled room temperature 59° to 86° F (15° to 30° C). Protect from light. For clinical trial use only. Keep out of the reach of children.

Exp. Date: 09 1999
CT10725

Caution: New drug-Limited by Federal law to investigational use.
YQ 4300 AMQ
ELI LILLY AND COMPANY
Indianapolis, IN 46285, U.S.A.

P06114 10 vials
VIAL LY231514 Disodium For Injection
Equiv. to 500 mg LY231514
H3E-MC-JMBR For I.V. Use Only

Each vial contains: LY231514 Disodium, equiv. to 500 mg LY231514; Mannitol, USP, 500 mg. Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust pH. To reconstitute, add 10 to 50 mL of 0.9% sodium chloride injection, USP, (without preservatives) to make a solution containing 10 mg/mL to 50 mg/mL LY231514. Use solution within 24 hours. Discard unused portion. Store at controlled room temperature 59° to 86° F (15° to 30° C). Protect from light. For clinical trial use only. Keep out of the reach of children. Caution: New drug - Limited by Federal law to investigational use.

Exp. Date: 07 1999
CT10726

ZK 0187 CTX
ELI LILLY AND COMPANY Lilly Indianapolis, IN 46285, U.S.A.

P06114
VIAL
LY231514
Disodium
For Injection
Equiv to
500 mg LY231514
H3E-MC-JMBR
For I.V. Use Only

Each vial contains: LY231514 Disodium, equiv. to 500 mg LY231514; Mannitol, USP, 500 mg. Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust pH. To reconstitute, add 10 to 50 mL of 0.9% sodium chloride injection, USP, (without preservatives) to make a solution containing 10 mg/mL to 50 mg/mL LY231514. Use solution within 24 hours. Discard unused portion. Store at controlled room temperature 59° to 86° F (15° to 30° C). Protect from light. For clinical trial use only. Keep out of the reach of children.

Exp. Date: 07 1999
CT10726

Caution: New drug-Limited by Federal law to investigational use.
YQ 4300 AMQ
ELI LILLY AND COMPANY
Indianapolis, IN 46285, U.S.A.

NTF
IND 40,061
8/5/98

# FOOD AND DRUG ADMINISTRATION
## OFFICE OF DRUG EVALUATION I

**DIVISION OF ONCOLOGY DRUG PRODUCTS**
**HFD-150, 5600 Fishers Lane**
**Rockville, Maryland 20857**
**PHONE: (301) 594-5781 FAX: (301) 594-0498**

**TO:** Dr. Steven A. Hamburger/Eli Lilly
Fax #: (317) 276-1652

**FROM:** Christy Wilson, Technical Information Assistant for Linda McCollum, Project Manager

**DATE: 8/5/98** **Total number of pages, including cover sheet: 2**

**COMMENTS:**
Dear Dr. Hamburger,

This fax is to confirm the scheduling of your meetings with our Division for development guidance regarding MTA (LY 231514) – IND 40,061. Due to the anticipated length of the originally requested meeting, we have decided to hold two separate meetings, one for clinical discussion and one for biopharmaceutics discussion. The following dates and times are tentatively being held for these meetings:

**CLINICAL MEETING:**

**Date:** September 25, 1998

**Time:** 1:00 p.m.
(Eastern Time)

**Location:** Conference Room I, Room 6041
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

**FDA Participants:** (**BOLD**- Attendees; Other- Invitees)

Robert Temple, M.D., Office Director
Rachel Behrman, M.D., Deputy Office Director
**Robert Justice, M.D., Acting Division Director**
Julie Beitz, M.D., Acting Deputy Division Director
**John Johnson, M.D., Medical Team Leader**
**Robert White, M.D., Medical Reviewer**
Paul Andrews, Ph.D., Pharm/Tox Team Leader
Doo Young Lee-Ham, Ph.D., Pharm/Tox Reviewer
Gang Chen, Ph.D., Biometrics Team Leader

**Biometrics Reviewer**
Atiq Rahman, Ph.D., Biopharmaceutics Team Leader
Biopharmaceutics Reviewer
Chemistry Team Leader
Chemistry Reviewer
John Simmons, Ph.D., Deputy Director, Division of New Drug Chemistry I
**Linda McCollum, Project Manager**

**BIOPHARMACEUTICS MEETING:**

**Date:** September 23, 1998

**Time:** 1:00 p.m.
(Eastern Time)

**Location:** Conference Room G, Room 6002
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

**FDA Participants:** (**BOLD**- Attendees; Other- Invitees)

Robert Temple, M.D., Office Director
Rachel Behrman, M.D., Deputy Office Director
**Robert Justice, M.D., Acting Division Director**
Julie Beitz, M.D., Acting Deputy Division Director
John Johnson, M.D., Medical Team Leader
Robert White, M.D., Medical Reviewer
Paul Andrews, Ph.D., Pharm/Tox Team Leader
Doo Young Lee-Ham, Ph.D., Pharm/Tox Reviewer
Gang Chen, Ph.D., Biometrics Team Leader
Biometrics Reviewer
**Atiq Rahman, Ph.D., Biopharmaceutics Team Leader**
**Biopharmaceutics Reviewer**
Chemistry Team Leader
Chemistry Reviewer
John Simmons, Ph.D., Deputy Director, Division of New Drug Chemistry I
**Linda McCollum, Project Manager**

We have tried to schedule these meetings as close together as possible for your convenience. If you have any questions, or are unable to attend on these dates, please contact either Linda McCollum at (301) 594-5771 or me at (301) 594-5781.

Thank you,

Christy Wilson

AUG 11 1998

**Lilly Research Laboratories**
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 11, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Suite 200 North
1451 Rockville Pike
Rockville, Maryland 20852-1448

RE: IND 40,061 Compound LY231514
Serial No. 127

The following Drug Experience Report(s) are enclosed:

Control No: US_980808005 Initial

Please call Mr. John Worzalla at (317) 276-5052 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure

GTB:dmm

dmm 7027.2

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date:* December 31, 1999
*See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
ELI LILLY AND COMPANY

2. DATE OF SUBMISSION
August 11, 1998

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, IN 46285

4. TELEPHONE NUMBER *(Include Area Code)*
(317) 276-2000

5. NAME(S) OF DRUG *(include all available names: Trade, Generic, Chemical, Code)*
Compound LY231514 Disodium (MTA)

6. IND NUMBER *(If previously assigned)*
IND 40,061

7. INDICATION(S) *(Covered by this submission)*
Cancer

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER NA *(Specify)*

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SERIAL NUMBER
128

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

| PROTOCOL AMENDMENT(S): | INFORMATION AMENDMENT(S): | IND SAFETY REPORT(S): |
|---|---|---|
| ☐ NEW PROTOCOL | ☐ CHEMISTRY/MICROBIOLOGY | ■ INITIAL WRITTEN REPORT |
| ☐ CHANGE IN PROTOCOL | ☐ PHARMACOLOGY/TOXICOLOGY | ☐ FOLLOW-UP TO A WRITTEN REPORT |
| ☐ NEW INVESTIGATOR | ☐ CLINICAL | |

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

**CHECK ONLY IF APPLICABLE**

**JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.**

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)**

**FOR FDA USE ONLY**

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | IND NUMBER ASSIGNED: |
|---|---|---|
| | | DIVISION ASSIGNMENT: |

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- ☐ 6. Protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ a. Study protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ b. Investigator data [21CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
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- ☐ ☐ Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
- ☐ 8. Pharmacology and toxicology data ]21 CFR 312.23(a)(8)]
- ☐ 9. Previous human experience [21 CFR 312.23(a)(9)]
- ☐ 10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

NA

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Steven J. Nicol, M.D.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Same as #14 Above

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

| 16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | 17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | |
|---|---|---|
| Gregory T. Brophy, Ph.D., Director<br>U.S. Regulatory Affairs | | |
| 18. ADDRESS *(Number, Street, City, State and Zip Code)* | 19. TELEPHONE NUMBER *(Include Area Code)* | 20. DATE |
| Eli Lilly and Company<br>Lilly Corporate Center<br>Indianapolis, IN 46285 | (317) 277-3799 | 8/11/98 |

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**Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:**

**DHHS Reports Clearance Officer**
**Paperwork Reduction Project 0910-0014**
**Hubert H. Humphrey Building, Room 531-H**
**200 Independence Avenue, S.W.**
**Washington, DC 20201**

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**Please DO NOT RETURN this application to this address.**

Approved by FDA on 3/22/94

# MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Eli Lilly and Company

Mfr report # US_980808005

UF/Dist report #

FDA use Only



## A. Patient information

| 1. Patient identifier | 2. Age at time of event: | 3. Sex | 4. Weight |
|---|---|---|---|
| * in confidence | 57 yrs or Date of birth: * | ☐ female ☒ male | 114 lbs or 52 kgs |

## B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☒ death 07/24/98 (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

| 3. Date of event (mo/day/yr) | 4. Date of this report (mo/day/yr) |
|---|---|
| 21/JUL/1998 | 10/AUG/1998 |

5. Describe event or problem

THIS CLINICAL TRIAL CASE CONCERNS A 57 YEAR OLD, CAUCASIAN MALE PATIENT, WITH A HISTORY OF CREST SYNDROME SINCE 1986, ARTERITIS AND EPILEPSY, WHO RECEIVED INTRAVENOUS (IV) STUDY DRUG, LY231514, 750 MG ONCE EVERY THREE WEEKS FOR THE TREATMENT OF HEAD AND NECK CANCER. CONCOMITANT MEDICATIONS INCLUDED ACENOCOUMAROL (SINTROM) AND PENTOXIFYLLINE (TORENTAL 400) FOR ARTERITIS AND CARBAMAZEPINE (TEGRETOL) FOR EPILEPSY. THE PATIENT DEVELOPED EPISTAXIS AND VARICOSE ULCER WITH INFECTION IN MAY-1998 (SEE CASE ID US_980503417).

THE PATIENT BEGAN STUDY DRUG ON 20-APR-1998 AND RECEIVED HIS FOURTH INJECTION ON 07-JUL-1998. ON 13-JUL-1998, HE WAS HOSPITALIZED *

6. Relevant tests/laboratory data including dates

Lab data:
Lab test or Procedure / Result Units / Date and Time / Reference to normal range

1) LEUKOCYTE COUNT/1.1 1 X 10E9/LITER/UNK/ BELOW *

7. Other relevant history, including preexisting medical conditions (eg., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Relevant history / Concurrent conditions:
HISTORY OF CREST SYNDROME SINCE 1986; ARTERITIS; EPILEPSY; HEAD AND NECK CANCER.

Origin: CAUCASIAN

## C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LY231514

#2

| 2. Dose, frequency & route used | 3. Therapy dates (if unknown, give duration) from/to (or best estimate) |
|---|---|
| #1 750 mg/1/3W MONTH | #1 20-APR-98 to 07-JUL-98 |
| #2 | #2 |

| 4. Diagnosis for use (indication) | 5. Event abated after use stopped or dose reduced |
|---|---|
| #1 HEAD AND NECK CANCER | #1 ☐ yes ☐ no ☒ doesn't apply |
| #2 | #2 ☐ yes ☐ no ☐ doesn't apply |

| 6. Lot # (if known) | 7. Exp. date (if known) | 8. Event reappeared after reintroduction |
|---|---|---|
| #1 NI | #1 NI | #1 ☐ yes ☐ no ☐ doesn't apply |
| #2 | #2 | #2 ☐ yes ☐ no ☐ doesn't apply |

9. NDC # - for product problems only (if known)

#1 #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

1) SINTROM(ACENOCOUMAROL)
Dose: 4 mg/1/D DAY, Dates: ??-JUN-1996to NI, Route: POIndication: ARTERITIS
2) TORENTAL(PENTOXIFYLLINE) *

## G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

2. Phone number: NI

3. Report source (check all that apply)
- ☒ foreign
- ☒ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

10 AUG 98

| 4. Date received by manufacturer (mo/day/yr) | 5. (A)NDA # / IND # / PLA # | 6. If IND, protocol # |
|---|---|---|
| 28/JUL/1998 | IND # 40,061 | JMAJ |

pre-1938 ☐ yes

OTC product ☐ yes

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☒ 10-day ☐ periodic
- ☒ Initial ☐ follow-up #____

FR

8. Adverse event term(s)

SEPSIS
21-JUL-1998 to 24-JUL-1998
SKIN ULCER

SCLERODERMA *

9. Mfr. report number: US_980808005

## E. Initial reporter

1. Name, address & phone #

Redacted

| 2. Health professional? | 3. Occupation | 4. Initial reporter also sent report to FDA |
|---|---|---|
| ☒ yes ☐ no | INVESTIGATOR | ☐ yes ☐ no ☐ unk |

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

Eli Lilly and Company

| MEDWATCH | A.1. Patient Identifier | G.9. Mfr. report number | Page 2 of 2 |
|---|---|---|---|
| | H3E-MC-JMAJ-302-3025 | US_980808005 | |

A.1. Patient identifier

H3E-MC-JMAJ-302-3025

A.2. Date of birth(mo/day/yr)

57 years Redacted

Redacted 1941

B.5. Describe event or problem

[continuation:] FOR A SCLERODERMA AND ULCERS ON THE UPPER AND LOWER LIMBS. HEMATOLOGY PERFORMED ON 15-JUL-1998 SHOWED NEUTROPENIA AND LEUKOPENIA (GRADE 3). THESE EVENTS RESOLVED ON 17-JUL-1998, BUT A FEVER OF 38.5 DEGREES CELSIUS DEVELOPED THE SAME DAY. LABORATORY RESULTS SHOWED DECREASED LEUKOCYTES (1.1 GIGA/L- -DATE NOT SPECIFIED), DECREASED NEUTROPHILS (0.8 GIGA/L) ON 15-JUL-1998, AND DECREASED LEUKOCYTES (3.5 GIGA/L) ON 17-JUL-1998. NEUTROPHILS WERE WITHIN NORMAL RANGE ON 17-JUL-1998. CULTURE RESULTS ON 20-JUL-1998 SHOWED THE PRESENCE OF PSEUDOMONAS AERUGINOSA AND STAPHYLOCOCCUS AUREUS. ON 24-JUL-1998, THE PATIENT DIED OF SEPTICEMIA PROBABLY RELATED TO INFECTION OF THE ULCERS. NO AUTOPSY WAS PERFORMED. IN THE OPINION OF THE INVESTIGATOR, THE UPPER AND LOWER LIMB ULCERS, SCLERODERMA, LEUKOPENIA, NEUTROPENIA, SEPTICEMIA, AND FEVER WERE RELATED TO STUDY DRUG BUT NOT RESEARCH CONDITIONS. ADDITIONAL INFORMATION IS BEING REQUESTED.

LILLY ANALYSIS STATEMENT: THIS PATIENT HAD A HISTORY OF CREST SYNDROME SINCE 1986. IT IS LIKELY THAT THIS REPRESENTS THE ORIGIN OF THE SCHLERODERMA AND UPPER AND LOWER LUMB ULCERS. HOWEVER, IT IS POSSIBLE THAT THE STUDY DRUG MAY HAVE EXACERBATED THESE. THE SEPSIS EVENT WITH THE OUTCOME OF DEATH WAS SECONDARY TO NEUTROPENIA AND THESE EVENTS ARE EXPECTED FOR THIS STUDY TREATMENT. THEREFORE, THIS DEATH MUST BE CONSIDERED AS STUDY DRUG RELATED.

07-AUG-1998: ADDED LILLY ANALYSIS STATEMENT.
Cause of Death: SEPTICEMIA

B.6. Relevant tests/laboratory datancluding dates

[continuation:] 2) NEUTROPHILS /0.8 1 X 10E9/LITER/15-JUL-1998/BELOW
3) LEUKOCYTE COUNT/3.5 1 X 10E9/LITER/17-JUL-1998/BELOW
4) NEUTROPHILS /2.1 1 X 10E9/LITER/17-JUL-1998/WITHIN

C.10. Concomitant medical productand therapy dates (exclude treatment of event)

[continuation:] Dose: 1200 mg/1/D DAY, Dates: ??-DEC-1994to NI, Route: POIndication: ARTERITIS
3) TEGRETOL(CARBAMAZEPINE)
Dose: 200 mg/1/D DAY, Dates: ??-JUN-1996to NI, Route: POIndication: EPILEPSY

G.5. IND #

US IND 40,061

G.8. Adverse event term(s)

[continuation:]
LEUKOPENIA
15-JUL-1998 to 17-JUL-1998
FEVER

E.1. Name, address & phone #

[continuation:] Redacted

AUG 25 1998

Lilly

**Lilly Research Laboratories**
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 25, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncologic Drug Products, HFD-150
Attn: Division Document Control Room, 3rd Floor
5600 Fishers Lane
Rockville, MD 20857

**Subject: IND 40,061, LY231514 (MTA); Serial No.: 129**
**Protocol Amendment: New Protocol**

Dear Sirs,

In accordance with 21 CFR 312.30, Eli Lilly and Company hereby submits the original protocol [H3E-MC-JMBU] entitled "A Phase 1 Dose-Escalating Study of LY231514 and Docetaxel Administered Every 21 Days in Patients with Locally Advanced or Metastatic Cancer". Dr. John D. Roberts, Virginia Commonwealth University, 401 College Street, P.O. Box 9800037, Richmond, VA 23298-0037, will be the primary Investiagor. The subinvestigator reporting to Dr. Roberts will be Louise Helen Cragg. The Form FDA 1572 and appropriate curriculum vitae for the primary investigator are being retained in our files per instructions in your letter of April 27, 1992.

Please contact Mr. John F. Worzalla at (317) 276-5052 or me at (317) 277-3799 if you require any additional information or clarifications.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Enclosures
GTB:dmm

dmm

7030.2

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

**INVESTIGATIONAL NEW DRUG APPLICATION (IND)**
*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date:* December 31, 1999
*See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
ELI LILLY AND COMPANY

2. DATE OF SUBMISSION
August 25, 1998

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, IN 46285

4. TELEPHONE NUMBER *(Include Area Code)*
(317) 276-2000

5. NAME(S) OF DRUG *(include all available names: Trade, Generic, Chemical, Code)*
Compound LY231514 Disodium (MTA)

6. IND NUMBER *(if previously assigned)*
IND 40,061

7. INDICATION(S) *(Covered by this submission)*
Cancer

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ■ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.
NA

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submission should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
129

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
■ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

**CHECK ONLY IF APPLICABLE**

**JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.**

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.34(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)**

**FOR FDA USE ONLY**

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | IND NUMBER ASSIGNED: |
|---|---|---|
| | | DIVISION ASSIGNMENT: |

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 [21 CFR 312.23(a)(1)]
- ☐ 2. Table of Contents [21 CFR 312.23(a)(2)]
- ☐ 3. Introductory statement [21 CFR 312.23(a)(3)]
- ☐ 4. General investigational plan [21 CFR 312.23(a)(3)]
- ☐ 5. Investigator's brochure [21 CFR 312.23(a)(5)]
- ☐ 6. Protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ a. Study protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ b. Investigator data [21CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)]
- ☐ ☐ Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
- ☐ 8. Pharmacology and toxicology data ]21 CFR 312.23(a)(8)]
- ☐ 9. Previous human experience [21 CFR 312.23(a)(9)]
- ☐ 10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ■ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Steven J. Nicol, M.D.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Same as #14 Above

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

| 16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | 17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE | |
|---|---|---|
| Gregory T. Brophy, Ph.D., Director<br>U.S. Regulatory Affairs | | |
| 18. ADDRESS *(Number, Street, City, State and Zip Code)* | 19. TELEPHONE NUMBER *(Include Area Code)* | 20. DATE |
| Eli Lilly and Company<br>Lilly Corporate Center<br>Indianapolis, IN 46285 | (317) 277-3799 | 8/25/98 |

**(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)**

**Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:**

**DHHS Reports Clearance Officer**
**Paperwork Reduction Project 0910-0014**
**Hubert H. Humphrey Building, Room 531-H**
**200 Independence Avenue, S.W.**
**Washington, DC 20201**

**"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."**

**Please DO NOT RETURN this application to this address.**

**LY231514 (MTA)**

**Protocol H3E-MC-JMBU**

# A Phase 1 Dose-Escalating Study of MTA and Docetaxel Administered Every 21 Days in Patients with Locally Advanced or Metastatic Cancer

Protocol Approved by Lilly: 26 January 1998

**A Phase 1 Dose-Escalating Study of MTA and Docetaxel Administered Every 21 Days in Patients with Locally Advanced or Metastatic Cancer**

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**A Phase 1 Dose-Escalating Study of MTA and Docetaxel Administered Every 21 Days in Patients with Locally Advanced or Metastatic Cancer**

# 1. Introduction

## 1.1. MTA

Inhibition of the enzyme thymidylate synthase (TS) is the primary mechanism of action of MTA, a folate antimetabolite [1-3]. Thymidylate synthase, a folate-dependent enzyme, catalyzes the transformation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Inhibition of TS results in decreased thymidine necessary for DNA synthesis [4,5].

MTA also inhibits dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT), folate-dependent enzymes that are involved in purine synthesis [6]. These targets are related to the cytotoxicity of MTA since both thymidine and hypoxanthine are required to circumvent cellular death caused by MTA [7]. MTA gains entry to the cell via the reduced folate carrier and once localized is an excellent substrate for folylpolyglutamate synthase (FPGS). The pentaglutamate form of MTA is the predominant intracellular form and is >60-fold more potent than the monoglutamate in its inhibition of TS [8].

MTA exhibits highly cytotoxic in vitro activity against the CCRF-CEM human leukemia cell line and has shown significant antitumor activity against thymidine-and hypoxanthine-deficient murine tumor cell lines as well as two human colon xenografts resistant to methotrexate [1]. Several dose schedules were studied in dogs with the predominant toxicities being gastrointestinal and hematological. Marked schedule dependency was noted, with a 34-fold increase in dose intensity found using a once weekly compared to daily dosing. Folinic acid treatment initiated 24 hours after a potentially fatal dose prevented lethality, suggesting a role for folinic acid in the treatment of severe, drug-induced toxicity [9].

Given the schedule dependency observed in animal models, Phase 1 studies were conducted exploring three treatment schedules: daily times 5 every 3 weeks (H3E-BP-001); weekly times 4 every 6 weeks (H3E-MC- JMAB); and once every 3 weeks (H3E-MC-JMAA).

Thirty-eight patients were treated at doses ranging from 0.2 to 5.2 mg/m$^2$ daily times 5 every 3 weeks in Study BP-001 [10]. The maximum tolerated dose (MTD) was 4 mg/m$^2$/day, with dose limiting toxicities (DLTs) on this schedule of reversible neutropenia and liver enzyme disturbance. Other toxicities included mucositis, diarrhea, rash, fatigue, and elevated transaminases. Minor responses were observed in 2 patients with colorectal and non-small cell lung cancer (NSCLC).

In Study JMAB, 24 patients were treated with a 10-minute infusion of MTA once per week for 4 weeks, with cycles repeated every 6 weeks [11]. Doses ranged from 10 to 40 mg/m$^2$/week. The DLT was myelosuppression, particularly leukopenia and granulocytopenia. Neutropenia prevented weekly dosing in some patients. Nonhematologic toxicities included mild fatigue, anorexia, and nausea. DLT was observed at 40 mg/m$^2$/week and the recommended dose for Phase 2 evaluation was 30 mg/m$^2$/week. Although the plasma phamacokinetic profile of the compound suggests a possible therapeutic advantage with repeated drug exposure, the polyglutamation-mediated intracellular half-life favors less frequent drug dosing. Therefore, the weekly schedule was not pursued in Phase 2 trials.

In study JMAA, MTA was administered to 37 patients as a 10-minute infusion once every 3 weeks at doses ranging from 50 to 700 mg/m$^2$ [12]. The DLTs on this schedule were neutropenia, thrombocytopenia, and fatigue. Of the 20 patients treated at 600 mg/m$^2$, Common Toxicity Criteria (CTC) Grade 4 neutropenia and CTC Grade 4 thrombocytopenia occurred in 4 and 1 patients, respectively, during the first cycle. CTC Grade 2 toxicities at that dose level included rash, mucositis, nausea, vomiting, fatigue, anorexia, and elevations of liver transaminases. Ten patients who developed rashes received dexamethasone 4 mg twice daily for 3 days starting 1 day prior to treatment with MTA which improved or prevented the rash during subsequent cycles of therapy. There was evidence of cumulative toxicities of neutropenia, thrombocytopenia, and mucositis which may have been due to the prolonged intracellular half-life of the polyglutamate of MTA and decreasing renal function over time with decreased renal drug clearance. Based upon this study, the recommended dose for Phase 2 studies was 600 mg/m$^2$. Partial responses were observed in two patients with pancreatic cancer and two patients with advanced colorectal cancer. Three of the 4 patients with partial responses had failed previous treatment with thymidylate synthase inhibitors including either 5-FU, FUDR, or Tomudex.

The pharmacokinetics of MTA have been determined in 3 separate studies, with dosing given once a week for 3 consecutive weeks and also once every 3 weeks [11,12]. Doses were given as 10-minute infusions in all studies. Doses ranged from 10 to 40 mg/m$^2$ weekly for 3 weeks in the first study, 50 to 700 mg/m$^2$ as a single administration every 3 weeks in the second study, and 0.2 to 6.0 mg/m$^2$ given daily for 5 consecutive days, every 3 weeks in the third study.

Pharmacokinetic determinations were made in 20 patients with various cancers (primarily colorectal cancer) at the MTD dose (600 mg/m$^2$). A mean maximum concentration of 137 μg/mL was attained, with a mean half-life of 3.1 hours (range, 2.2 to 7.2 hours). Mean respective clearance and steady-state volume of distribution values of 40 mL/min/m$^2$ and 7.0 L/m$^2$ were also measured. This mean clearance value is similar to that of creatinine clearance in the age range of the patients enrolled (approximately 45 to 55 mL/min/m$^2$), and the volume of distribution reflects limited distribution outside the bloodstream.

Samples collected from the first dose in each course of therapy showed the disposition of MTA to be linear over the entire dose range (0.2 to 700 mg/m$^2$). The clearance of the compound is primarily renal, with 80% or greater of the dose recovered unchanged in the urine during the first 24 hours after dosing. No accumulation appears to occur with multiple courses, and the disposition of MTA does not change after multiple doses. MTA clearance does appear to be dependent upon age, although this dependence is secondary to renal function. An increase in age results in a decrease in MTA clearance, but this relationship is likely a reflection of decreasing renal function with age.

Two Phase 2 studies in colorectal cancer, one in pancreas cancer, two in NSCLC and one in breast cancer began in late 1995. These studies were designed to include patients with advanced disease who were either chemonaive or had received limited prior chemotherapy in the metastatic setting, with a starting dose of 600 mg/m$^2$ once every 21 days. Results from these studies are preliminary.

Clinical activity of MTA in metastatic colorectal carcinoma has been demonstrated in two multicenter trials performed in Canada and the US [13,14]. Prior adjuvant chemotherapy was allowed if completed at least 1 year prior to study entry. In the Canadian study, the starting dose of 600 mg/m$^2$ was reduced to 500 mg/m$^2$ after dose reductions were required in five of the first eight patients. Toxicities leading to these reductions included rash, mucositis, neutropenia, and febrile neutropenia. Responses were seen at this reduced dose in 5 patients for an overall response rate of 17% (95% CI: 6 to 36%) [13]. In the US colorectal study, objective tumor responses were seen in 6 of 40 patients for an overall response rate of 15%(95% CI: 6 - 31%) [14].

Two responses, one complete and one partial, were observed in 35 evaluable patients in the pancreatic cancer Phase 2 study for an overall response rate of 6% [15]. Importantly, there were 13 additional patients with stable disease lasting for over 6 months of treatment, suggesting a clinical benefit not immediately apparent from objective tumor measurements.

A Phase 2 study in patients with locally advanced and/or metastatic breast cancer is ongoing and includes patients who have received prior adjuvant chemotherapy as well as one prior therapy for metastatic disease. Fourteen of 22 patients had received prior chemotherapy, ten as adjuvant treatment, seven for metastatic disease, and three patients who received both. Of the 22 patients evaluable for response, one complete and five partial responses have been documented for an overall response rate of 30%. Responses have been seen in pulmonary and hepatic metastases. Three of the 6 responding patients had received recent prior therapy with paclitaxel, docetaxel or an anthracycline for metastatic disease [16].

One multi-institutional study in NSCLC has been completed in Canada [17] and an additional study is ongoing in Australia and South Africa [18]. All patients were chemonaive. The majority of patients on the Canadian study used the lower starting dose of 500 mg/m$^2$, which was reduced from 600 mg/m$^2$ during the course of the study after

one of the first three patients experienced CTC Grade 3 mucositis and Grade 4 vomiting and myalgia. Seven partial responses have been observed in 30 evaluable patients for an overall response rate of 23.3% (95% CI 9.9 to 42.3%) [17]. All responding patients were treated at the 500 mg/m$^2$ dose level.

The second NSCLC study, which is being carried out jointly between Australia and South Africa, has enrolled 21 patients to date, with 20 evaluable for response. All patients are receiving 600 mg/m$^2$ every 3 weeks in this study. Five partial responses have been noted for an overall response rate of 25% [18]. The initial Phase 2 experience is summarized in Table JMBU.1.

**Table JMBU.1 Phase 2 experience**

| Study | JMAC | JMAD | JMAN | JMAO | JMAG | JMAL |
|---|---|---|---|---|---|---|
| Site | US | US | Canada | Canada | UK | Aus/S Africa |
| Tumor site | colorectal | pancreas | NSCLC | colorectal | breast | NSCLC |
| No. evaluable patients | 39 | 35 | 30 | 29 | 18 | 20 |
| Median cycles | 4 | 2 | 3 | 3 | 4 | 4 |
| (Range) | (1 -12) | (1-12) | (1-8) | (1-8) | (1-9) | (1-9) |
| CR | 1 | 1 | 0 | 1 | 1 | 0 |
| PR | 5 | 1 | 7 | 5 | 5 | 5 |
| Overall RR (%) | 16 | 6 | 23 | 21 | 30 | 25 |
| (95% CI, %) | | | (9.9-42.3) | (8-39.7) | | |

A total of 209 patients have been treated on the once every 3 weeks schedule in the Phase 2 setting at 600 mg/m$^2$ and are evaluable for safety analysis. The most frequent, serious toxicity has been hematologic in nature. CTC Grade 3 and 4 hematologic toxicity included neutropenia (25 and 26%, respectively) and thrombocytopenia (7 and 10%, respectively). Although severe neutropenia is common, the frequency of serious infection has been low (CTC Grade 4 infection 2%). Likewise, thrombocytopenia has been apparent, and yet serious episodes of bleeding have been rare (<1%). While 8% of patients experienced CTC Grade 3 (4% with Grade 4) skin rash, prophylactic dexamethasone is reported to ameliorate or prevent the rash in subsequent cycles. Other Grade 3 and 4 non-hematologic toxicities included stomatitis, diarrhea, vomiting, and infection. As seen in clinical studies of other antifolates, transient Grade 3 and 4 elevation of liver transaminases are common but not dose limiting. There have been no cases of persistent transaminase elevation. Tables JMBU.2 and JMBU.3 summarize the laboratory and non-laboratory toxicity data from the Phase 2 studies conducted at a starting dose of 600 mg/m$^2$.

**Table JMBU.2 Laboratory toxicity (n=209)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Alk Phos | 49 | 13 | 4 | 0 |
| ALT | 33 | 26 | 22 | 0 |
| AST | 42 | 30 | 10 | 0 |
| Bilirubin | | 18 | 7.3 | 2 |
| Creatinine | 13 | 5 | 0 | 0 |
| ANC | 9 | 21 | 27 | 27 |
| Hb | 34 | 43 | 12 | 2.4 |
| Platelets | 31 | 6 | 7 | 8 |

**Table JMBU.3 Non-laboratory toxicity (n=209)**

| | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| Cutaneous | 19 | 39 | 11 | 5 |
| Diarrhea | 17 | 11 | 4 | 3 |
| Infection | 13 | 8 | 2 | 2 |
| Nausea | 33 | 30 | 9 | 0.5 |
| Fatigue | 13 | 11 | 6 | 0 |
| Pulmonary | 0.5 | 7 | 2 | 2 |
| Stomatitis | 23 | 16 | 6 | 1 |
| Vomiting | 13 | 30 | 2 | 3 |

## 1.2. Docetaxel

Docetaxel is an antineoplastic member of the taxoid family, prepared by semisynthesis, from a noncytotoxic precursor extracted from the renewable needle biomass of the Taxus baccata (European yew) [19]. Esterification through the addition of a side chain forms the complete molecule, and is believed to be the source of cytotoxicity in taxoids [20]. Like paclitaxel, a natural product of the T. Brevifolia, the target of docetaxel is tubulin. The mechanism of action of both compounds is promotion and stabilization of microtubule assembly, preventing their depolymerization. However, docetaxel has been shown to be twice as potent as paclitaxel as an inhibitor, in both in vitro and in vivo assays [21]. The stabilization of the microtubules blocks the cell cycle in the mitotic phase [22].

The in vivo antitumor activity of docetaxel has been investigated using murine transplantable tumors with positive results (including B16 melanoma, pancreatic ductal adenocarcinoma, colon adenocarcinoma, and breast tumors) [19]. Phase 2 trials have demonstrated activity in a variety of human solid tumors, with reproducible responses greater than 20% observed in non-small cell lung (NSCL), breast, ovarian, gastric, squamous head and neck, and bladder cancers [21]. Preclinical studies have found

docetaxel to be schedule-independent; splitting the total dose did not alter the antitumor activity. Extensive studies have also demonstrated preclinical synergism with other cytotoxic agents [23-26]. Studies using radiolabeled docetaxel have shown that the drug is approximately 98% protein-bound in humans [27]. Isoenzymes of the cytochrome P450-3A subfamily are thought to be responsible for the metabolism of docetaxel. Following intravenous administration, 75% of drug is eliminated in feces, and 5 to 6% in urine after 7 days, although the majority of drug is recoverable within the first 2 days [19, 27].

Phase 1 trials consistently found the dose-limiting toxicity (DLT) to be neutropenia, but this was not cumulative. Additionally, heavily pre-treated patients were not at increased risk for severe neutropenia [28]. Thrombocytopenia and anemia tended to be relatively insignificant. Non-hematologic toxicity, less severe than hematologic, was noted more frequently in the Phase 2 setting. Oral mucositis appeared to coincide with neutrophil nadirs, but was more pronounced with longer infusion times [28-31]. A syndrome of potentially severe fluid retention has been identified following docetaxel therapy, characterized by peripheral edema, pleural effusion, and ascites. Premedication with corticosteroids (eg, dexamethasone) has been shown to be effective in reducing the incidence and severity of the retention [32] as well as any hypersensitivity reaction associated with the drug. Fluid retention is responsive to treatment with diuretics, but is completely, if somewhat slowly, reversible following discontinuation of docetaxel therapy [33].

Other non-hematologic toxicities include alopecia, mild cutaneous reactions, gastrointestinal events, such as nausea, vomiting, and diarrhea, neurosensory events (eg, mild paresthesias), and asthenia. Patients with bilirubin >upper limit of normal (ULN), or those with transaminases >1.5 × ULN concomitant with alkaline phosphatase >2.5 ULN, are at increased risk to develop Grade 4 neutropenia, febrile neutropenia, infections, Grade 4 thrombocytopenia, Grade 4 stomatitis, Grade 4 cutaneous toxicities, and toxic death [34].

The current recommendation on dosing is 60 to 100 mg/m$^2$ intravenously every 21 days, preceded by premedication with oral corticosteroids, such as dexamethasone, to prevent hypersensitivity reactions and reduce the incidence/severity of fluid retention. The recommended dose of dexamethasone is 16 mg/day for 5 days, beginning on the day prior to docetaxel administration [34].

The demand for effective treatment of advanced and metastatic cancers is increasing, particularly with combination chemotherapy regimens. It is therefore proposed to study the combination of MTA, which has demonstrated activity in solid tumors such as, colorectal, NSCL, and breast cancers, and docetaxel, known for its single agent activity in a variety of solid tumors [21], notably breast and NSCLC (in common with MTA).

# 2. Objectives

## 2.1. Primary Objective

The primary objective of this study is to determine the maximum tolerated dose (MTD) of MTA and docetaxel combination therapy in the treatment of patients with locally advanced or metastatic cancer.

## 2.2. Secondary Objectives

The secondary objectives of this study are:

- To determine the quantitative and qualitative toxicities of MTA in combination with docetaxel in this patient population.
- To determine the recommended dose of MTA and docetaxel for subsequent Phase 2 studies.
- To assess the pharmacokinetics of MTA in this combination.

# 3. Investigational Plan

## 3.1. Summary of Study Design

This is a nonrandomized Phase 1, dose-finding, open label study of combination therapy with MTA and docetaxel in patients with locally advanced or metastatic cancer.

MTA will be administered as a 10-minute intravenous infusion on Day 1 of a 21-day cycle. Docetaxel will be administered immediately following MTA administration as a 1-hour intravenous infusion on Day 1 of a 21-day cycle.

A cycle is comprised of one treatment of MTA and one treatment of docetaxel every 21 days. This 3-week schedule defines a cycle of treatment. Several dose levels of MTA and docetaxel will be tested until the MTD is established. Three to 6 patients will be treated at each dose level. For the definition of MTD, see Section 3.7.3.2.

Subject to the continuing approval of Eli Lilly and Company (Lilly), each patient may remain in the study until disease progression is noted, until either the patient or investigator thinks that it is in the patient's best interest to discontinue or if unacceptable toxicity occurs.

## 3.2. Discussion of Design and Control

A single-arm, open label study without controls is appropriate for this group of patients. Both drugs used in this combination have proven to be effective as single agents in selected solid tumors. The dose-limiting toxicities (DLTs) of MTA are neutropenia and thrombocytopenia. In addition to the dose, another factor determining the severity of myelosuppression is the extent of prior chemotherapy and the schedule of drug administration.

The initial dose of MTA will be 300 mg/m$^2$ administered on Day 1 of a 21-day cycle. The initial dose of docetaxel will be 75 mg/m$^2$ administered immediately after MTA administration. Dose escalations will proceed as outlined in Section 3.7.3.1.

## 3.3. Investigator Information

The name, title, and institution of the investigator(s) are listed on the Investigator/Contacts cover pages provided with this protocol. If an investigator is changed after the study has been approved by Lilly, an ethical review board, or a regulatory agency, this addition will not be considered a change to the protocol, but the Investigator/Contacts cover pages will be updated to provide this information.

### 3.3.1. Final Report Signature

The final report coordinating investigator will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The investigator with the greatest number of evaluable patients will serve as the final Lilly report coordinating investigator.

## 3.4. Study Population

### 3.4.1. Entry Procedures

Informed consent will be obtained from each patient after the nature of the study is fully explained.

### 3.4.2. Criteria for Enrollment

Enter — The act of obtaining informed consent for participation in a clinical study from individuals deemed potentially eligible to participate in the clinical study. Individuals entered into a study are those for whom informed consent documents for the study have been signed by the potential study participants or their legal representatives.

Enroll — The act of assigning an individual to a treatment group. Individuals who are enrolled in the study are those who have been assigned to a treatment group.

A person who has been entered into the study is potentially eligible to be enrolled in the study, but must meet all criteria for enrollment specified in the protocol before being enrolled (assigned to a treatment group). Individuals who are entered into the study but fail to meet the criteria for enrollment are not eligible to participate in the study and will not be enrolled.

Adverse events are reported for all individuals who receive study drug.

The expected recruitment will be a maximum of 40 patients. The total patient population will depend on the number of patients required at each dose level before MTD is established. Informed consent will be obtained from each patient after the nature of the study is fully explained.

#### 3.4.2.1. Inclusion Criteria

Patients may be included in the study only if they meet **all** of the following criteria: