CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-462

Medical Review(s)

Division Director's Memorandum

Date: February 4, 2004
NDA: 21-462
Sponsor: Eli Lilly and Company
Proprietary Name: Alimta® (pemetrexed for injection)

Administrative History
On July 8, 1992, the initial IND was submitted. The product received Orphan designation on August 28, 2001. On June 10, 2002, this application received Fast Track designation for malignant pleural mesothelioma and the Division accepted Lilly's plan for a rolling submission. The first parts of the NDA were submitted October 24, 2002 and the last reviewable unit (CMC) was received on September 30, 2003. The PDUFA goal date for this priority review is March 30, 2004.

Proposed Indication
ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.

Available Therapies
No drug treatment has been shown to prolong survival in this setting.

Clinical Review (see reviews by Dr. White, Dr. Hazarika, and Dr. Johnson)
A single randomized clinical trial was conducted, entitled, "A Single-blind Randomized Phase 3 Trial of Alimta plus Cisplatin versus Cisplatin Alone in Patients with Malignant Pleural Mesothelioma."

This multi-center study included 88 principal investigators at a total of 88 study centers located in 20 countries. The primary objective was to compare survival in chemonaive patients with malignant pleural mesothelioma treated with Alimta plus cisplatin combination therapy to survival in the same patient population treated with cisplatin alone.

A total of 574 patients were entered into the study (signed the informed consent document). Four hundred fifty-six of these patients were randomized to a treatment arm and 448 were treated and constitute the randomized and treated (RT) population.

During this study, after about 25% of the randomized population had been treated, vitamin B_{12} and folic acid supplementation was found to reduce Alimta toxicities. At that time all patients in both treatment groups in the randomized trial were supplemented with vitamins. This resulted in three subgroups in each treatment arm regarding vitamin supplementation. These groups are never supplemented (NS), partially supplemented (PS) and fully

supplemented (FS). Patient totals for the Alimta/cisplatin group are RT 226, FS 168, PS or never supplemented 58, and for the cisplatin alone group are RT 222, FS 163 and PS or NS 59. The FDA review focuses on all RT patients (the primary analysis) and the FS patients (the proposed labeled administration.)

The primary efficacy analysis was comparison of survival between the study arms in the RT population. Differences were assessed using a two-sided log rank test. Because an interim analysis was conducted (resulting in a decision to continue the trial to planned completion), the comparison of survival was tested at the p=0.0476 level.

In the RT patient analysis, the combination of Alimta and cisplatin demonstrated a statistically significant improvement in survival with median survivals of 12.1 versus 9.3 months, respectively (p=0.020). This superiority in the combination arm was also demonstrated in the fully supplemented subgroup with median survivals of 13.3 and 10.0 months in the combination and cisplatin alone groups, respectively (p=0.051). In an exploratory analysis, the effect on survival was larger in females (n=83, 15.7 vs. 7.5 months median survival) than in males (n=305, 11 months vs. 9.4 months).

Pathologic diagnosis of malignant pleural mesothelioma may be difficult. Because of concern that some patients may have other kinds of cancer, a subgroup survival analysis was performed, including only the 303 patients with a histologic diagnosis of malignant pleural mesothelioma confirmed by a central independent pathology review. This subgroup analysis corroborates the primary survival analysis. The median survival times were 13 and 10.2 months in the RT combination and cisplatin alone groups, respectively (p=0.06). The median survival times were 14.4 and 10.3 months in the RT fully supplemented combination and cisplatin alone groups, respectively (p=0.058).

Prior to the trial's initiation, the FDA indicated to the Applicant that tumor response in this disease cannot be reliably assessed and that the FDA would not form primary efficacy decisions based on tumor response or time-to-tumor progression. Tumor response and time-to-progression were assessed, but the results were not interpretable. Tumor response criteria are not well established in pleural malignant mesothelioma. The tumor often grows in sheets rather than well demarcated spherical configurations. The tumor response assessments were inconsistent between the study investigators and the two independent reviewers. The FDA review of the submitted films could confirm tumor response in only 47 of the 94 patients in the combination group for whom the Applicant claimed responses. Patients in the combination group did appear to have a better response rate and longer time-to-progression; however, numerical results for tumor response and time-to-progression are not included in the product label.

Patients were assessed with the Lung Cancer Symptom Scale (LCSS). Although there were statistically significant changes favoring the combination group in some components and in the overall score, none of the changes was judged to be clinically important. No claims regarding the LCSS were included in the label.

Patients were also assessed during the study for pulmonary function by measuring slow vital capacity, forced vital capacity and forced expiratory volume in one second. There were

statistically significant changes in the pulmonary function tests favoring the combination group. However, consultation from the FDA's Division of Pulmonary Drug Products indicated that the reported mean changes were within the range of normal variation of the tests and are not considered clinically important.

The Division of Pulmonary Drugs recommended forced vital capacity (FVC) as the most appropriate pulmonary function test in these patients because the disease effect is constrictive rather than obstructive. To further assess the effect of treatment on pulmonary function, the Oncology Drug Products Division performed the following two analyses intended to consider meaningful changes in pulmonary function using the electronic database.

In the first analysis 337/448 (75%) of RT patients who had a baseline and at least one follow-up FVC, 26.6% and 21.3% of combination group patients had an increase over baseline FVC of $\geq$ 400 mL and $\geq$ 500 mL, respectively, on at least one follow-up visit. The differences between the combination and cisplatin alone groups are statistically significant. However, the increases in FVC were maintained for at least 6 weeks in only about half of the combination group patients. The difference between treatment groups was no longer statistically significant.

In the second analysis 28.4% and 17.2% of combination group patients had an increase from baseline FVC of $\geq$ 20% and $\geq$ 30% on at least one follow-up visit, respectively. The differences between the combination and cisplatin alone treatment groups are statistically significant. The increases in FVC were maintained for at least 6 weeks in only about half of the combination group patients. But the difference between treatment groups remains statistically significant.

Based on these two analyses, together with the overall mean increase, a labeling claim for a modest beneficial effect on pulmonary function can be made.

The adverse effects of the combination regimen are acceptable for chemotherapy drug products. The principal adverse effects that are greater with the combination than with cisplatin alone are myelosuppression, severe nausea and vomiting, and rash/desquamation. Patients in both groups were fatigued and had dyspnea and chest pain, probably related to the underlying disease. Severe hematologic and gastrointestinal adverse effects are significantly reduced by supplementation with vitamin B_{12} and folic acid without any decrement in efficacy.

Alimta is eliminated primarily by the renal route. In clinical studies, patients with creatinine clearance $\geq$ 45 mL/min required no dose adjustments other than those recommended for all patients, although AUC's were increased by about 50-60% in patients with CLcr of 45-50 mL/min. Insufficient patient numbers with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this patient group. Alimta should not be administered to patients whose creatinine clearance is < 45 mL/min using the Cockcroft and Gault formula or GFR measured by Tc99m-DPTA serum clearance method.

Biostatistical Review (see Dr. Wang's review)
The results of the biostatistical review are presented in the table below and have been previously discussed in the clinical section.

Primary Endpoint: Survival for RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	Combo (N=226) n (%)	Cis (N=222) n (%)	Combo (N=168) n (%)	Cis (N=163) n (%)	Combo (N=58) n (%)	Cis (N=59) n (%)
Patients dead[a]	145 (64)	159 (72)	95 (57)	103 (63)	50 (86)	56 (95)
Survival time (months)						
Median	12.1	9.3	13.3	10.0	9.5	7.2
(95% CI)	(10.0,14.4)	(7.8, 10.7)	(11.4,14.9)	(8.4, 11.9)	(8.1, 10.8)	(6.5, 9.9)
p-value[b]						
Long-rank	0.021		0.051		0.253	
Wilcoxon	0.028		0.039		0.440	
Hazard Ratio[c]	0.766		0.758		0.798	
95% CI for Hazard Ratio[c]	(0.61, 0.96)		(0.57, 1.0)		(0.54, 1.17)	

Results based on the analysis of data sets provided by the sponsor.
Combo = combination of cisplatin plus Alimta; Cis = single-agent cisplatin
[a] Patients were died for different reasons: study disease related, study toxicity, and other causes.
[b] P-value is based on the test results for the two treatment groups.
[c] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

Chemistry/Manufacturing and Controls Review (see Dr. Liang's review for details)
ALIMTA, pemetrexed (L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-,disodium salt heptahydrate) drug substance, contains one chiral center and is a disodium salt containing seven water molecules of hydration (heptahydrate) in the solid state of the drug product. The molecular formula is $C_{20}H_{19}N_5O_6Na_2.7H_2O$, and the molecular weight is 597.49 daltons.

Pemetrexed drug substance is —— and its structure is well characterized. During the review process, several discrepancies related to stereoisomer control and correct USAN nomenclature were resolved.

Alimta drug product is supplied in glass vials as a single-use sterile lyophilized powder for intravenous infusion. Each —— of Alimta contains —— pemetrexed disodium heptahydrate (equivalent to 500 mg pemetrexed free acid) and 500 mg of mannitol. Sodium hydroxide and, if necessary, hydrochloric acid are added to adjust the pH. Eli Lilly manufactures the drug product in Fegersheim, France.

Each vial of Alimta is reconstituted with 20 mL of commercially available 0.9% Sodium Chloride Injection without preservatives to a concentration of 25 mg/mL of pemetrexed as free acid. This reconstituted pemetrexed solution must be further diluted to 100 mL with

0.9% Sodium Chloride Injection prior to intravenous infusion. The final concentration of drug product solution to be administrated is 0.25 mg/mL pemetrexed as free acid.

During the review process, deficiencies related to the control of drug product total impurities were resolved. The applicant agreed to restrict the limit for total impurities from NMT — % to NMT — % as an interim specification and to reevaluate the limit for total impurities within 24 months (or after ten commercial batches of drug product have been manufactured).

raise clinical concern. Any impurity profile — within the specified — range will be within current impurity limits.

The drug substance, drug product, and the reconstituted drug product solution have adequate stability characteristics to support a 24-month shelf life for the drug product based on primary and supportive stability data.

Nonclinical Review (see Dr. Lee Ham's review and Dr. Morse's team leader memo)
Alimta® (pemetrexed disodium) is a pyrrolopyrimidine antifolate. Although it's mechanism of action is not fully understood, multiple non-clinical studies suggest pemetrexed exerts antineoplastic activity by interfering with folate-dependent metabolic processes essential for cell replication. After entrance into the cell (via reduced folate carrier [RFC] and membrane folate-binding protein [FBP]), pemetrexed is rapidly polyglutamated by folypolyglutamate synthetase. Both parent and polyglutamated pemetrexed act as competitive inhibitors of several folate-dependent enzymes, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide transferase (GARFT), which are key enzymes for de novo nucleotide biosynthesis. These actions are similar to methotrexate, which has inhibitory effects on thymidylate synthase (TS) and dihydrofolate reductase (DHFR).

When tested in a series of *in vitro* and *in vivo* (xenograft) models of cancer, pemetrexed demonstrated activity against a variety of tumor types, including leukemia (CCRF-CEM, L1210), lung (A549), mesothelioma (NCI-H2052 and MSTO-211H), breast (MCF7), colon (GC3 and HCT8), and ovarian cancer (SKOV1).

Non-clinical toxicity studies were conducted to determine the acute and repeat-dose effects when administered to mice, rats, and dogs. Toxicity studies included: single and repeat dose studies of 2- and 6-weeks intraperitoneal (ip) dosing in mice, and 4- and 6-weeks, and 6-months intravenous (iv) dosing in dogs. In single dose studies, pemetrexed demonstrated limited acute toxicity in mice and rats, but more extensive toxicity in dogs. Six week repeat dose studies were conducted using daily, twice weekly or weekly ip doses in mice and iv doses in dogs. Mice tolerated weekly ip doses of up to 944 mg/m^2 (twice the clinical dose) without death or toxicity, whereas weekly iv dosing at 2099 mg/m^2 (four times the clinical

dose) resulted in the early termination of several dogs. Repeat-dose adverse effects at higher doses caused decreased food consumption, emesis, diarrhea, mucositis, decreased red cell parameters, leukopenia, neutropenia, and increased hepatic enzymes in dogs. In mice, weight loss and leukopenia were the predominant drug toxicities. Histopathologic indices generally occurred in the thymus, lymph nodes, GI tract, testis, bone marrow, and skin.

Pemetrexed (intravenous) doses of $\geq$ 0.3 mg/m^2 caused testicular atrophy and reduced fertility. Further, pemetrexed was embryotoxic and teratogenic in mice when administered at 0.6 mg/m^2. Pemetrexed caused no genetic damage in a standard battery of *in vitro* tests, mutation and clastogenicity assays, although, pemetrexed was clastogenic in the micronucleus assay. Carcinogenicity studies of pemetrexed disodium have not been conducted.

Limited non-clinical investigations of "rescuing agents" (leucovorin and thymidine) were conducted with pemetrexed administration. Results suggest that the co-administration of leucovorin (20 mg/kg im days 5-10; 25 mg/kg im days 4, & 5, and 50 mg/kg iv day 4) reduced or reversed the toxicity of pemetrexed (50 mg/kg iv days 1 & 4) in dogs. Dogs given pemetrexed (50 mg/kg, iv days 0 & 3) with thymidine (8 mg/kg, days 4-7, administration as a continuous infusion) had no toxic alterations associated with pemetrexed compared to the saline-treated controls.

AUC values for pemetrexed were approximately dose proportional following single ip or iv administration to mice, and iv administration to dogs and humans. Elimination half-life was significantly shorter in dogs and man when compared to mice. The PK profile was biphasic following radiocarbon tracer administration, with rapid tissue distribution following an iv dose and subsequent elimination (tissue levels generally did not persist beyond 3 hrs post-dose).

Clinical Pharmacology and Biopharmaceutic Review (see Dr. Booth's review)
The pharmacokinetics of Alimta follow a 2-compartment model, and excretion is predominantly renal. Alimta was not metabolized by any cytochrome P-450, nor did it inhibit any cytochrome P-450 isozyme. Total systemic clearance is 91.8 mL/min and is correlated with glomerular filtration rate and creatinine clearance (CLcr) (Cockcroft-Gault formula). The elimination half-life is 3.5 hours; accumulation was not noted. The pharmacokinetics were unaffected by sex, age or ethnicity.

Cisplatin co-administration did not alter the Alimta's pharmacokinetics or vice versa. Co-administration of carboplatin did not alter the pharmacokinetics of Alimta, but the pharmacokinetics of carboplatin may have been affected. Neither folic acid/vitamin B_{12} nor aspirin (1.3 mg/day) altered Alimta pharmacokinetics. However, ibuprofen increased Alimta AUC by approximately 20% at a moderate dose of 1.6 gm/day. Renal impairment studies of Alimta as a single agent indicated that the Alimta AUC increased by 130% in patients with moderate renal impairment (CLcr 30-50 mL/min; n=6), suggesting that neutropenia might be exacerbated in these patients. These studies were not considered sufficient to provide dosing recommendations for patients with CLcr < 45 mL/min.

Labeling (see DMETS review)
DMETS reviewed the draft container labels, carton, and insert labeling for Alimta and focused on safety issues relating to possible medication errors. DMETS recommended the following changes to minimize potential user errors.

- Carton labeling (500 mg Single-Use Vial): Increase the prominence of the route of administration on the principal display panel by bolding or other means. Repeat the statement, "Caution: Cytotoxic Agent" on the principal display panel.
- [redacted]

Data Integrity Issues (see Dr. Gan's Clinical Inspection Summary)
The Division of Scientific Investigation investigated four sites (University of Chicago Hospital, Chicago, IL; Texas Oncology, Dallas, TX; and sites in Milano, Italy and Hamburg, Germany) and found the data adequate for safety and efficacy evaluation.

Tradename consultation
The tradename, Alimta, is acceptable to DDMAC and DMETS (see DMETS review).

Pediatric Considerations
Malignant pleural mesothelioma does not occur in children.

Conclusions and Recommendations: **Approval**
The trial contained in this application demonstrates a survival advantage in patients with malignant pleural mesothelioma treated with Alimta plus cisplatin compared to those treated with single-agent cisplatin. These patients were either unresectable or were otherwise not candidates for curative surgery. No other drug, including cisplatin, has demonstrated a survival advantage in this life-threatening disease setting associated with a short survival. The Division has consistently accepted a survival improvement to demonstrate clinical benefit. Hence, this application was not presented to the Oncologic Drugs Advisory Committee (ODAC). The trial's design allows demonstration of Alimta's effect on the primary study endpoint (survival).

Although a single randomized trial supports this NDA, this trial was multi-institutional with over 88 study centers enrolling over 574 patients and is the largest randomized study ever conducted in this disease. The primary efficacy analysis was confirmed in the randomized and treated (RT) population as well as in a subset population--the fully vitamin supplemented group (FS). Although the Division did not allow specific numbers to be included in response rate and time-to-progression analyses because of the inaccuracies and difficulties in

measuring disease in mesothelioma patients, the Division acknowledges that the combination treatment group did appear to show an improvement in these secondary endpoints. An additional secondary endpoint of improvement in pulmonary function (forced vital capacity) was also included in the product label.

The safety profile of the proposed combination of Alimta plus cisplatin with vitamin supplement (and corticosteroids for skin rash prophylaxis) is consistent with other cytotoxic chemotherapy agents approved by the Division. The primary toxicities include myelosuppression, fatigue, nausea, vomiting, and dyspnea. The product label clearly advises physicians of specific vitamin use to reduce the toxicity. Hence, an acceptable risk-benefit relationship is noted with the combination. The recommended regulatory action is approval of NDA 21-462.

Richard Pazdur, MD
Director, Division of Oncology Drug Products

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/s/

Dianne Spillman
2/4/04 12:26:54 PM
CSO

Richard Pazdur
2/4/04 12:31:55 PM
MEDICAL OFFICER

ONCOLOGY DRUGS CLINICAL TEAM LEADER REVIEW OF NDA

NDA 21462

NAME OF DRUG Alimta (pemetrexed)

APPLICANT Eli Lilly

CLINICAL TEAM LEADER John R. Johnson M. D.

DATE REVIEW COMPLETED December 10, 2003

ADMINISTRATIVE 8-28-01 Orphan Drug Designation
6-10-02 Fast Track Designation
10-24-02 Initial Rolling Submission
9-30-03 Final Rolling Submission

PROPOSED INDICATION

ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are not otherwise candidates for curative surgery.

PRESENT ARMAMENTARIUM

No treatment has been shown to prolong survival in this setting.

CLINICAL TRIAL

One randomized clinical trial was conducted.

Title:

A Single-blind Randomized Phase 3 Trial of Alimta plus Cisplatin versus Cisplatin Alone in Patients with Malignant Pleural Mesothelioma

This multicenter study included 88 principal investigators who entered patients at a total of 88 study centers located in 20 countries.

Primary Objective:

To compare survival in chemonaive patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery when treated with Alimta plus cisplatin combination therapy to survival in the same patient population when treated with cisplatin alone.

Secondary Objectives:

To compare between the two treatment arms: (1) time-to-event efficacy measures, including: a) duration of response for responding patients, b) time to progressive disease, c) time to treatment failure; (2) tumor response rate; (3) clinical benefit response rate; (4) Lung Cancer Symptom Scale (LCSS) patient and observer scores; (5) pulmonary function tests; (6) lung density; (7) relative toxicities; (8) to assess the impact of folic acid and vitamin B12 supplementation on toxicity; (9) pharmacokinetic effects; (10) information regarding vitamin metabolite status in this patient population.

Treatment:

Alimta plus cisplatin treatment arm: Alimta was administered at a dose of 500 mg/m2 diluted in approximately 100 mL normal saline as a 10-minute intravenous infusion. Approximately 30 minutes after the administration of Alimta, cisplatin was administered at a dose of 75 mg/m2 over 2 hours. Both drugs were administered on Day 1 of a 21-day period. This 21-day period defined one cycle of therapy.

Cisplatin alone treatment arm: Approximately 100 mL normal saline was given as an intravenous infusion over approximately 10 minutes. Approximately 30 minutes after the administration of normal saline, cisplatin was administered at 75 mg/m2 over 2 hours on Day 1 of a 21-day period. This 21-day period defined one cycle of therapy.

Both treatment arms:

Dexamethasone 4 mg (or an equivalent corticosteroid) was taken by all patients orally twice a day 1 day before, on the day of, and 1 day after each dose of Alimta for primary prophylaxis against rash.

Folic acid and vitamin B12 for supplementation were standard components of therapy for all patients participating in the study from December 2, 1999 onwards. Folic acid 350 to 1000 µg was administered orally daily, beginning approximately 1 to 3 weeks before the first dose of therapy and continued daily for 1 to 3 weeks after the patient discontinued treatment. A vitamin B12 injection 1000 µg was administered intramuscularly approximately 1 to 3 weeks before the first dose of therapy and was repeated approximately every 9 weeks until the patient discontinued study therapy.

Patient Population:

A total of 574 patients were entered into the study (that is,signed the Informed Consent Document). Four hundred fifty six of these patients were randomized to a treatment arm and 448 of these patients were treated and constitute the randomized and treated (RT) population.

Initially no vitamin supplementation was given. Part way through the study it became apparent from other Alimta studies that vitamin supplementation was beneficial from a safety standpoint. At that time all patients in both treatment groups in the randomized trial were supplemented with vitamins. This resulted in three subgroups in each treatment arm regarding vitamin supplementation. These groups are never supplemented (NS), partially supplemented (PS) and fully supplemented (FS). Results are reported for each group. This review will focus on all RT patients (the primary analysis) and the FS patients (the proposed labeled administration.)

Alimta plus cisplatin: Total RT 226, Male 184, Female 42,
Fully Supplemented (FS) 168, Partially Supplemented (PS) or
Never Supplemented (NS) 58.

Cisplatin alone: Total RT 222, Male 181, Female 41,
Fully Supplemented (FS) 163, Partially Supplemented (PS) or
Never Supplemented (NS) 59.

Statistics:

The primary efficacy analysis was comparison of survival time between the study arms in the RT population. Differences were assessed using a two-sided log rank test. Because an interim analysis was conducted (resulting in a decision to continue the trial to planned completion), the comparison of survival was tested at the p=0.0476 level.

Patient Characteristics:

The following Tables compiled by the Applicant show the disease and demographic factors for the study patients. These are well balanced between the treatment groups.

Table JMCH.11.3. Summary of Patient Characteristics RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Sex				
Male	136 (81.0%)	48 (82.8%)	134 (82.2%)	47 (79.7%)
Female	32 (19.0)	10 (17.2)	29 (17.8)	12 (20.3)
Origin				
Caucasian	150 (89.3)	54 (93.1)	153 (93.9)	53 (89.8)
Hispanic	10 (6.0)	1 (1.7)	7 (4.3)	5 (8.5)
Asian[1]	7 (4.2)	3 (5.2)	3 (1.8)	1 (0.7)
African	1 (0.6)	0	0	0
Age				
Median	60	62	60	61
Minimum	29	32	19	35
Maximum	85	77	82	84

[1] Western and East/Southeast Asian have been combined.

Table JMCH.11.5. Baseline Stratification Factors Used for Randomization RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
KPS				
Low (≤80)	83 (49.4%)	26 (44.8)	69 (42.3%)	28 (47.5)
High (≥90)	85 (50.6)	32 (55.2)	94 (57.7)	31 (52.5)
Degree of Measurability[1]				
Unidimensional	61 (36.5)	12 (20.7)	62 (38.0)	11 (18.6)
Bidimensional	106 (63.5)	46 (79.3)	101 (62.0)	48 (81.4)
Histologic Subtype				
Epithelial	117 (69.6)	37 (63.8)	113 (69.3)	39 (66.1)
Mixed	25 (14.9)	12 (20.7)	25 (15.3)	11 (18.6)
Sarcomatoid	14 (8.3)	4 (6.9)	17 (10.4)	8 (13.6)
Other	12 (7.1)	5 (8.6)	8 (4.9)	1 (1.7)
WBC				
Low (<8.3 Gl/L)	72 (42.9)	25 (43.1)	68 (41.7)	23 (39.0)
High (≥8.3 Gl/L)	96 (57.1)	33 (56.9)	95 (58.3)	36 (61.0)
Pain Intensity[2]				
Low (<20 mm)	82 (49.4)	30 (51.7)	80 (49.1)	33 (55.9)
High (≥20 mm)	84 (50.6)	28 (48.3)	83 (50.9)	26 (44.1)
Analgesic Consumption				
Low (<60 mg morp eq/day)	129 (76.8)	44 (75.9)	124 (76.1)	46 (78.0)
High (≥60 mg morp eq/day)	39 (23.2)	14 (24.1)	39 (23.9)	13 (22.0)
Dyspnea[2]				
Low (<20 mm)	66 (39.8)	25 (43.1)	68 (41.7)	24 (40.7)
High (≥20 mm)	100 (60.2)	33 (56.9)	95 (58.3)	35 (59.3)
Homocysteine				
Low (<12 umol/L)	119 (70.8)	36 (62.1)	118 (72.4)	38 (64.4)
High (≥12 umol/L)	49 (29.2)	22 (37.9)	45 (27.6)	21 (35.6)
Sex				
Male	136 (81.0)	48 (82.8)	134 (82.2)	47 (79.7)
Female	32 (19.0)	10 (17.2)	29 (17.8)	12 (20.3)

1 A single patient was missing their evaluable disease measurement at baseline.

2 Patients 302-3025 and 720-7209 completed the patient LCSS at baseline, but outside of the protocol defined window, those data are not included in the reporting database.

Table JMCH.11.7. Summary of Baseline Disease Characteristics RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Diagnosis / Histology				
Epithelial	117 (69.6%)	37 (63.8%)	113 (69.3%)	39 (66.1%)
Mixed	25 (14.9)	12 (20.7)	25 (15.3)	11 (18.6)
Sarcomatoid	14 (8.3)	4 (6.9)	17 (10.4)	8 (13.6)
Other	12 (7.1)	5 (8.6)	8 (4.9)	1 (1.7)
Stage at Entry				
Ia	8 (4.8)	1 (1.7)	7 (4.3)	1 (1.7)
Ib	7 (4.2)	0	5 (3.1)	1 (1.7)
II	27 (16.2)	8 (13.8)	27 (16.8)	6 (10.2)
III	51 (30.5)	22 (37.9)	49 (30.4)	19 (32.2)
IV	74 (44.3)	27 (46.6)	73 (45.3)	32 (54.2)
Unspecified	1 (0.6)	0	2 (1.2)	0
Performance Status				
70	25 (14.9)	12 (20.7)	22 (13.5)	9 (15.3)
80	58 (34.5)	14 (24.1)	47 (28.8)	19 (32.2)
90	67 (39.9)	26 (44.8)	69 (42.3)	25 (42.4)
100	18 (10.7)	6 (10.3)	25 (15.3)	6 (10.2)

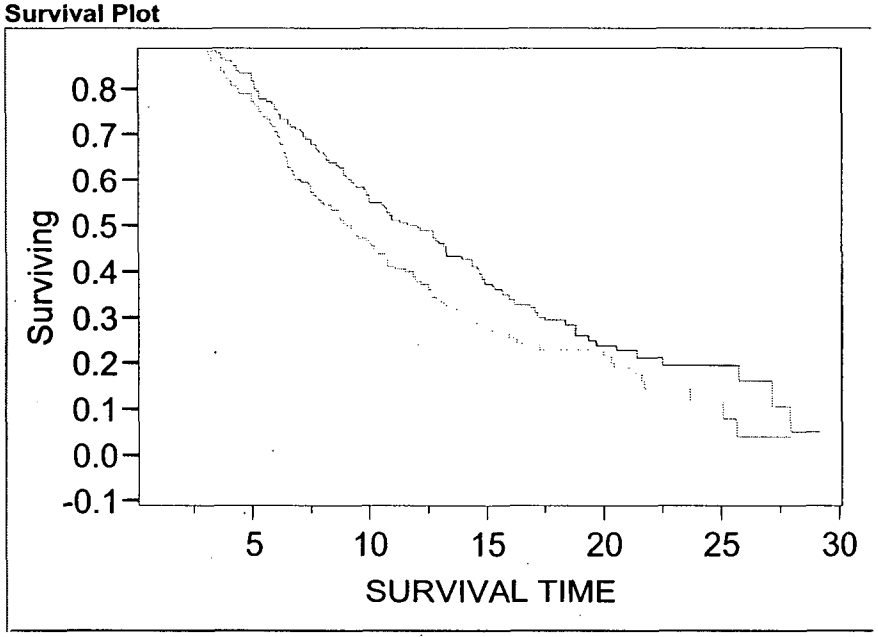
Efficacy Results:

Survival

In the all RT patients analysis the combination of Alimta and cisplatin demonstrates a statistically significant improvement in survival compared to cisplatin alone with median survivals of 12.1 versus 9.3 months, respectively (p=0.020). An ITT analysis on all randomized patients, including 8 patients not in the RT analysis, yields nearly identical results to the RT analysis. This superiority in the Alimta/cisplatin arm is also demonstrated in the fully supplemented subgroup with median survivals of 13.3 and 10.0 months in the Alimta/cisplatin and cisplatin alone treatment groups, respectively (p=0.051).

All Randomized Treated Patients (448)

Product-Limit Survival Fit
Survival Plot



Time intervals are in months.

M2 = Alimta/cisplatin (upper curve)
M39 = cispaltin alone (lower curve)

Summary

Group	N Failed	N Censored	Mean	Std Dev
M2	145	81	13.5305 Biased	0.64943
M39	159	63	11.485 Biased	0.56377
Combined	304	144	12.5648 Biased	0.44228

Quantiles

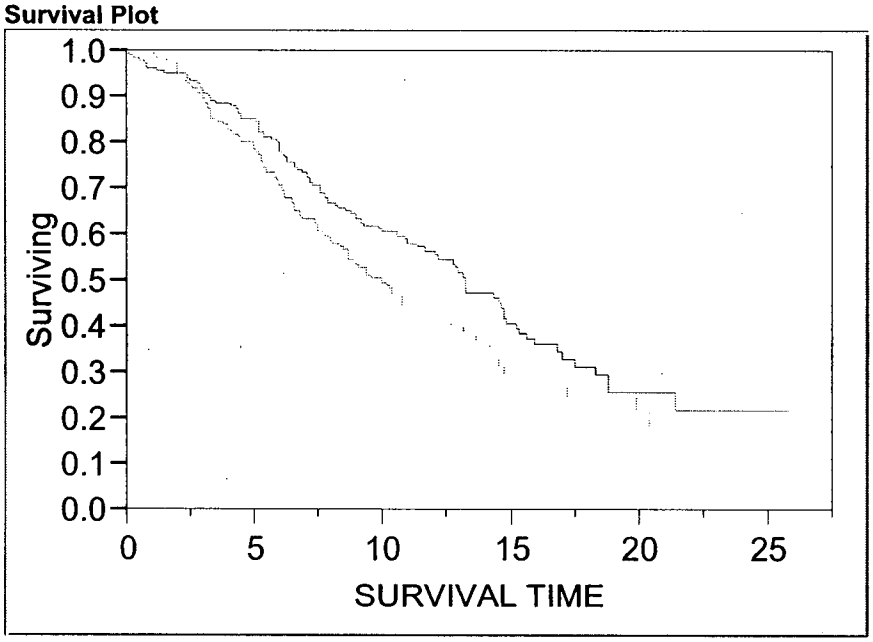
Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
M2	12.1	10	14	6.1	19.7
M39	9.3	7.8	10.7	5.5	16.4
Combined	10.4	9.3	11.9	5.9	18.9

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.4033	1	0.0201
Wilcoxon	4.8458	1	0.0277

RT Fully Supplemented Patients (331)

Product-Limit Survival Fit
Survival Plot



Time intervals are in months.

M2 = Alimta/cisplatin (upper curve)
M39 = cispaltin alone (lower curve)

Summary

Group	N Failed	N Censored	Mean	Std Dev
M2	95	73	12.8946 Biased	0.57646
M39	103	60	11.1832 Biased	0.55631
Combined	198	133	12.1377 Biased	0.41116

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
M2	13.3	11.4	14.9	6.6	21.5
M39	10	8.4	11.9	5.4	17.3
Combined	11.9	10	13.3	6	18.9

Tests Between Groups

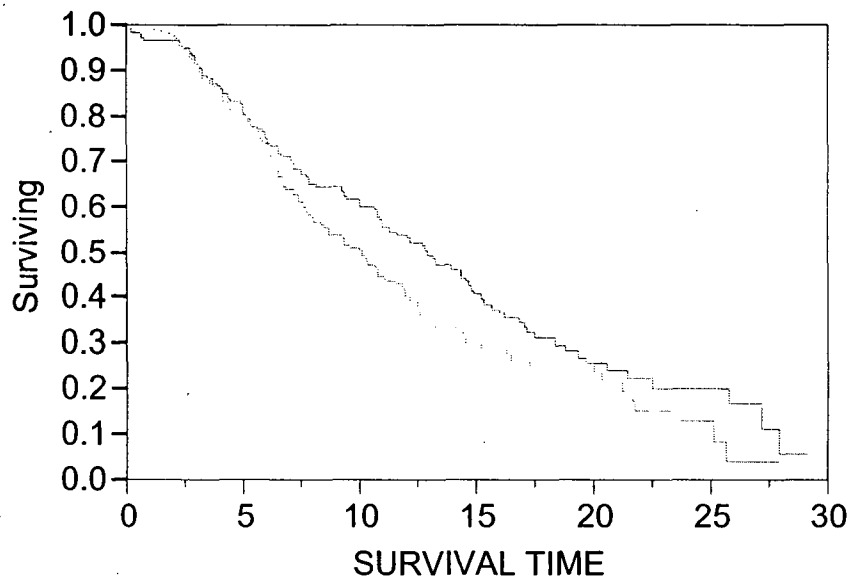
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.8084	1	0.0510
Wilcoxon	4.2649	1	0.0389

Pathologic diagnosis of malignant pleural mesothelioma is sometimes difficult. Because of concern that some patients may have other kinds of cancer a subgroup analysis of survival was done including only patients with a histologic diagnosis of malignant pleural mesothelioma confirmed by central independent pathology review. This subgroup

analysis supports the primary survival analysis. The median survival times were 13 and 10.2 months in the RT Alimta/cisplatin and cisplatin alone treatment groups, respectively (p=0.06). The median survival times were 14.4 and 10.3 months in the RT fully supplemented Alimta/cisplatin and cisplatin alone treatment groups, respectively (p=0.058).

Confirmed Mesothelioma Diagnosis
All RT Patients (303)

Product-Limit Survival Fit
Survival Plot



Time intervals are in months.

M2 = Alimta/cisplatin (upper curve)
M39 = cispaltin alone (lower curve)

Summary

Group	N Failed	N Censored	Mean	Std Dev
M2	101	52	13.9642 Biased	0.76937
M39	107	43	12.0324 Biased	0.68229
Combined	208	95	13.0605 Biased	0.52762

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
M2	13	10.8	14.8	6.1	20.6
M39	10.2	8	12	5.9	20
Combined	11.1	10.1	12.9	6	20

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.3892	1	0.0656
Wilcoxon	2.6854	1	0.1013

Tumor Response and Time to Tumor Progression

Tumor response and time to progression were assessed, but the results were not satisfactory. Tumor response criteria are not well established in pleural malignant mesothelioma where the tumor often grows in sheets rather than more spherical configurations. As shown below, the tumor response assessments were not consistent between the study Investigators and the two Independent reviewers. In addition FDA review of the submitted films could confirm the tumor response in only 47 of the 94 patients in the Alimta/cisplatin treatment group for whom the Applicant claimed a tumor response. Thus the FDA does not believe it is appropriate to include numerical results for tumor response and time to progression in the labeling. It did appear that there is a better tumor response rate and longer time-to-tumor progression in the Alimta/cisplatin group.

Prior to start of the study the FDA indicated to the Applicant that tumor response in this disease can not be reliably assessed and that the FDA would not make any important decisions regarding efficacy based on tumor response or time to tumor progression.

Tumor response was assessed by the study Investigators and by two Independent reviewers. The protocol specified primary result was the assessment by the Independent reviewers. If the two Independent reviewers disagreed, a third Independent reviewer broke the tie. The Independent reviewers did not assess progression.

LILLY
ALIMTA RESPONSES
N=226

Investigator		94
	Independent #1	60
	Independent #2	71
	Independent	68
Independent #1		72
	Independent #2	66
	Investigator	61
Independent #2		88
	Independent #1	66
	Investigator	71
Independent		84
Independent #1 and #2 Disagree		28
Independent #3 Resp		21of 28
FDA		47

LILLY
CISPLATIN RESPONSES
N=222

Investigator		37
	Independent #1	20
	Independent #2	24
	Independent	23
Independent #1		27
	Independent #2	23
	Investigator	20
Independent #2		38
	Independent #1	23
	Investigator	24
Independent		30
Independent #1 and #2 Disagree		19
Independent #3 Resp		9 of 19
FDA		Not Done

Lung Cancer Symptom Scale

Patients were assessed during the study using the Lung Cancer Symptom Scale (LCSS). Although there were statistically significant changes favoring the Alimta/cisplatin treatment group in some of the components and in the overall score, none of the changes were clinically important.

Pulmonary Function Studies

Patients were assessed with FVC, SVC and FEV1. The FDA Division of Pulmonary Drug Products recommends FVC as the most appropriate test of pulmonary function in this patient population because their main impairment is constrictive rather than obstructive.

The Applicant's analysis compares the average change from baseline in RT patients in each treatment group. The average change in FVC from baseline is + 110 ml for the Alimta/cisplatin group and - 50 ml for the cisplatin alone group. This difference is statistically significant ($p=0.001$), but it falls within the normal variation of the test (200 ml) per the American Thoracic Society and is not considered clinically important, per the recommendation of the FDA Division of Pulmonary Drug Products.

To further assess the effect of treatment on pulmonary function this reviewer employed the electronic database to determine the proportions of patients in each treatment group having an increase from baseline in FVC of $\geq$ 400 ml and $\geq$ 500 ml on at least one follow-up visit and on at least two follow-up visits. Follow-up visits were six weeks apart. A second similar analysis determined the proportions of patients in each treatment group having an increase from baseline in FVC of $\geq$ 20% and $\geq$ 30% on at least one follow-up visit and at least two follow-up visits.

In the 337/448 (75%) of RT patients who had a baseline and at least one follow-up FVC, 26.6% and 21.3% of Alimta/cisplatin group patients had an increase over baseline FVC of $\geq$ 400 ml and $\geq$ 500 ml on at least one follow-up visit, respectively. The differences between the Alimta/cisplatin and cisplatin alone treatment groups are statistically significant. However, the increases in FVC were maintained for at least 6 weeks in only about half of the Alimta/cisplatin group patients. The difference between treatment groups was no longer statistically significant.

In the second analysis 28.4% and 17.2% of Alimta/cisplatin group patients had an increase from baseline FVC of $\geq$ 20% and $\geq$ 30% on at least one follow-up visit, respectively. The differences between the Alimta/cisplatin and cisplatin alone treatment groups are statistically significant. The increases in FVC were maintained for at least 6 weeks in only about half of the Alimta/cisplatin group patients. But the difference between treatment groups remains statistically significant. Based on the results of these

two analyses, a claim for a modest beneficial effect on pulmonary function (FVC) can be made in the label.

The results are presented in the following Tables.

FVC Increase from Baseline
All Patients with Baseline and at
Least One Follow-up FVC
N=337

	Alimta/Cisplatin N=169	Cisplatin alone N=168	P Value *
Increase ≥ 400 ml ≥ 1 Visit	26.6 %	17.9 %	P=0.03
Increase ≥ 500 ml ≥ 1 Visit	21.3 %	11.9%	P=0.01
Increase ≥ 400 ml ≥ 2 Visits	13.6 %	9.5 %	P=0.19
Increase ≥500 ml ≥ 2 Visits	11.2 %	6.0 %	P=0.09

* P values are Fishers Exact test, two-sided.

FVC Per Cent Increase from Baseline
All Patients with Baseline and at
Least One Follow-up FVC
N=337

	Alimta/Cisplatin N=169	Cisplatin alone N=168	P Value *
Increase ≥ 20% ≥ 1Visit	28.4 %	13.7 %	P=0.001
Increase ≥ 30% ≥ 1 Visit	17.2 %	5.4 %	P=0.0009
Increase ≥ 20% ≥ 2 Visits	14.2 %	7.1 %	P=0.051
Increase 30% ≥ 2 Visits	8.3%	2.4%	P=0.026

* P values are Fishers Exact test, two-sided.

Safety Results:

Adverse events are presented in the following Tables.

Alimta is eliminated primarily by the renal route. In clinical studies, patients with creatinine clearance ≥45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients. Therefore, Alimta should not be administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula or GFR measured by Tc99m-DPTA serum clearance method. Supplementation with vitamin B 12 and folic acid and concomitant treatment with dexamethasone are necessary to decrease adverse effects.

Adverse Events Summary (≥5% Incidence) in RT Population

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Neutrophils granulocytes	139	61.5	65	28.8	33	14.9	5	2.3
Fatigue	187	82.7	41	18.1	167	75.2	34	15.3
Leukocytes	130	57.5	41	18.1	45	20.3	3	1.4
Nausea	195	86.3	33	14.6	177	79.7	14	6.3
Vomiting	145	64.2	31	13.7	117	52.7	8	3.6
Dyspnea	149	65.9	25	11.1	146	65.8	32	14.4
Hypertension	56	24.8	21	9.3	74	33.3	36	16.2
Chest pain	90	39.8	18	8.0	69	31.1	16	7.2
Hemoglobin	73	32.3	14	6.2	34	15.3	1	0.5
Platelets	66	29.2	13	5.8	19	8.6	0	0.0
Thrombosis/embolism	14	6.2	12	5.3	10	4.5	9	4.1
Diarrhea without colostomy	64	28.3	11	4.9	35	15.8	1	0.5
Tumor pain	42	18.6	11	4.9	37	16.7	12	5.4
Dehydration	20	8.8	10	4.4	2	0.9	2	0.9
Stomatitis/pharyngitis	81	35.8	9	4.0	20	9.0	0	0.0
Anorexia	87	38.5	8	3.5	61	27.5	1	0.5
Constipation	103	45.6	8	3.5	90	40.5	3	1.4
Renal Genitourinary-Other	73	32.3	8	3.5	66	29.7	6	2.7
Constitutional Symptoms-Other	22	9.7	6	2.7	18	8.1	2	0.9
Pleuritic pain	39	17.3	6	2.7	39	17.6	10	4.5
Other pain	33	14.6	5	2.2	46	20.7	7	3.2
Pulmonary-Other	42	18.6	5	2.2	37	16.7	4	1.8
Febrile neutropenia *	4	1.8	4	1.8	0	0.0	0	0.0
Infection with grade 3 or 4 Neutropenia	20	8.8	4	1.8	13	5.9	1	0.5
Infection without Neutropenia	25	11.1	4	1.8	12	5.4	2	0.9
Other Gastrointestinal	44	19.5	4	1.8	30	13.5	1	0.5
Dysphagia, esophagitis, odynophagia	12	5.3	3	1.3	11	5.0	1	0.5
Mood alteration-anxiety agitation	26	11.5	3	1.3	24	10.8	1	0.5
Other endocrine	18	8.0	3	1.3	18	8.1	0	0.0
Rash desquamation	61	27.0	3	1.3	26	11.7	0	0.0
Abdominal pain or cramping	21	9.3	2	0.9	16	7.2	1	0.5
Edema	34	15.0	2	0.9	33	14.9	5	2.3
Fever	36	15.9	2	0.9	18	8.1	0	0.0
Infection Febrile Neutropenia-Other *	5	2.2	2	0.9	4	1.8	0	0.0
Inner ear hearing	21	9.3	2	0.9	30	13.5	2	0.9
Mood alteration-depression	28	12.4	2	0.9	21	9.5	3	1.4
Other auditory hearing	15	6.6	2	0.9	11	5.0	0	0.0

Other musculoskeletal	18	8.0	2	0.9	18	8.1	2	0.9
Alopecia	31	13.7	1	0.4	15	6.8	0	0.0
Cough	90	39.8	1	0.4	82	36.9	2	0.9
Creatinine	39	17.3	1	0.4	26	11.7	2	0.9
Dizziness/lightheadedness	20	8.8	1	0.4	19	8.6	0	0.0
Dyspepsia/heartburn	26	11.5	1	0.4	10	4.5	0	0.0
Headache	29	12.8	1	0.4	24	10.8	1	0.5
Other neurology	18	8.0	1	0.4	13	5.9	1	0.5
SGPT(ALT)	17	7.5	1	0.4	20	9.0	1	0.5
Sweating	29	12.8	1	0.4	27	12.2	0	0.0
Tearing	15	6.6	1	0.4	1	0.5	0	0.0
Weight loss	42	18.6	1	0.4	31	14.0	2	0.9
Insomnia	36	15.9	0	0.0	40	18.0	3	1.4
Neuropathy-sensory	36	15.9	0	0.0	30	13.5	1	0.5
SGOT(AST)	18	8.0	0	0.0	12	5.4	1	0.5
Allergic rhinitis	20	8.8	0	0.0	8	3.6	0	0.0
Conjunctivitis	21	9.3	0	0.0	1	0.5	0	0.0
Other Dermatology/Skin	16	7.1	0	0.0	15	6.8	0	0.0
Other ocular/visual	12	5.3	0	0.0	6	2.7	0	0.0
Taste disturbance	21	9.3	0	0.0	15	6.8	0	0.0
Urinary frequency/urgency	16	7.1	0	0.0	9	4.1	0	0.0

* Included because of importance

Adverse Events Summary (≥ 5% Incidence) in RT Fully Supplemented Population

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	96	57.1	41	24.4	22	13.5	5	3.1
Fatigue	137	81.5	29	17.3	120	73.6	21	12.9
Leukocytes	92	54.8	26	15.5	30	18.4	1	0.6
Nausea	142	84.5	20	11.9	128	78.5	9	5.5
Dyspnea	110	65.5	19	11.3	103	63.2	15	9.2
Hypertension	44	26.2	19	11.3	56	34.4	29	17.8
Vomiting	99	58.9	18	10.7	83	50.9	7	4.3
Chest pain	68	40.5	14	8.3	50	30.7	11	6.7
Hemoglobin	57	33.9	10	6.0	24	14.7	1	0.6
Thrombosis/embolism	12	7.1	10	6.0	6	3.7	6	3.7
Platelets	44	26.2	9	5.4	15	9.2	0	0.0
Tumor pain	31	18.5	8	4.8	24	14.7	7	4.3
Dehydration	12	7.1	7	4.2	2	1.2	2	1.2
Constipation	78	46.4	6	3.6	66	40.5	1	0.6
Diarrhea without colostomy	43	25.6	6	3.6	25	15.3	1	0.6
Other pain	26	15.5	5	3.0	42	25.8	7	4.3
Pulmonary-Other	34	20.2	5	3.0	31	19.0	4	2.5
Renal/Genitourinary-Other	52	31.0	5	3.0	50	30.7	4	2.5
Stomatitis/pharyngitis	47	28.0	5	3.0	13	8.0	0	0.0
Anorexia	59	35.1	4	2.4	44	27.0	1	0.6
Constitutional Symptoms-Other	18	10.7	4	2.4	14	8.6	2	1.2
Infection without Neutropenia	21	12.5	4	2.4	7	4.3	0	0.0
Other Gastrointestinal	33	19.6	3	1.8	26	16.0	1	0.6
Pleuritic pain	29	17.3	3	1.8	31	19.0	8	4.9
Dysphagia, esophagitis, odynophagia	10	6.0	2	1.2	9	5.5	0	0.0
Edema	24	14.3	2	1.2	25	15.3	4	2.5
Hyperglycemia	8	4.8	2	1.2	11	6.7	6	3.7
Infection/Febrile Neutropenia-Other *	5	3.0	2	1.2	3	1.8	0	0.0
Mood alteration-depression	23	13.7	2	1.2	15	9.2	2	1.2
Other cardiovascular/general	19	11.3	2	1.2	19	11.7	3	1.8
Other musculoskeletal	14	8.3	2	1.2	13	8.0	2	1.2
Cough	64	38.1	1	0.6	61	37.4	2	1.2
Creatinine	26	15.5	1	0.6	18	11.0	2	1.2
Dizziness/lightheadedness	16	9.5	1	0.6	16	9.8	0	0.0
Dyspepsia/heartburn	20	11.9	1	0.6	6	3.7	0	0.0
Headache	21	12.5	1	0.6	18	11.0	1	0.6
Infection with grade 3 or 4 Neutropenia	10	6.0	1	0.6	6	3.7	0	0.0
Mood alteration-anxiety/agitation	22	13.1	1	0.6	14	8.6	0	0.0
Other auditory/hearing	11	6.5	1	0.6	8	4.9	0	0.0
Other endocrine	12	7.1	1	0.6	16	9.8	0	0.0
Rash/desquamation	37	22.0	1	0.6	16	9.8	0	0.0
Sweating	24	14.3	1	0.6	17	10.4	0	0.0
Abdominal pain or cramping	13	7.7	0	0.0	13	8.0	1	0.6
Inner ear/hearing	13	7.7	0	0.0	21	12.9	2	1.2
Insomnia	28	16.7	0	0.0	31	19.0	1	0.6
Neuropathy-sensory	29	17.3	0	0.0	24	14.7	1	0.6
Other neurology	14	8.3	0	0.0	11	6.7	1	0.6
SGOT(AST)	14	8.3	0	0.0	10	6.1	1	0.6
SGPT(ALT)	10	6.0	0	0.0	17	10.4	1	0.6
Weight loss	32	19.0	0	0.0	18	11.0	1	0.6

Included because of importance

Grade 3/4 Adverse Events in Fully Supplemented versus Never Supplemented Patients treated with Alimta/Cisplatin

Adverse Events	Fully Supplemented % N=168	Never Supplemented % N=32
Neutrophils/granulocytes	24.4	37.5
Fatigue	17.3	31.3
Leukocytes	15.5	34.4
Nausea	11.9	31.3
Dyspnea	11.3	12.5
Hypertension	11.3	3.1
Vomiting	10.7	34.4
Chest pain	8.3	6.3
Hemoglobin	6.0	9.4
Thrombosis/embolism	6.0	3.1
Platelets	5.4	9.4
Tumor pain	4.8	6.3
Dehydration	4.2	9.4
Constipation	3.6	3.1
Diarrhea without colostomy	3.6	9.4
Febrile neutropenia	0.6	9.4
Infection with Grade3/4 Neutropenia	0.6	6.3

CONCLUSION

Safety and efficacy have been adequately demonstrated.

RECOMMENDATION

This NDA is approvable with labeling revisions. Please see labeling revisions by the FDA Alimta review team.

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/s/

John Johnson
1/24/04 03:00:06 PM
MEDICAL OFFICER

Clinical Review

NDA 21-462

ALIMTA (pemetrexed, MTA, LY231514) for injection

Indication: ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are not candidates for curative surgery.

Applicant:
Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Clinical Review Team
CDER, OND, ODE1, Division of Oncology Drug Products

- Robert M. White, Jr., MD, FACP
- Maitreyee Hazarika, MD (Safety)
- John R. Johnson, MD, Clinical Team Leader

Documents reviewed: 10/24/2002 (Rolling Submission), 11/22/2002, 11/26/2002, 1/10/2003, 2/13/2003, 3/24/2003 (financial disclosure), 5/9/2003, 5/29/2003, 7/23/2003 (Safety Update), 7/30/2003, 8/8/2003, 8/15/2003, 8/21/2003, 8/28/2003, 9/2/2003, 9/12/2003, 9/15/2003, 9/19/2003, 9/22/2003, 9/29/2003, 10/6/2003 (labeling), 10/20/2003, 11/4/2003 (labeling), 11/6/2003, 11/14/2003 (labeling), 11/14A/2003, 11/18/2003, 11/24/2003 (labeling), 11/26/2003, 12/4/2003 (financial disclosure), 12/4A/2003, 12/5/2003 (labeling), 12/10/2003 (financial disclosure), 12/15A/2003 (labeling), 12/16/2003.

TABLE OF CONTENTS

Clinical Review for NDA 21-462

Executive Summary

I. Recommendations

1. Recommendation on Approvability

One single-blind, randomized, controlled trial, demonstrating the efficacy and safety of Alimta in combination with cisplatin for the treatment of malignant pleural mesothelioma patients whose disease is either unresectable or who are not candidates for curative surgery has been submitted and reviewed. The pivotal trial was multicenter with United States and non-US sites. The combination of Alimta plus cisplatin is the first chemotheraupetic regimen to demonstrate a survival benefit in malignant pleural mesothelioma in comparison to a control regimen.

The overall survival analyses of the randomized and treated (RT) and the intent-to-treat populations demonstrated a statistically significant improvement in survival in favor of the alimta/cisplatin arm compared to cisplatin alone. In the fully folic acid/vitamin B12 supplemented group, the alimta/cisplatin arm was favored and was marginally statistically significant. Sixty-seven percent of the patients enrolled on study had pathologically confirmed mesothelioma; in the confirmed mesothelioma subset, survival analyses of the RT and the fully folic acid/vitamin B12 supplemented groups demonstrated a marginally significant survival advantage in favor of the alimta/cisplatin arm. The under-powered female subgroup demonstrated in RT and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm[1]. The white subgroup demonstrated, in the RT and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the RT group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the RT and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age $\geq$ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

Alimta in combination with cisplatin has satisfactorily demonstrated a consistent survival advantage compared to cisplatin alone in patients with pleural malignant mesothelioma in a randomized, single-blinded study.

[1] Lilly did a multifactorial survival analysis considering prognostic factors and there was no gender effect; ISE document submitted 3/24/2003.

The common grade 3 or grade 4 laboratory toxicities in the RT group treated with Alimta plus cisplatin were neutropenia (28.8%), leucopenia (18.1%), thrombocytopenia (5.8%) and anemia (6.2%). In a subgroup analysis of patients fully supplemented with folic acid + vitamine B12 (FS), the Alimta + cisplatin treated arm had neutropenia (24.4%), leucopenia (15.5%), anemia (6%), thrombocytopenia (5.4%) while the cisplatin only arm had neutropenia (3.1%), leucopenia (0.6%) and decreased creatinine (1%). The common nonlaboratory grade 3 and grade 4 adverse events in the RT group treated with Alimta + cisplatin were fatigue (18.1%), nausea (14.6%), vomiting (13.7%), diarrhea (4.9%), dehydration (4.4%), stomatitis (4%), anorexia (3.5%) and rash (1.3%). In the FS group, the patients treated with Alimta + cisplatin had fatigue (17.3%), nausea (11.9%), vomiting (10.7%), dehydration (4.2%), diarrhea (3.6%), stomatitis (3%) and anorexia (2.4%). Supplementation with folic acid + vitamin B12 reduced many of the laboratory and non-laboratory toxicities in comparison to a never supplemented subgroup.

However, the demonstration of the survival benefit is based on only one randomized, control trial which had challenges with regard to pathology confirmation, eligibility based on measurable disease, response evaluation, the addition of folic acid plus vitamin B12 into the ongoing pivotal trial, and financial disclosure. In view that these deficiencies could be the result of bias and affect the survival benefit, replication of the survival benefit in another randomized, controlled trial appears desirable although not required for approval.

Based on this review of NDA 21-462, Alimta in combination with cisplatin is clinically approvable for the treatment of malignant pleural mesothelioma patients whose disease is either unresectable or who are not candidates for curative surgery.

2. Recommendation on Phase 4 Studies and/or Risk Management Steps

No clinical Phase 4 studies are recommended

II. Summary of Clinical Findings

1. Brief Overview of Clinical Program

Product name: ALIMTA (pemetrexed, MTA, LY231514) for injection
Class of Drug: antineoplastic (cytotoxic); antimetabolite (antifolate)
Route of Administration: Intravenous

Indication studied: ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are not candidates for curative surgery.

Important Trials:

Protocol H3E-MC-JMCH(g): A Single-blind Randomized Phase 3 Trial of MTA[2] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma (Pivotal trial; reviewed by FDA)

Enrolled: 226 alimta plus cisplatin arm (168 folic acid + Vitamin B12 supplemented 168; 58 partially supplemented or never supplemented); 222 cisplatin alone arm (163 folic acid + Vitamin B12 supplemented, 59 partially supplemented or never supplemented).

Protocol H3E-MC-JMDR Phase 2: A Phase 2 Trial of LY231514 Administered Intravenously Every 21 Days in Patients with Malignant Pleural Mesothelioma (Supported trial; not reviewed by FDA)

Enrolled: 64 (43 folic acid + Vitamin B12 supplemented; 21 never supplemented)

2. Efficacy

In the pivotal trial, A Single-blind Randomized Phase 3 Trial of MTA[3] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma, survival was the primary endpoint. The following table illustrates the survival benefit achieved in this randomized, controlled trial.

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Randomized and treated (n=448)	12.1 months	9.3 months	0.021
Fully folic acid/vitamin B12 supplemented (n=331))	13.3 months	10 months	0.051
Partial supplemented + never supplemented (n=117)	9.5 months	7.2 months	0.253
Intent-to-treat (n=456)	12 months	9.3 months	0.0205
Confirmed mesothelioma pathology Randomized and treated (n=303)	13 months	10.2 months	0.066

[2] alimta
[3] alimta

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Confirmed mesothelioma pathology Fully folic acid/vitamin B12 supplemented (n=220)	14.4 months	10.3 months	0.058
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388
Race White Randomized and treated (n=410)	12.2 months	9.3 monts	0.024
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white Fully folic acid/vitamin B12 supplemented (n=28)	8.8 months	9.55 months	0.619
Age < 65 years Randomized and treated (n=279)	13.3 months	10.2 months	0.02

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The data supports the following indication:

ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are not candidates for curative surgery.

The combination of Alimta plus cisplatin is the first chemotheraupetic regimen to demonstrate a survival benefit in malignant pleural mesothelioma in comparison to a control regimen.

Response rate was a secondary endpoint for study JMCH. The following table illustrates the response rate demonstrated in patients with a confirmed pathological diagnosis of mesothelioma.

	ALIMTA + CISPLATIN, FDA CONFIRMED RESPONDERS			CISPLATIN ALONE, LILLY LISTED RESPONDERS		
	Proportion	Response rate	95% CI	Proportion	Response rate	95% CI
overall response rate	38/153	25%	18,32	25/149	17%	11,23
epithelial	35/130	27%	29,35	22/127	17%	11,24
Mixed	3/15	20%	-0.2,37	1/13	8%	-7,22
Sarcomatoid	0/8	0%		2/9	22%	-5, 49
folic acid/vitamin B12 supplementation	29/111	26%	18,34	21/108	19%	12,27
Partial supplementation	3/20	15%	-0.7,31	3/14	21%	-0.1, 43
never supplemented	6/22	27%	9,46	1/27	4%	-3,11

In contrast to the survival endpoint and although the response rate of the alimta + cisplatin arm was higher than the cisplatin alone arm, response rate was not a rigorous endpoint in study JMCH for a number of reasons.

At the End of Phase II meetings, the FDA indicated to Lilly that tumor response rate in mesothelioma could not be reliably assessed and that the FDA would not make any important decisions regarding efficacy based on tumor response rate or time to tumor progression.

3. Safety

The pivotal trial was a multicenter, randomized, single-blind Phase III trial in chemo-naïve patients with malignant pleural mesothelioma (MPM) treated with Alimta in combination with cisplatin compared to patients who received cisplatin alone. Alimta was administered at a dose of 500 mg/m^2 intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/ m^2 intravenously over approximately 2 hours on Day 1 of each 21- day cycle. In the cisplatin only arm, normal saline which did not contain Alimta was administered intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/ m^2 intravenously over approximately 2 hours on Day 1 of each 21- day cycle. Patients in both arms were pre- and post- hydrated according to local practice. Dexamethasone 4 mg, or equivalent corticosteroid was taken orally twice per day on the day before, the day of,

and the day after each dose of Alimta plus cisplatin. Folic acid supplementation, 350–1000 µg or equivalent was taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of Alimta plus cisplatin and continued daily until the patient discontinued from study therapy. A vitamin B_{12} injection, 1000 µg was given intramuscularly approximately 1 to 3 weeks prior to the first dose of Alimta plus cisplatin and was repeated approximately every 9 weeks until the patient discontinued from study therapy.

The median age of patients at the time of randomization was 60 years. Although 456 patients were randomized, 8 patients did not receive the study drug; a total of 448 patients were treated and received at least one dose of study drug(s). The primary analysis of this study was performed on the population of all patients who received study drug in the treatment arm. A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy. Randomized and treated patients completed a median of 6 cycles of the Alimta/cisplatin arm and 4 cycles of the cisplatin only arm. Supplemented patients completed a median of six cycles and nonsupplemented patients completed a median of 2 cycles of Alimta/cisplatin. The planned mean dose for Alimta and cisplatin were 166.7 and 25 $mg/m^2/wk$ respectively. The mean dose delivered was 153.4 $mg/m^2/wk$ of Alimta and 23.2 $mg/m^2/wk$ of cisplatin in the RT group and 154.6 $mg/m^2/wk$ and 23.4 $mg/m^2/wk$ in the FS group. When used alone, cisplatin was given at 24.1 $mg/m^2/wk$. The percent of planned dose intensity was 92/92.8% for Alimta/cisplatin in the RT group and 92.7/93.6% Alimta/cisplatin in the FS group. 96.4% of cisplatin alone could be given in both the RT and FS groups. In the RT group, 308 (28.9%) dose delays were reported in the Alimta/cisplatin arm and 171 (19.5%) in the cisplatin alone arm. Scheduling conflicts constituted the majority of dose delays. The most common clinical cause of dose delay on both arms was neutropenia. On both arms, cycle 4 was the cycle with the most delays. The common grade 3 or grade 4 laboratory toxicities in the RT group treated with Alimta/cisplatin were neutropenia (28.8%), leucopenia (18.1%), thrombocytopenia (5.8%) and anemia (6.2%); in the cisplatin only arm, neutropenia (2.3%), leucopenia (1.4%) and decreased creatinine (1%) were the common toxicites. In the FS group, the Alimta/cisplatin treated arm had neutropenia (24.4%), leucopenia (15.5%), anemia (6%), thrombocytopenia (5.4%) while the cisplatin only arm had neutropenia (3.1%), leucopenia (0.6%) and decreased creatinine (1%). The common nonlaboratory grade 3 and grade 4 adverse events in the RT group treated with Alimta/cisplatin were fatigue (18.1%), nausea (14.6%), vomiting (13.7%), diarrhea (4.9%), dehydration (4.4%), stomatitis (4%), anorexia (3.5%) and rash (1.3%). In the cisplatin alone arm the common adverse events were fatigue (15.3%), nausea (6.3%), and vomiting (3.6%). In the FS group, the patients treated with Alimta/cisplatin had fatigue (17.3%), nausea (11.9%), vomiting (10.7%), dehydration (4.2%), diarrhea (3.6%), stomatitis (3%) and anorexia (2.4%). Those in the cisplatin alone arm had fatigue (12.9%), nausea (5.5%) and vomiting (4.3%). A comparison between the two treatment arms in the FS group showed a statistically significant difference for neutrophils and leukocytes with more neutropenia and leucopenia in the Alimta/cisplatin group. Effect of supplementation reduced many of the laboratory and non-laboratory toxicities.

Use of vitamin supplementation by patients must be emphasized. Patients treated with Alimta must be instructed to take low-dose folic acid daily so that at least 5 doses are

taken during the 7-day period preceding the first dose of Alimta and continuing until 21 days after the last dose. Patients must also receive 1 injection of vitamin B_{12} during the week prior to receiving the first dose of Alimta and every 3 cycles thereafter during therapy. Subsequent vitamin B_{12} injections may be given the same day as Alimta. Alimta with dexamethasone or equivalent reduces the incidence and severity of cutaneous reactions.

As a class, folic acid antimetabolites have been demonstrated to produce manifestations of developmental toxicity such as growth retardation, embryo lethality, and malformations. Alimta was found to be embryo toxic at doses of 10 mg/ kg (30 mg/ m^2) and fetotoxic causing fetal malformations (cleft palate) at doses of 5 mg/ kg (15 mg/ m^2). There are no studies of Alimta in pregnant women. If Alimta is used during pregnancy, or if the patient becomes pregnant while taking Alimta, the patient should be apprised of the potential hazard to the fetus.

As with other anti-folate drugs, there is a potential for serious adverse reactions in nursing infants and nursing should be discontinued if the mother is treated with Alimta.

Alimta is eliminated primarily via the renal route. Patients with a creatinine clearance of < 45 ml/min, calculated with the mean body weight by the formula of Cockcroft and Gault, should not receive Alimta.

As with other antifolates, caution should be exercised when concomitant administration of Alimta with nonsteroidal anti-inflammatory drugs are used.

Patients with clinically significant pleural effusions have been excluded in studies performed with Alimta. Before starting treatment, pleural effusions should be drained.

The safety evaluation seems adequate for marketing for this indication. Areas of caution and limited safety experience have been noted above.

Extent of Exposure

Drug Administration

Of the 456 patients randomly assigned to a treatment arm, 448 (98.2%) received Alimta/ cisplatin or cisplatin monotherapy. These patients constitute the randomized and treated (RT) population for this study. Of these, 226 patients were randomized to and treated with Alimta/cisplatin and 222 patients were randomized to the cisplatin alone arm and received at least one dose of cisplatin. Among these 448 patients, 331 patients were fully supplemented and constituted the fully supplemented (FS) population for this study. Of the 331 patients, 168 were randomized and treated with Alimta/cisplatin and 163 were randomized and treated with cisplatin alone.

Among the RT patients, a median of six cycles (range: 1 – 12 cycles) were completed on the Alimta/ cisplatin arm compared with four cycles (range: 1 – 9 cycles) completed on the cisplatin alone arm. A total of 120 (53.1%) patients on the Alimta/ cisplatin arm and 89 (40.1%) patients on the cisplatin alone arm completed at least six cycles of therapy while 18 (8.0%) patients on the Alimta/ cisplatin arm compared with 19 (8.6%) patients on the cisplatin alone arm completed only one cycle. The duration of treatment was greater in the Alimta/cisplatin arm than in the cisplatin alone arm.

Among the FS patients, a median of six cycles of therapy were delivered on the Alimta/ cisplatin arm compared with four cycles delivered on the cisplatin alone arm. In addition, among FS patients, a total of 97 (57.7%) patients on the Alimta/ cisplatin arm versus 66 (40.5%) patients on the cisplatin alone arm completed at least six cycles of therapy. Thirteen (7.7%) patients on the Alimta/ cisplatin arm compared with 15 (9.2%) patients on the cisplatin alone arm completed only one cycle.

Within the Alimta/ cisplatin arm, FS patients received a median of six cycles compared with two cycles in the never-supplemented (NS) patients ($p=< 0.001$). For the cisplatin alone arm, there was also a difference favoring a larger number of cycles in the FS group ($p= 0.049$).

Among RT patients, 1066 cycles were administered to patients on the Alimta/cisplatin arm while 877 cycles were administered to patients on the cisplatin alone arm. On the Alimta/ cisplatin arm, 96.6% of the Alimta cycles and 96.5% of the cisplatin cycles were administered at full dose. On the cisplatin alone arm, 99.7% of cycles were given without any dose adjustment.

Alimta exposure was for a median of 18 weeks. The median doses of Alimta and cisplatin were higher in those fully supplemented. Patients in both arms received > 90% of the planned dose intensity. Patients receiving Alimta in the RT group received a relative dose intensity of 92% of the protocol specified Alimta dose intensity and patients treated with cisplatin in the same group received 92.3% of the projected dose intensity with Alimta compared to 96.5% cisplatin alone. Similarly, after supplementation, 92.7% Alimta, 93% cisplatin when given with Alimta and 96.4% cisplatin when given alone were the relative dose intensities.

4. Dosing

The results of the pivotal trial, JMCH, provided confidence in the efficacy and safety of alimta + cisplatin (plus folic acid and vitamin B12) in patients with malignant pleural mesothelioma. However, the underlying science of the addition of folic acid and B12 to an antifolate regimen did not provide confidence with known *in vitro* and *in vivo* antifolate pharmacology. This issue is discussed in

detail in section 5 (Important Issues with Pharmacologically Related Agents) of this review.

5. Special Populations

5.1 Gender, Race, and Age

Below are the survival analyses for gender, race, and age from the pivotal trial, study JMCH.

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388
Race White Randomized and treated (n=410)	12.2 months	9.3 monts	0.024
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white Fully folic acid/vitamin B12 supplemented (n=28)	8.8 months	9.55 months	0.619

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Age < 65 years Randomized and treated (n=279)	13.3 months	10.2 months	0.02
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The under-powered female subgroup demonstrated in randomized and treated and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm[4]. The white subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the randomized and treated group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age ≥ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

5.2 Pregnancy and Nursing

As a class, folic acid antimetabolites have been demonstrated to produce manifestations of developmental toxicity such as growth retardation, embryo lethality, and malformations. Alimta was found to be embryo toxic at doses of 10 mg/ kg (30 mg/ m^2) and fetotoxic causing fetal malformations (cleft palate) at doses of 5 mg/ kg (15 mg/ m^2). There are no studies of Alimta in pregnant women. If Alimta is used during pregnancy, or if the patient becomes pregnant while taking Alimta, the patient should be apprised of the potential hazard to the fetus.

[4] Lilly did a multifactorial survival analysis considering prognostic factors and there was no gender effect; ISE document submitted 3/24/2003.

Clinical Review

I. Introduction and Background

1. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Product name: ALIMTA (pemetrexed, MTA, LY231514) for injection

Drug Class: antineoplastic (cytotoxic); antimetabolite (antifolate)

Indication Proposed: ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are not candidates for curative surgery.

Regimen:

- ALIMTA, 500 mg/m^2 administered as an intravenous infusion over 10 minutes on day 1 of each 21-day cycle.
- Cisplatin, 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of ALIMTA administration. Patients should receive hydration consistent with local practice prior to and/or after receiving cisplatin.
- Premedication Regimen

  dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after ALIMTA administration.

  Folic acid (at least 5 daily doses must be taken during the 7-day period preceding the first dose of ALIMTA) 350 to 1000 µg orally per day; folic acid dosing should continue during the full course of therapy and for 21 days after the last dose of ALIMTA.

  Vitamin B_{12} 1000 µg by intramuscular injection during the week preceding the first dose of ALIMTA; vitamin B12 is repeated every 3 cycles thereafter.

Age group: greater than 18 years of age

2. State of Armamentarium for Indication

There are no other approved chemotherapeutic agents for malignant pleural mesothelioma.

3. Important Milestones in Product Development--From IND to NDA

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
July 8, 1992	Original IND submission	Phase 1 trial of LY231514 administered as a bolus infusion every 7 days proposed starting dose: 40 mg/m2	
August 7, 1992	Clinical hold		Animal data does not support proposed starting dose
September 11, 1992	Removal of clinical hold		New proposed starting dose: 10 mg/m2 (DLT @ 40 mg/m2)
September 25, 1998	1st End of Phase 2 meeting	Indication: treatment of pleural mesothelioma[5] 600 mg/m2 vs. 500 mg/m2 dose q 3 wks Endpoints for mesothelioma: reesponse rate, clinical benefit Accelerated approval based on response rate	 FDA advice: 500 mg/m2 FDA advice: survival as primary endpoint; blinded study; addition of vitamins to MTA without data that efficacy is not reduced is risky Survival (superior) as the endpoint for full approval or clinical benefit (e.g., reduction in pain, shortness of breath, tumor-related symptoms) in a blinded trial

[5] There was also a discussion of NSCLC: Treatment of advanced NSLC whose disease has recurred or progressed following platin- or taxane based therapy

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		Unidimensional measurements will provide sufficient information for response	FDA uncertain Two studies for mesothelioma lead indication; confirmatory evidence may come from a closely related disease, i.e., NSCLC
December 3, 1998 Serial #149	Telecon in follow-up to 9/28/98 EOP2 meeting	Double-blinding problematic: Placebo approval by foreign regulatory authorities was a problem	Division not familiar with placebo restrictions in other countries Sponsor to go back to foreign regulatory authorities and submit a proposal to the Division
December 18, 1998	Telecon in follow-up to 9/28/98 EOP2 meeting and 12/3/98 telecon	European investigators will not do a double-blinded trial	Improved clinical benefit would be considered more robust in a double-blind trial Sponsor to submit a proposal describing how a single-blinded study of clinical benefit would be appropriated for study JMCH
February 12, 1999 Serial #150	Single blinded study with clinical benefit as basis for full approval Mesothelioma protocol review	A single-blind muti-center randomized Phase III study in patients with malignant pleural mesothelioma Interim analysis comparing clinical	FDA: • Double-blinded trial • Separate assessment of each component of clinical benefit endpoint

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		benefit response on 75 qualified patients per arms Efficacy analysies will be perfomed on intent-to-treat population Survival will be primary endpoint	2nd pivotal trial in mesothelioma: cisplatin + MTA vs. cisplatin + gemcitabine; superior survival
April 23, 1999	1st patient entered on JMCH		
May 12, 1999	1st patient randomized on JMCH		
June 25, 1999	2nd End of Phase 2 meeting	Indication: MTA in patients with mesothelioma Unidimensional tumor measurements Response rate, TTP, clinical benefit as endpoints for accelerated approval Submission of NDA based on interim analysis of response rate, TTP, and clinical benefit	See EOP2 meeting 9/23/98 FDA: Survival is the primary endpoint; full survival data to be submitted with NDA If clinical benefit is to suffice for approval: double-blinding strongly advised Commitment to complete 280-patient trial even if results are positive at interim analysis because clinical benefit has not been shown to correlate with survival Confirmatory evidence from a closely related disease, i.e., NSCLC FDA urged Lilly to design

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
			a 2nd RCT in pleural mesothelioma Positive evidence of clinical efficacy for TTP, CB, or RR at interim analysis + Phase 2 data FDA: Phase 2 data from mesothelioma would be supportive if responses can be convincingly demonstrated Rolling submission under Fast Track: review clock starts when submission complete
November 8 and December 3, 1999 FDA response faxed 12/21/99	Protocol amendment Serial #191 and #195	Proposed adding vitamins to ongoing mesothelioma trial	Disagreement with addition of vitamins: • No statistical plan • Commitment to completing 280-patient trial FDA proposed MTA ± vitamins trial
December 2, 1999	Implementation of vitamin supplementation		
December 22, 1999	Serial #200 and #201	Proposed adding vitamins to ongoing mesothelioma trial	Non-support for adding vitamins to the ongoing mesothelioma registration trial
March 1, 2000	3rd End of Phase 2 meeting	MTA in patients with mesothelioma Proposed addition of vitamins to ongoing	FDA options: 1. Temporarily closing

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		trial	trial; conduct a Phase 1 trial with MTA + vitamins 2. Stop current trial and open a new trial with a new protocol and new dose 3. Continue current trial with addition of vitamins and recalculate sample size Lilly opted for #3 After 150 patients are treated with vitamin supplementation, a survival analysis will be done polling the approx. 150 patient without vitamin supplementation FDA concern about ability to determine the benefit of adding vitamins to trial; no standard dose of vitamins Lilly to provide patient diary and pill count FDA not convinced that clinical benefit response data will warrant early filing
March 8, 2000 (serial #212) and April 13, 2000 (serial #220)	Follow-up questions on EOP2	2nd-line NSCLC trial as supporting trial for mesothelioma or Phase II data from mesothelioma trial(s) for support of mesothelioma	2nd-line NSCLC trial as supporting trial for mesothelioma

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		early submission of the NDA based on an interim analysis of clinical benefit endpoints	FDA expects mature survival data
June 21, 2000	Follow-up to EOP2 re: mesothelioma indication	2nd-line NSCLC trial to support mesothelioma indication acceptance of an interim analysis secondary endpoints on the mesothelioma trial	2nd-line NSCLC trial (superiority in survival) to support mesothelioma indication no double-blinding of mesothelioma trial demonstration of an improved survival associated with MTA would provide confidence that MTA is an effective agent providing clinical benefit
July 6, 2000	Serial #240 Special Protocol assessment of 2nd-line NSCLC trial (JMEI: a Phase 3 trial of alimta vs docetaxel in patients with locally advanced or metastatic non-small cell lung cancer previously treated with chemotherapy)	As support for mesothelioma indication: Demonstrate superiority assessment Demonstrate non-inferiority assessment	8/24/2000: Demonstrate superiority
July 12, 2000	Serial #242 Mesothelioma privotal trial revisions	Statistical analysis issues, regarding the addition of vitamins to the treatment regimens after the study had accrued about 150 patients Potential approval	

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		strategies for MTA via an interim analysis or the final analysis 430 (75 without vitamin-supplemented patients/arm) + (140 vitamin-supplemented patients/arm) Final analysis p-value 0.0236	
July 12, 2000	A single-blind randomized phase 3 trial of MTA plus cisplatin vs. cisplatin in patients with malignant pleural mesothelioma	Revisions: statistical analysis issues, regarding the addition of vitamins to treatment regimens	
March 20, 2001	Special protocol assessment: a randomized Phase 3 trial comparing alimta plus best supportive care vs. best supportive care alone in previously treated patients with locally advanced or metastatic malignant pleural mesothelioma (JMEW)	JMEW to support the front-line mesothelioma claim	Comments about strategy (5/7/2001): • Interim analysis of JMCH planned later in year • Pre-NDA meeting scheduled 8/2001 • JMEW projected to accrue over 15-months plus 12-months of follow-up
July 11, 2001	Interim database lock		
August 23, 2001	Orphan drug status granted		
October 29, 2001	Communication of data safety monitoring board conclusions	Indication: treatment of mesothelioma	Conclusion: follow the statistical analysis plan as stated in protocol and base

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
			the final primary analysis on the mixed population of both supplemented and non-supplemented patients; final significance level of • ≤ 0.0476
November 7, 2001	Last patient on-study visit		
January 30, 2002	Pre-NDA meeting	 Lilly proposed to provide for electronic reader capability at the FDA and providing images for responders at baseline and at best response Proposal for Protocol for Treatment: alimta + cisplatin, alimta + carboplatin, alimta alone	Alimta in combination with cisplatin is indicated for patients with advanced malignant pleural mesothelioma
March 19, 2002	Serial #394	Change in formulation (formulation→lyophilized product); CMC package and data delayed until 2nd quarter 2003	
March 26, 2002	1st single patient IND for compassionate and emergency use for malignant mesothelioma based on results from JMCH (JMCH to be		

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
	presented at the plenary session of ASCO annual meeting)		
April 3, 2002	Protocol for treatment for chemonaive patients with malignant pleural mesothelioma	Regimens: alimta + cisplatin, alimta + carboplatin, alimta alone	FDA: alimta + cisplatin
April 10, 2002	Request for fast track designation	Supported by JMCH data in abstract submitted to ASCO for 2002 annual meeting	
May 20, 2002	Presentation of the results of JMCH at plenary session of ASCO annual meeting Abstract was one of top five out of 3500 abstracts submitted		
June 10, 2002	Fast track designation granted for malignant pleural mesothelioma indication		
October 31, 2002	Rolling submission of NDA begins		

4. Other Relevant Information

Alimta is not approved in the United States or in any other country

5. Important Issues with Pharmacologically Related Agents

5.1 Introduction of folic acid and vitamin B12 for safety reasons

The introduction of folic acid and B12 into the pivotal trial, JMCH, was based on a Lilly initiated multivariate analysis conducted in late 1997 to assess the relationship of vitamin metabolites, drug exposure, and other pre-specified baseline patient characteristics to toxicity following therapy with MTA. Data were examined from 139 Phase 2 patients

with tumors of the colon, breast, pancreas, and esophagus who had been treated with MTA at 600 mg/m2 intravenously over 10 minutes once every 21 days. These patients had homocysteine (Hcys), cystathionine, and methylmalonic acid levels measured at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity, and to predict which patients were at high risk of experiencing such toxicity. Prognostic factors then considered were age, gender, prior therapy, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, and AUC.

The findings from this investigation led to the following conclusions:

- Toxicity resulting from therapy with MTA appeared to be higher in patients with elevated pre-therapy homocysteine levels.

- Elevated baseline homocysteine levels ($\geq$10 • mol/L, for the 139 patients included in this initial analysis) highly correlate with severe hematological and nonhematological toxicity following therapy with MTA.

- Homocysteine was found to be better than baseline albumin (another predictor of toxicity identified in the analysis) at predicting toxicity and was not altered with MTA therapy.

Because of the observation that pre-therapy homocysteine levels were critically important in predicting toxicity, the same multivariate analysis was repeated on data from 305 patients who had their baseline homocysteine levels measured and recorded using a single laboratory. To eliminate the confounding factor of the effect of folic acid supplementation on toxicity, patients on Study JMAS who received folic acid supplementation (n=38) were removed from the analysis, leaving a final sample size of 267 patients. Prognostic factors considered in this second wave of analysis were age, gender, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, pretherapy weight, AUC, tumor type, and prior treatment. Baseline homocysteine was identified as a highly statistically significant predictor of febrile neutropenia ($p < 0.00001$), Grade 4 neutropenia ($p = 0.0191$), Grade 4 thrombocytopenia ($p < 0.00001$), and Grade 3 or 4 diarrhea ($p < 0.00001$). According to Lilly, these results confirmed the original findings and supported the conclusion that homocysteine may provide an ideal prognostic variable for predicting toxicity during MTA therapy.

During the conduct of the JMCH trial, a programmatic change was made by Lilly in the clinical development of MTA whereby every patient treated with MTA must be supplemented with folic acid and vitamin B12 to improve patient safety. Initiation of vitamin supplementation in this study was done in both treatment arms and at the same time point to preserve study blinding at the patient level. By this time a total of 112 patients had been randomized in the study and received therapy without vitamin supplementation from the start, while a total of 40 patients received vitamin supplements

after at least one cycle of study therapy. For the purpose of this study, a patient was classified as supplemented with vitamins if he/she received study vitamin supplement during his/her entire study participation. The two groups of patients described above were classified as not supplemented with vitamins in this study while those who received vitamin supplementation with all cycles of study therapy were be classified as supplemented with vitamins. As such, approximately 150 patients were considered treated without study vitamin supplementation (initial study cohort) while an anticipated 280 qualified patients were considered treated with vitamin supplementation on the revised protocol.

5.2 The effect of folic acid and vitamin B12 on the efficacy of an antifolate

The narrative above does not take into account the potential negative effect on efficacy by the addition of folic acid + B12. The commentary below seeks to understand the enhanced efficacy from the addition of a folate to an antifolate.

Natural folates and antifolates have two important properties, such as: 1) the requirement for cellular uptake via a reduced folate carrier (RFC); and 2) the ability to be polyglutamylated. Increased extracellular folate concentrations and expanded intracellular folate pools may contribute to decreased antifolate sensitivity due to competition for transport and polyglutamylation, thus, decreasing the inhibitory effect on TS and GARFTase.[6]

5.3 Transport

In comparison to all other transport routes identified in rodent and human neoplastic cell types, the basic kinetic properties and preferences among structurally related folates and their analogues as permeants for the one-carbon, reduced-folate system are remarkably similar.[7] Enhanced RFC activity promotes the efficient transport of RFC-dependent antifolates and thus, more potent TS inhibition.[8] Folic acid is a poor substrate for RFC1 and enters cells by other mechanisms.[9]

Carrier-mediated systems transporting folates have a variety of properties in common. The internalization (influx) of folates by these systems is saturable, conforming to Michaelis-Menten kinetics. However, they exhibit differences in preferences for structurally related folates and their analogues, which are *competitive* inhibitors.[10] The carrier was encoded by the RFC1 gene.[11] There is also a receptor-mediated process. The

[6] Bachus et al. Int J Cancer. 2000;87:771-778.
[7] Sirotnak FM. Annual Review of Nutrition. 1999;19: 91-122
[8] Bachus et al. Int J Cancer. 2000;87:771-778.
[9] Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695
[10] Sirotnak FM. Annual Review of Nutrition. 1999;19: 91-122
[11] Khokhar, Lam, Rusch, Sirotnak. J Thoracic Cardiovasc Surg. 2002; 123:862-868

extent to which carrier- or receptor-mediated processes contribute to net translocation of folates in cell types where both processes are found is controversial, but it will depend on the level of expression of the corresponding gene in each cell type. Because the translocation efficiency of carrier-mediated processes is much greater than that of receptor-mediated processes, the relative level of expression required for the latter to contribute significantly to net translocation of folates is proportionally greater.[12] The exact mechanism of transport has not been established for MTA. MTA does have high affinity for RFC1 and folate receptor-alpha.[13]

In one cell type, L1210, free levels of folates and antifolates are governed by RFC1.[14] For mesothelioma cells, there are varying views on MTA transport. One reason for MTA activity in mesothelioma may be due to a highly expressed, high-affinity alpha folate receptor on mesothelioma cells of all histologic subtypes. This type of highly expressed receptor was thought to contribute to MTA transport into mesothelioma cells.[15] However, other evidence suggests that human mesothelioma cell lines predominately internalize tritiated methotrexate (MTX shares a transport route and is polyglutamylated in tumor cells in a manner similar to natural folate compounds[16]) by means of a carrier-mediated mechanism, with little transport by a receptor-mediated mechanism.[17] Recently, a high-affinity transport activity in three human mesothelioma cell lines was characterized. The researchers reported that the transport activity was specific for MTA and had low affinity for other antifolate inhibitors of dihydrofolate reductase (MTX, aminopterin, PT523) and thymidylate synthase (ZD1694, ZD9331); also, *this activity may be another transport route for mesothelioma cells of 5-methyl-tetrahydrofolate, the predominate folate in the plasma of man and rodents.*[18] The degree of expression of this transport activity in comparison to the RFC1 has not been elucidated.

5.4 Polyglutamylation

Pharmacological activity of MTA depends on conversion to polyglutamylated derivatives inside the cell; polyglutamylation increases the affinity of the MTA derivative. Polyglutamylated forms also ensure cellular retention. Only inhibition of DHFR is not affected by the degree of polyglutamylation. The effect of polyglutamylation on the inhibitory activity of MTA is shown below.[19]

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[12] Sirotnak FM. Annual Review of Nutrition. 1999;19: 91-122
[13] Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695
[14] Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695
[15] Scagliotti et al. J Clin Oncol. 2003;21:1556-1561
[16] Egan MG, Sirlin S, Rumberger BG, Garrow TA, Shane B, Sirotnak FM..J Biol Chem. 1995.270(10):5462-8.
[17] Khokhar NZ, Lam AF, Rusch VW, Sirotnak FM. J Thorac Cardiovasc Surg. 2002. 123(5):862-8.
[18] Wang, Zhao, Chattopadhyay, Goldman. Cancer Res. 2002;62:6434-6437
[19] Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695

	MTA MONOGLUTAMATE	MTA PENTAGLUTAMATE
Human TS, Ki	109 nM	1.3 nM
Murine GARFT, Ki	9.3 uM	65 nM
DHFR, Ki	~ 7 nM	~ 7 nM

5.5 The effect of increased folate levels

Antifolates, under conditions of increased extracellular folate levels, have decreased sensitivity due to *competition* for transport and polyglutamylation. This diminishes the effect on thymidylate synthase (TS) and GARFTase. Cells grown in low folate conditions are more sensitive to antifolates, including MTA, than cells grown in high folate conditions.[20]

Intracellular folates rise as extracellular 5-formyl-THF increased and MTA sensitivity decreased in an inverse relationship. Intracellular levels of THF cofactors modulate the growth-inhibitory activity of MTA (figure below). THF cofactor pool size plays a critical role in modulating the growth-inhibitory effects of MTA.[21] In this system, an increase in folate pool size required an increase in MTA concentration for comparable inhibition.

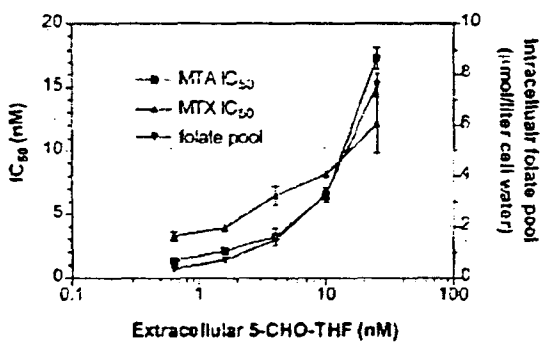

Fig. 7 Relationships among MTA or MTX IC_{50}, intracellular folate pool size, and extracellular 5-CHO-THF concentration in L1210 cells. L1210 cells were grown in folate-free RPMI 1640 supplemented with different concentrations of 5-CHO-THF for at least 1 week before MTA or MTX IC_{50}s were determined. Intracellular folate pools were measured after cells were grown exponentially for 1 week in folate-free medium supplemented with different concentrations of [^{3}H]5-CHO-THF. The data are the mean ± SE from three separate experiments.

MTA activity is modulated within cells by natural folates that *compete* for polyglutamation at the level of folylpolyglutamate synthetase. Contraction of the cellular folate pool decreases suppression of MTA polyglutamation.[22]

[20] Bachus et al. Int J Cancer. 2000;87:771-778.
[21] Zao, Babani, Gao, Liu, Goldman. Clin Cancer Res. 2000; 6:3687-3695
[22] Goldman ID, Zhao R. Semin Oncol. 2002 Dec;29(6 Suppl 18):3-17.

Changes in folate levels influence the competition between antifolates and natural folates. Below are processes that may be affected.

Natural folate pools within the cell may modulate MTA activity by:

- **competing with and inhibit MTA polyglutamation at the level of folyl-poly-gamma-glutamate synthetase**
- **competing with antifolates at the level of target enzymes**

For example, increased folate pools (*i.e., by folic acid supplementation*) may prevent polyglutamylation, resulting in faster efflux and a decrease in sensitivity of MTA.

Below is an *in vitro* example of the biochemical perturbations on MTA activity, resulting from changing folate levels.

> In the murine colon cancer cell lines (5-41x[23]), human colon cancer cell lines (1.2 x), and the human head and neck cancer lines (1.8-22x), IC50 values for MTA were higher in cells grown in standard folate media (8.8 uM folic acid and 2.2 uM folic acid, respectively) compared to cells grown in low folate media (2.5 nM leucovorin for murine colon cancer cells; 1 nM leucovorin for the human colon cancer cells; 0.5 nM leucovorin for head and neck cancer cell lines). FdUMP binding capacity and TS protein expression (by Western blotting) was lower in cells grown in low folate media. RFC activity was increased several fold (2-7x) in cells grown in low folate media compared to high folate media. In the case of lower activity of TS, lower concentrations of TS inhibitors are required for inhibition. No significant changes in polyglutamylation activity were found.[24]
>
> **MEDICAL OFFICER NOTE: It appears that in cell culture, MTA has biochemical advantages under low folate conditions. In marked contrast, in patients, i.e., the randomized JMCH trial, the addition of folic acid to the regimens increased efficacy without increasing the dose of MTA.**

Below is an *in vitro* example of the inhibitory activity of MTA, resulting from increasing folate levels. Again, note that for a comparable IC50, the concentration of MTA is increased as the folic acid concentration is increased.

> The table below illustrates that a several fold increase in MTA is required to give comparable inhibition of the cancer cell lines (none are mesothelioma cell lines) when folic acid is added to the media.[25]

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[23] Refers to IC50

[24] Bachus et al. Int J Cancer. 2000;87:771-778.

[25] Worzalla et al. Anticancer Research. 1998; 18:3235-3240

Table 1 *In vitro protective effects of folic or folinic acid on LY231514-induced cytotoxicity*

Cell line[a]	IC50 (nM)[b]	Relative (4-day) Change in IC_{50}						
		Folic acid conc. in medium[c]			Folinic acid conc. in medium			
		1 μM	10 μM	100 μM	0.1 μM	1 μM	10 μM	100 μM
IGROV1	44	1	14	25	2h	370	>970	>970
KB	34	2	3	17		6	78	>1270
GC3	12	1	3	9		195	47	640
LX-1	4	1	3	6		6	82	1440
CCRF-CEM	4	1	4	22	2	22	130	4440

[a]Cells were adapted to >4 weekly passages in low folate (2 nM folinic acid) medium.
[b]Cytotoxicity was determined by MTT assay with 72-h exposure to LY231514. Data represent mean of triplicate determinations.
[c]Folic or folinic acid was added two hours prior to LY231514 addition.

It is known that the MTD of antifolates in folated-depleted mice is much lower (50x) compared to mice on a standard diet.[26] Below is an *in vivo* example of the changes in MTA lethality, resulting from changing folate in the diet.

> In mouse strains, CD 1 nu/nu and DBA/2 (figure below), the MTA LD50s were 250x and 60x greater, respectively, in mice fed a standard diet (1-2 mg folate/kg/day) compared to a low folate diet (0.001-0.008 mg folate/kg/day) (figure below). Inspection of the figure shows that the two mouse strains had approximately the same MTA LD50 same on standard diet. On a low folate diet, the strains could be differentiated; there was a 10-fold difference in MTA LD50, i.e., DBA/2 > CD 1 nu/nu.[27] In view of the data in the next figure, a MTA LD50 study with low folate + folate supplement (15 mg folate/kg/day) would have been helpful.

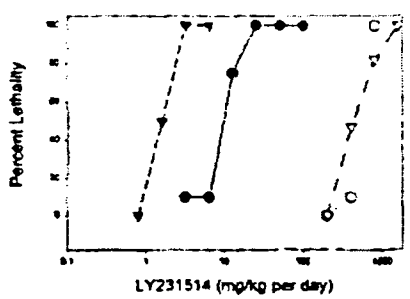


Figure 1. The toxicity of LY231514 in mice is increased by a folate-deficient diet. DBA/2 and CD1 nu/nu mice were fed either a standard laboratory diet (○ and ▽, respectively) or a folate-deficient diet for 2 weeks prior to the first dose of LY231514 (● and ▼, respectively) and for the duration of the study. Groups of mice (n = 10 animals/group) on each diet were given 10 daily doses of LY231514 i.p. at the indicated doses. The data present the percent lethality within 3 weeks after the last dose of LY231514.

[26] Bachus et al. Int J Cancer. 2000;87:771-778.
[27] Worzalla et al. Anticancer Research. 1998; 18:3235-3240

In mouse strain DBA/2 on a low folate diet, there was 100% inhibition of L5178Y/TK-/HX- lymphoma (figure below), at a MTA dose of 0.3 and 1 mg/kg/day administered intraperitoneal for 10 days, starting the day after tumor transplant. In mice fed a low fat diet + folate supplementation, 100% inhibition of L5178Y/TK-/HX- lymphoma was achieved at MTA doses of 30 - 1000 mg/kg/day or *the dose of MTA had to be increased 30x to obtain comparable efficacy with folate supplementation*(figure below).

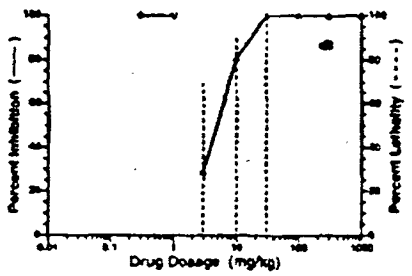


Figure 2 [illegible]

MEDICAL OFFICER NOTE: These preclinical results are counterintuitive to the results of the pivotal clinical trial, JMCH. In JMCH, after accrual of 70 of patients to the trial, subsequent patients were supplemented with folic acid + B12 without an increase in the dose of MTA. In comparison to the never supplemented group, efficacy parameters appear to have improved with folic acid + B12 supplementation, *including in the cisplatin arm.* Similar clinical findings of increased efficacy with the addition of folic acid + B12 were reported from a Phase 2 trial of MTA alone in mesothelioma patients; i.e., in the non-supplemented patients the median survival was 8 months and in the supplemented patients the median survival was 13 months.[28]

In mice, folic acid supplementation required a significant increase in the dose of MTA to obtain comparable efficacy as the non-supplemented mice. In humans, the dose of MTA was not increased with folic acid + B12 supplementation and the efficacy increased in comparison to the non-supplemented group.

However, the in vivo experiment below appears to mimic the clinical data.

[28] Scagliotti et al. J Clin Oncol. 2003;21:1556-1561

To assess the effect of vitamins involved in the folate pathway on the anitumor efficacy of LY231514 disodium in a human tumor xenograft model, female nude mice bearing human MX-1 breast carcinoma were treated with LY231514 disodium (MTA or alimta) alone or along with super physiologic doses of folic acid, vitamin B6 (pyridoxine), or vitamin B12 (cobalamin). The doses used in these growth delay experiments were: LY231514 (alimta, 100 or 150 mg/kg) administered by intraperitoneal injection on Days 7 through 11 and Days 14 through 18 post-tumor implantation alone or along with folic acid (6 or 60 mg/kg), vitamin B6 (100 mg/kg) or vitamin B12 (165 mg/kg).[29]

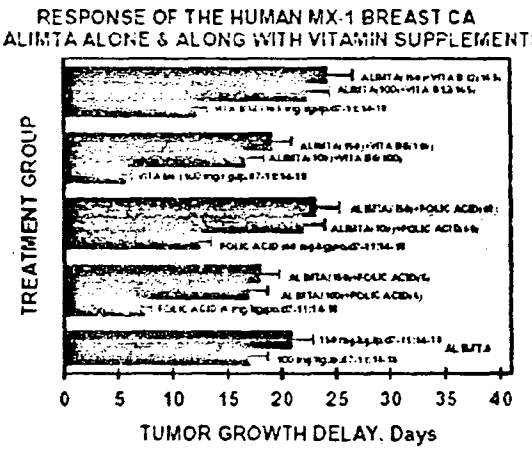
MEDICAL OFFICER NOTE: The schedule of vitamins is different in JMCH. In JMCH, the protocol indicated that patients should take oral folic acid (350 - 600 ug) daily beginning approximately 1 to 3 weeks before treatment with MTA plus cisplatin or cisplatin alone and continuing daily until 3 weeks after discontinuation from study therapy; in the animal study, folic acid was given *by intraperitoneal injection* (the METHODS section suggests IP and the figure indicates PO) concurrently with MTA, i.e., d 7-11 and d 14-18. In JMCH, the protocol indicated that a vitamin B12 (1000 ug) injection must be administered approximately 1 to 3 weeks before treatment with MTA plus cisplatin or cisplatin alone and should be repeated approximately every 9 weeks until the patient discontinues from study therapy; in the animal study, B12 was given by intraperitoneal injection concurrently with MTA, i.e., d 7-11 and d 14-18. In JMCH, patients received both folic acid and B12; in the animal study, only one of the vitamins was given. It is not stated why these doses of vitamins were used. For example, the folic acid doses were 6 mg/kg and 60 mg/kg *by intraperitoneal injection*; in another Lilly Research study, a standard mouse diet contained 1-2 mg/kg/day of folate and mice on a low folate diet received 15 mg/kg/day of oral folic acid.[30] The full dose response of these vitamins is not provided; i.e., the dose of the super physiological doses of vitamins may be on the inhibitory portion of a bell-shaped dose response curve.

Also, the schedule of MTA was different in another Lilly Research study. In this study, nude mice transplanted with MX-1 breast cancer were treated with MTA 100, 150, and 200 mg/kg/day on a day 7-11 schedule.[31] In the study described below, the mice were treated with MTA on a day 7-11 and day 14-18 schedule or twice the amount of MTA. In the other Lilly Research study, the definition of tumor growth delay was defined as the time taken by each individual tumor

[29] Lilly Research Laboratories: Nonclinical Pharmacology Report 30, March 2002
[30] Worzalla et al. Anticancer Research. 1998; 18:3235-3240
[31] Teicher et al. Clin Cancer Res. 2000; 6:1016-1023

to reach 500 mm3 compared with the time in the untreated controls; in study described below, the goal for the tumor size was 1000 mm3.

A figure with the results is below.



The table below illustrates the same data. MTA alone @ 100 mg/kg delayed tumor growth by 17 days. Although the addition of folate @ 6 mg/kg did not change tumor growth delay, folate @ 60 mg/kg increased the tumor growth delay to 22 days. The addition of B6 did not change tumor growth delay of MTA. The addition of B12 increased the tumor growth delay to 22 days. MTA alone @ 150 mg/kg delayed tumor growth by 21 days. Although the addition of folate @ 6 mg/kg did not change tumor growth delay, folate @ 60 mg/kg increased the tumor growth delay to 23 days. The addition of B6 did not change tumor growth delay of MTA. The addition of B12 increased the tumor growth delay to 24 days. With regard to folate *alone*, in a dose-response fashion, folate 6 and 60 mg/kg delayed tumor growth by 7 and 12 days, respectively. B6 alone delayed tumor growth by 5.7 days. B12 *alone* delayed tumor growth by 12 days. It appears that at these doses, in this tumor, folate (in a dose-response fashion) and B12 alone and in combination with MTA contribute to the delay of tumor growth without an increase in MTA dose. This is in marked contrast to another Lilly Research study.[32]

[32] Worzalla et al. Anticancer Research. 1998; 18:3235-3240

REGIMEN, MG/KG	TUMOR GROWTH DELAY (DAYS)
MTA 100 alone	17
+ 6 folate	17
+ 60 folate	22
+ 100 B6	17
+ 165 B12	22
MTA 150 alone	21
+ 6 folate	21
+ 60 folate	23
+ 100 B6	21
+ 165 B12	24
Folate alone	
6	7
60	12
B6 alone	
100	5.7
B12 alone	
165	12

MEDICAL OFFICER NOTE: Although not a mesothelioma cell line, these results are consistent with the results in JMCH, i.e., the addition of folate or B12 to an antifolate enhances antineoplastic activity. In fact, high dose folate alone and B12 alone may have antineoplastic activity independent of the antifolate, MTA. These results also run counter to the other *in vitro* and *in vivo* models presented above.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

1. **Statistical Review and Evaluation, completed and entered into DFS 12/10/2003**

   - Yong-Cheng Wang, Primary Reviewer
     Ming Li, Acting Team Leader

2. **Clinical Pharmacology and Biopharmaceutics Review, completed and entered into DFS, 12/4/2003**

   - Brian Booth, Primary Reviewer/Pharmacometrics
   - Roshni Ramchandani, Atul Bhattram, Pharmacometrics
     Joga Gobburu, Pharmacometrics, Team Leader
     N.A.M. Atiqur Rahman, Team Leader

3. **Pharmacology/Toxicology Review and Evaluation, completed and entered into DFS 12/19/2003**

   - Doo Y. Lee Ham, Primary Reviewer
     David Morse, Team Leader

   There were three consultations (e.g., medical imaging, [redacted], and pulmonary). The medical imaging consultation is not snown below because the findings of the consultation were blended into the Medical Officer's evaluation of tumor response.

4.

4.1 Recommendations for labeling:

1. [
2.
3.

BACKGROUND:
The LCSS cannot be interpreted as a general measure of either [redacted]. The LCSS is based on a conceptual model in which the physical and functional dimensions are the main determinants of a patient's health-related quality of life (HRQL), however, it specifically excludes items that focus on the psychological, social and spiritual domains.[33] The LCSS has been shown to explain only half the variability in overall HRQL.[34] In addition, the LCSS does not directly measure symptoms of treatment toxicity except in the situation where the symptoms of the condition are similar to the symptoms of treatment toxicity, e.g., fatigue.

The LCSS has been documented psychometrically to measure (as demonstrated by content, construct and criterion-related validity) the physical symptoms and function from the perspective of the lung cancer patient.[35] Patients with both NSCLC and SCLC have been tested. The extent that the same conclusions can be reached in malignant pleural mesothelioma would depend in part on whether the symptoms measured include all important symptoms specific to the mesothelioma experience. Symptoms measured by the LCSS are fatigue, decreased activity, cough, dyspnea, decreased appetite, pain and haemoptysis. The LCSS also includes a general symptom distress item a single-item global quality of life item.

Item 9 of the LCSS asks the broad question, "How would you rate the quality of your life today?" This broad question cannot be considered support for a broad claim, i.e., "improved QOL," since the determinants of that broad concept are not captured and it cannot be ascertained what treatment or non-treatment related changes are impacting the broad concept.

[33] Hollen P, Gralla R, et al. Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). Eur J Cancer 29A: S51-S58, 1993.
[34] Hollen P, Gralla R, et al. Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer 2: 213-222, 1994.
[35] Hollen p, Gralla R, etal. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies: Psychometric assessment of the Lung Cancer Symptom Scale. Cancer 73: 2087-2098, 1994.

Administration of the LCSS requires that the respondents adequately understand the visual analog scale (VAS) response options. However, the LCSS is rated at a Grade 2 level of comprehension and consists of only 9 VAS items. It asks about the patient's experience in the previous 24 hours. It takes only 3-5 minutes to complete. Some experts suggest that the VAS is the scale of choice when trying to reduce respondent burden and limit the attrition in ill patients. Nonetheless, evidence that patients were given standardized instructions and procedures for completing the questionnaire should be documented. The instrument developers recommend the LCSS be administered on a day of treatment, before the patient receives results from any clinical test, and before the patient receives chemotherapy.

In the literature I reviewed, the developers of the LCSS did not determined the minimum change that can be considered clinically important when interpreting clinical trial results. Other researchers have compared a variety of methods for estimating the smallest change that can be interpreted as clinically meaningful finding that 0.5 standard deviation has generally approximated those estimates.[36]

The LCSS has been translated into many languages, but status of the linguistic validation of those translations is unknown.

The following paragraph appears in Lilly's draft label for permetrexed (Alimta).

[

]

Comments on Lilly's draft labeling language above:

The study results do not support a conclusion of a treatment impact as demonstrated by the LCSS. The LCSS total score was not statistically significant. It appears that the only scale item that showed a statistically significant difference is the pain scale, and there is no indication that there was adjustment for multiple comparisons. Furthermore, there is no evidence that the LCSS was developed for individual item analysis.

The LCSS is not a measure of ' ' nor has the LCSS been shown to represent the global concept of ' ' for reasons stated above. In addition, there is no evidence in the authors' published documentation of LCSS development that the LCSS is designed to be used as a measure of the individual symptoms of "dyspnea, pain, fatigue, symptom distress, or interference with activity" but rather as a measure of physical symptoms and function. In addition, if permetrexed would have specific adverse

[36] Norman G, Sloan J, Wyrwich K. Interpretation of changes in health-related quality of life remarkable universality of half a standard deviation. Med Care 41:582-592, 2003.

events associated with its treatment that have an impact on a patient's clinical benefit, those adverse effects on patients' clinical benefit may not be measured by this instrument.

MEDICAL OFFICER COMMENTS FORWARDED TO LILLY

Although changes in some of the in the components of the LCSS are statistically significant, none of the changes are clearly clinically significant.

5. Pulmonary Function Tests

The table below illustrates the number of patients randomized and treated, the number of patients eligible for response evaluation, and the number of patients providing data for each of the pulmonary function tests. In general, 23-43% of patients did not provide pulmonary function data on the alimta/cisplatin arm compared to 28-44% of patients on the cisplatin alone arm. With regard to FVC, 26-32% of patients did not provide pulmonary function data on the alimta/cisplatin arm compared to 30-37% of patients on the cisplatin alone arm. This is an excessive amount of missing data. In a single-blinded study, this may suggest bias in testing and reporting.

	TOTAL NUMBER OF PATIENTS	ALIMTA/CISPLATIN NUMBER OF PATIENTS	CISPLATIN NUMBER OF PATIENTS
Entered (consented) in NDA	574		
Enrolled (randomized)	456		
Randomized and treated	448		
Eligible for response evaluation	447	225	222
PULMONARY FUNCTION			
Slow vital capacity Liters % predicted		145 143	140 140

	TOTAL NUMBER OF PATIENTS	ALIMTA/CISPLATIN NUMBER OF PATIENTS	CISPLATIN NUMBER OF PATIENTS
change from baseline			
liters		131	125
% predicted		129	125
Force vital capacity			
liters		167	156
% predicted		167	155
change from baseline			
liters		152	141
% predicted		152	139
FEV1			
liters		173	159
% predicted		173	159
change from baseline			
liters		158	145
% predicted		158	145

Consult from Division of Pulmonary and Allergy Drug Products (HFD-570) (Sally Seymour)

Below, in part, is the consult:

Table 1 and Table 2 summarize the results of the forced vital capacity for the Phase 3 clinical trial. Per the Sponsor's protocol, to be included in the analysis of a particular PFT parameter, a patient must have had data from the baseline period and data from at least one cycle among cycles 2, 4, and 6.

Table 1
Forced Vital Capacity
(Liters, % predicted)
RT Population **

		ALIMTA/CISPLATIN		CISPLATIN
Cycle	N	LS Mean	N	LS Mean
Baseline	167	2.37 (61.52)	156/155	2.45 (62.12)
Cycle 2	152	2.51 (65.37)	141/139	2.44(63.21)
Cycle 4	117	2.57 (67.11) *	89/88	2.41 (63.44) *
Cycle 6	66	2.55 (67.12) *	54/53	2.33 (60.72) *
Average	167	2.54 (66.53) *	156/155	2.40 (62.45) *

**Randomized & Treated * $p < 0.05$

Table 2
Forced Vital Capacity - Change from Baseline
Liters (% predicted)
RT Population **

		ALIMTA/CISPLATIN		CISPLATIN
Cycle	N	LS Mean	N	LS Mean
Cycle 2	152	0.08 (2.90)	141/139	0 (0.67)
Cycle 4	117	0.14 (4.62) *	89/88	-0.03 (0.70) *
Cycle 6	66	0.12 (4.57) *	54/53	-0.11 (-2.01) *
Average	167	0.11 (4.03) *	156/155	-0.05 (-0.21) *

**Randomized & Treated * $p < 0.05$

The Division of Oncology Drug Products asked three questions. Below are the questions and answers.

5.1 What are the appropriate pulmonary function tests to demonstrate benefit in this disease?

Malignant mesothelioma causes a loss of lung volume and therefore would be expected to produce a restrictive pattern on pulmonary function tests. Measurement of lung volumes such as total lung capacity and vital capacity would be the most appropriate variables to monitor a restrictive disease, while FEV1 is less useful. Unless a significant amount of obstruction and/or air trapping is present, the FVC and SVC should be similar and performing analysis on both is redundant. Although the FVC can suggest restriction, it is effort dependent and lung volumes are necessary to confirm the restrictive defect. Therefore, the ideal parameter for assessing restrictive physiology would be lung volume measurements, which can be performed using helium dilution or body plethysmography. However, of the variables the Sponsor measured, the FVC could reasonably be used to monitor and analyze trends. Therefore, the remainder of this consult will focus on the FVC results.

5.2 What degree of improvement in pulmonary function is clinically important?

The degree of improvement in pulmonary function that is clinically important is not well defined. Therefore even though the data shows a

statistically significant difference between groups in FVC, the clinical relevance of the magnitude of change is unclear.

When measuring FVC, several acceptable maneuvers are recorded to show reproducibility. According to the American Thoracic Society, the two largest FVCs from acceptable maneuvers can vary up to 200 mL.[37] In addition, serial measurement of FVC is subject to a certain amount of variability often termed the coefficient of variation. The amount of within subject variability is not well defined but is often estimated to be around 5% over the course of day-to-day measurement.[38]

The Sponsor's data for FVC reported in Table JMCH.11.69 and Table JMCH.11.70 is summarized in Table 1 and Table 2, above. The average mean increase in FVC from baseline in the alimta/cisplatin arm was 110mL while the average mean decrease from baseline in the cisplatin arm was 50mL. Thus, the difference between groups in average mean change in FVC totals 160mL.

Because the difference between groups in mean change from baseline FVC in this trial is less than the range of variability allowed by the ATS in a single test session and less than generally accepted day-to-day variability, it is the opinion of this Reviewer that the difference in FVC is not clinically significant.

If the effects of multiple cycles of alimta are felt to be cumulative, one could argue that it would be more appropriate to base conclusions on the Cycle 6 data, rather than the data representing the average values over multiple cycles. One difficulty with this approach is that the numbers of patients for which data are available become quite small with successive cycles. That said, the largest change in FVC was in cycle 6 in which the alimta/cisplatin arm showed a mean increase from baseline FVC of 120mL while the cisplatin arm showed a mean decrease from baseline FVC of 110mL. The difference between groups in mean change from baseline FVC was 230mL. Although this is a larger increase in FVC, the value is only slightly out of the range of variability allowed by the ATS in a single test session. In addition, as mentioned above, the significant decline in patient data available during the course of the trial makes any interpretation of the data very difficult. Therefore, it remains the opinion of this Reviewer that the difference in FVC is not clinically significant.

5.3 Does the data on pulmonary function support the label claims of improvement in pulmonary function and clinical benefit?

[37] Am J Respir Crit Care Med 1995; 152:1107-1136.
[38] Am Rev Respir Dis 1991; 144:1202-1218.

It doesn't appear that appropriate statistical methods were specified to account for multiplicity among the various secondary endpoints. DPADP defers to DODP in regards to whether this alone would preclude inclusion of the proposed claims in the label.

Although the data on pulmonary function does support a statistically significant difference between the two treatment groups (issues of multiplicity aside), the effect size is not considered clinically meaningful

The observation that we see in this study is interesting. To support a specific labeling claim of an improvement in lung function which is clinically meaningful, the Sponsor should do a 'second' trial where assessment of lung function is declared as the primary variable. A 'second' trial is recommended because of the secondary nature of the observation in this trial as well as lack of control of multiplicity. Furthermore, the choice of variables to be measured would need further explanation with a detailed discussion in the protocol of what would constitute a favorable response. Finally, in the design of the 'second' trial, the Sponsor would need to address the significant decline in the numbers

MEDICAL OFFICER COMMENTS FORWARDED TO LILLY

Although changes in pulmonary function evaluations are statistically significant, the changes are within the variability range for these tests (i.e., FVC) allowed by the American Thoracic Society and thus, the changes are not clinically significant. Also, over 20% of the patients did not contribute data to the pulmonary function evaluations; in a single-blinded study, this may suggest bias in testing and reporting.

III. Human Pharmacokinetics and Pharmacodynamics

1. Pharmacokinetics

Refer to:

Clinical Pharmacology and Biopharmaceutics Review, completed and entered into DFS, 12/4/2003

- Brian Booth, Primary Reviewer/Pharmacometrics
  - Roshni Ramchandani, Atul Bhattram, Pharmacometrics
    Joga Gobburu, Pharmacometrics, Team Leader
    N.A.M. Atiqur Rahman, Team Leader

2. Pharmacodynamics

Refer to:

Clinical Pharmacology and Biopharmaceutics Review, completed and entered into DFS, 12/4/2003

- Brian Booth, Primary Reviewer/Pharmacometrics
  - Roshni Ramchandani, Atul Bhattram, Pharmacometrics
    Joga Gobburu, Pharmacometrics, Team Leader
    N.A.M. Atiqur Rahman, Team Leader

IV. Description of Clinical Data and Sources

1. Overall Data

1.1 Sources used in review:

- Literature
- Study reports
- For Financial disclosure: data tabulations and source documents
- Electronic datasets: "SURVLOCK" (Date "24-OCT-2002" and "6-DEC-2002"), "LABRESLT.XPT"
- [redacted] the independent review database of CT scans and the independent review findings
- Laptop containing the [redacted] database ([redacted] /BASE) of the independent reviewers' evaluations
- Pre-NDA meeting Briefing Documents

- Documents reviewed: 10/24/2002 (Rolling Submission), 11/22/2002, 11/26/2002, 1/10/2003, 2/13/2003, 3/24/2003 (financial disclosure), 5/9/2003, 5/29/2003, 7/23/2003 (Safety Update), 7/30/2003, 8/8/2003, 8/15/2003, 8/21/2003, 8/28/2003, 9/2/2003, 9/12/2003, 9/15/2003, 9/19/2003, 9/22/2003, 9/29/2003, 10/6/2003 (labeling), 10/20/2003, 11/4/2003 (labeling), 11/6/2003, 11/14/2003 (labeling), 11/14A/2003, 11/18/2003, 11/24/2003 (labeling), 11/26/2003, 12/4/2003 (financial disclosure), 12/4A/2003, 12/5/2003 (labeling), 12/10/2003 (financial disclosure), 12/15A/2003 (labeling), 12/16/2003.

2. Tables Listing the Clinical Trials

Protocol H3E-MC-JMCH(g): A Single-blind Randomized Phase 3 Trial of MTA[39] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma (Pivotal trial; reviewed by FDA)

Enrolled: 226 alimta plus cisplatin arm (168 folic acid + Vitamin B12 supplemented 168; 58 partially supplemented or never supplemented); 222 cisplatin alone arm (163 folic acid + Vitamin B12 supplemented, 59 partially supplemented or never supplemented).

Protocol H3E-MC-JMDR Phase 2: A Phase 2 Trial of LY231514 Administered Intravenously Every 21 Days in Patients with Malignant Pleural Mesothelioma (Supported trial; not reviewed by FDA)

Enrolled: 64 (43 folic acid + Vitamin B12 supplemented; 21 never supplemented)

3. Postmarketing Experience

N/A

[39] alimta

4. Literature Review

4.1 The FDA's Background on Malignant Pleural Mesothelioma

Introduction

In the last two decades, there has been remarkable progress in understanding the clinical and biological manifestations and treatment of mesothelioma. The first edition of Cancer. Principles and Practice of Oncology (1982)[40] mentioned mesothelioma in one paragraph (5 lines) in the chapter Neoplasms of the Mediastinum, and in two separate paragraphs (7 and 6 lines, respectively) in the chapter Sarcomas of the Soft Tissue and Bone. In comparison, lung cancer had a dedicated chapter, Cancer of the Lung, with 78 pages. In the latest edition of Cancer. Principles and Practice of Oncology, 6th Edition (2001)[41], there is a chapter dedicated to mesothelioma, Benign and Malignant Mesothelioma, with 35 pages. Again, in comparison, lung cancer also had a dedicated chapter, Cancer of the Lung, with 103 pages.

The bulk of this background material on mesothelioma (and given credit in serial footnotes) is from two textbooks of oncology.[42],[43] This material is important because it may provide insight into the state-of-the-art knowledge and judgement of investigators entering and enrolling patients into the alimta pivotal mesothelioma trial.

In the United States, an estimated 2000 to 3000 new cases of mesothelioma are diagnosed each year or approximately 12.1 per million white men.[44] Males are affected by this malignancy five times more than females. The median age at the time of diagnosis is 60 years; incidence rises steadily with age and is approximately tenfold higher in men aged 60 to 64 years as compared with those aged 30 to 34. Asbestos exposure is the risk factor with an interval between exposure and malignancy of 3-4 decades. Median survival is about 10 to 17 months from onset of symptoms and 9 to 13 months from diagnosis. The 3- and 5-year survival probabilities are 10 and 3%, respectively, in one review of 92 cases, and 5.6% for 5-year survival in another review of 123 patients.[45] Mesotheliomas contain both epithelial and sarcomatoid elements; the designation of pathological type is dependent on the relative abundance of each component; 50% are epithelial, 34% are mixed, and 16% are sarcomatoid. This is important because the survival is influenced by the pathological type. Depending on the series cited, median survival for epithelial type is 22 months compared to 6 months for

[40] Edited by DeVita VT, Hellman S, Rosenberg SA. JB Lippincott Co., Philadelphia.
[41] Edited by DeVita VT, Hellman S, Rosenberg SA. JB Lippincott Co., Philadelphia.
[42] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.
[43] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London
[44] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.
[45] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

the other types.[46] The majority of patients who survive for 2 years have the epithelial histology.[47] Variations in prognostic factors may, in part, explain variations in survival in Phase II and III trials in malignant mesothelioma.[48] In contrast to lung cancer, this is a disease of local progression and rare hematogenous spread, including in the late stages of untreated disease.[49] In patients, who are considered completely resectable by surgery, clinical symptoms and radiographic studies are not sensitive enough to accurately diagnose early recurrence, making survival the major endpoint of interest.[50]

Asbestos Risk

Because of local asbestos industries, some locations in the U.S. have incidences as high as 636 male cases and 96 female cases per year per million population. Whether risk in such communities extends to the population at large who are not employed in the asbestos industry remains controversial. The standardized incidence of mesothelioma in Wittenoom, Australia, was 260 per million for both men and women once residents employed in the crocidolite industry were excluded. Purely residential exposure accounted for only 3% of incident cases in Yorkshire, England, but at least 18% of the cases in South Africa.[51]

The incidence of mesothelioma appeared to be increasing perhaps by as much as 50% in the last decade. Projections of incidence for the U.S. suggested that the numbers of cases would peak at the turn of the twentieth century or rise moderately in the twenty-first century, and then decline as a result of legislation to reduce asbestos exposure in the workplace and the ambient environment. In the Netherlands, the peak in annual male mesothelioma deaths is expected later, in approximately the year 2018. Pleural mesothelioma may account for 0.87% of all deaths in the 1943 to 1947 birth cohort of Dutch men. There are projections that the risk of dying of mesothelioma in Western Europe will double over the next 20 years, with the highest risk of approximately 1 in 150 men in the 1945 to 1950 birth cohort.[52]

Despite the obstacles to quantifying risk of mesothelioma, several consistent observations have emerged from studies worldwide. Crocidolite is associated with high risk of mesothelioma in miners, manufacturers, and workers who install asbestos products. Another amphibole, amosite, appears to carry an intermediate risk. Chrysotile, currently the major form of asbestos in production, shows the weakest association with mesothelioma.

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[46] Lee JS et al. Non-small-cell lung cancer , meothelioma, and thymoma. In: Cancer Management: A Multidisciplinary Approach. Edited by Pazdur R et al. New York: PRR, Inc., 2001. P. 117-120

[47] Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)

[48] Steele JPC, Rudd RM. Thorax 2000;55:725-726

[49] Sugarbaker et al. J Thora Cardiovasc Surg 1999;117:54-65

[50] Sugarbaker et al. J Thora Cardiovasc Surg 1999;117:54-65

[51] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[52] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

Occupations with highest risk appear to be insulators, asbestos producers and manufacturers, and heating and construction tradespeople. The projected lifetime risk among these workers exposed from early adulthood ranges up to 20%. Working in proximity to these occupational groups in construction sites confers a relatively lower risk. In addition, some patients with mesothelioma have reported only isolated or brief occupational exposures to asbestos.[53]

Antman and co-authors write that malignant mesothelioma is rarely curable at present, so screening of asbestos workers for mesothelioma is inappropriate. However, smoking greatly increases the risk of lung cancer (but not mesothelioma) in asbestos workers and smoking cessation efforts are needed in this high- risk group. Practicing physicians considering the diagnosis of malignant mesothelioma should take a detailed exposure history emphasizing the period 20 to 50 years before diagnosis and including possible household contact exposure. Brief exposures may be long forgotten.[54]

Presentation and Evaluation of the Patient

Malignant pleural mesothelioma most commonly develops in the fifth to seventh decade (median age, 60 years), typically 20 to 50 or more years since first documented asbestos exposure. The risk has been estimated to be linearly proportional to the intensity and duration of exposure, and to the time since first exposure to a power of between 3 and 4.

Latency periods between first exposure to asbestos and a diagnosis of mesothelioma may vary by occupation, with shorter latencies for insulators and dock workers and longer intervals for shipyard and maritime workers, as well as domestic exposures. A significant proportion of patients with mesothelioma diagnosed between the ages of 20 and 40 report household or neighborhood exposure during childhood. Children who present with the disease generally have no apparent asbestos exposure.[55]

Dyspnea, nonpleuritic chest wall pain, or both bring 90% of patients to medical attention. Examination is generally remarkable for dullness at one base, and chest radiography reveals a large freely movable unilateral pleural effusion. Occasional patients are asymptomatic, an effusion found incidentally on chest radiography. Five patients in one series presented with spontaneous pneumothorax with the unsuspected diagnosis of mesothelioma made at pleurectomy. Sixty percent have right-sided lesions, and less than 5% have bilateral involvement at the time of diagnosis.[56]

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[53] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.
[54] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.
[55] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.
[56] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943

Pulmonary function test results may document restrictive lung disease resulting from encasement of the lung and assess the potential tolerance for pneumonectomy. Obstructive spirometric changes are unrelated to mesothelioma or asbestosis. Laboratory evaluation is otherwise generally unremarkable except for an elevated platelet count and erythrocyte sedimentation rate.[57]

Bronchoscopy is usually normal or reveals extrinsic pressure. Thoracocentesis yields a serous to viscous, glutinous fluid, which is occasionally bloody. The fluid is an exudate, and pleural fluid glucose can be low, but this finding is nonspecific. The best positive marker for malignant mesothelioma is the detection of a high level of hyaluronic acid in the fluid. However, the diagnostic yield by cytology is disappointing. Cytologic studies in large series reveal malignant cells in 16 to 38% of patients, but their exact nature is often undetermined or misclassified, and they are diagnostic in only 3 to 16% of patients with mesothelioma. Greater awareness of the disease, increasing expertise, and use of special stains or electron microscopy may improve these disappointing results. Pleural needle biopsy shows malignant disease in 13 to 48% of cases, and a diagnosis of mesothelioma in 10 to 36%. Use of Tru-cut needles or CT-guided pleural biopsies need more evaluation. Thoracoscopy is a useful technique in cases where it is technically possible, yielding a diagnosis of mesothelioma in 70 to 80% of cases and false-negative results in up to 20% of cases, although it was diagnostic in virtually all patients in another study. Otherwise, thoracotomy with open surgical biopsy remains the best diagnostic procedure, yielding the diagnosis in 77 to 100% of patients.[58]

Pathology

Histopathology

The annual incidence of mesothelioma is not known with certainty because this malignacy is difficult to diagnose, even by expert pathologists. Initial misdiagnosis is common. Data from death certificates are unreliable for estimating disease frequency despite the usually rapidly fatal outcome of malignant mesothelioma. Cancer deaths are not coded by morphology (mesothelioma). The cause of mortality is assigned by primary site of the neoplasm (primary neoplasms of pleura and peritoneum). In a study of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, only 274 of 1130 white decedents with mesothelioma (approximately 95% diagnosed by microscopy) were recorded as having died of a primary neoplasm of pleura or peritoneum. The majority of

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Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[57] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943

Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[55] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

these mesothelioma cases were coded as having malignant neoplasm of the lung or unknown site.[59]

In the past, expert panels have been set up to review suspected malignant pleural mesothelioma cases. Pathologic opinion appeared particularly diverse when litigation is involved. Because a substantial percentage of mesotheliomas developed in patients with no known asbestos exposure and other malignancies were common in asbestos workers, asbestos exposure should not influence the diagnosis of mesothelioma. Because of the poor current prognosis of pleural mesothelioma, a major role of establishing the diagnosis was to exclude the possibility of a more treatable illness.[60],[61] Accurate diagnosis is also important in the event of subsequent litigation and for epidemiologic and therapeutic studies.[62] Again, one editorialist wrote about the need for a panel of experts to review pathological material to guarantee the accuracy of diagnosis.[63]

The histopathologic types of malignant pleural mesothelioma include: 1) epithelial or tubulopapillary (50 to 70% of cases), 2) mesenchymal or fibrosarcomatous (7 to 20% of cases), and 3) mixed or biphasic (20 to 35% of cases) (the mixed type contains both epithelial and mesenchymal elements).[64]

It is important to differentiate mesothelioma from adenocarcinoma--tumors with histologic similarities--since it may influence the treatment and avoid an extensive and expensive search for another primary lesion (see table below). Electron microscopy and immunohistochemistry are important adjuncts to routine microscopic evaluation in the diagnosis and classification of malignant mesothelioma.[65] Electron microscopy is a method to aid in differentiation with typical microvilli on epithelial mesothelioma cells (the fibrosarcomatous cells lack them) which are longer and thinner than in adenocarcinomas, as well as tonofilaments and cell junctions. Another method is through immunochemistry. A property of the mesothelial cell is the production of hyaluronic acid, a glycosaminoglycan which stains weakly with mucicarmine and strongly with colloidal iron or Alcian blue and disappears after preincubation with hyaluronidase.[66], [67]

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[59] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[60] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

[61] Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)

[62] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943. Epidemiology. In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[63] Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)

[64] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

[65] Nash G, Otis CN. Protocol for the examination of specimens from patients with malignant pleural mesothelioma. A basis for checklists. Arch Pathol Lab Med. 1999;123:39-44

[66] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

[67] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

Hyaluronic acid has been reported to be useful in diagnosis or for following response but is relatively nonspecific. The level of hyaluronic acid was studied in the pleural fluid of 19 patients with malignant mesothelioma, 27 with lung cancer, 1 with breast cancer, 1 with mediastinal tumor, and 51 with benign diseases. The pleural fluid concentration of hyaluronic acid was greater than 100 ug/mL in 37% of (7 of 19) mesotheliomas and 1.3% of (1 of 80) lung cancers and other malignant and benign diseases. A markedly elevated serum or pleural fluid carcinoembryonic antigen, however, suggests a diagnosis other than mesothelioma.[68]

Hematopoietic growth factors and blood group antigens have been produced by normal and malignant mesothelial cell lines. Serum levels of interleukin-6 (IL-6), C-reactive protein, alpha(1)-acid glycoprotein, and fibrinogen were significantly higher in 25 mesothelioma patients than in patients with lung adenocarcinoma with cytology-positive pleural effusions. Serum IL-6 levels correlated with the levels of the acute-phase proteins and significantly with platelet counts. The level of IL-6 in the pleural fluid of patients with mesothelioma was approximately 60 to 1400 times higher than in the serum. Even higher levels of IL-6 in the pleural fluid and of thrombocytosis were found in patients with tuberculous pleurisy. High cytokine levels were not specific to mesothelioma (similar profiles were found in patients with tuberculous pleurisy).[69] However, the detection of a markedly increased level of IL-6 in pleural fluid argues against a diagnosis of adenocarcinoma.[70]

Pulumonary adenocarcinoma tend to express CEA, LeuM1, B72.3, and BerEP4; malignant mesotheliomas, in general, do not express these markers.[71] Monoclonal antibodies against keratin proteins tend to be expressed in mesotheliomas.[72] The table below from Chahinian and Pass[73] compares mesothelioma and adenocarcinoma of the lung immunochemistry.

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[68] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

[69] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

[70] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943. Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[71] DeVita VT, Hellman S, Rosenberg SA. Cancer. Principles and Practice of Oncology, 2001, p. 2731

[72] DeVita VT, Hellman S, Rosenberg SA. Cancer. Principles and Practice of Oncology, 2001, p. 1947

[73] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

Table 89.1. Special Stains Useful in Differentiating Malignant Mesothelioma from Metastatic Adenocarcinoma

STAIN	Mesothelioma	Adenocarcinoma
Hyaluronic acid*	+	−
Mucicarmine*	−	+
PAS	+/−	−
D-PAS*	−	+
CEA*	−	+
Leu M1*	−	+
Keratin	+	+
Vimentin	+	−
HMFG	+/−	+
EMA	+	+

PAS = periodic acid-Schiff; D-PAS = with diastase digestion; CEA = carcinoembryonic antigen; Leu M1 = human myeloid-specific antigen; HMFG = human milk fat globules; EMA = epithelial membrane antigen.
* Most discriminating stains.

Benign inflammatory and reactive processes producing mesothelial hyperplasia or other malignant tumors may mimic mesothelioma but do not invade normal tissues and lack cytologic atypia and hyperchromatism. Repeated cytologic examination or biopsy results may be negative despite active tumor. When tumor tissue is obtained, light microscopy often provides documentation of malignancy, but usually does not distinguish adenocarcinoma from mesothelioma. Electron microscopy of either needle biopsy or cytocentrifuge specimens from pleural fluid may establish the mesothelial origin of the malignant tumor. Sputum cytology and bronchoscopy may be helpful in documenting an occult bronchogenic adenocarcinoma. The Cancer Committee of the College of American Pathologists has established a checklist protocol for the examination of specimens from patients with malignant pleural mesothelioma.[74]

Adenocarcinomas from primary lung, breast, ovary, stomach, kidney, or prostate cancer frequently metastasize to the pleura and can be extremely difficult to distinguish from epithelial mesothelioma cytologically or histologically. Metastatic adenocarcinoma with extensive pleural involvement may grossly resemble mesothelioma and has been called pseudomesothelioma. Sarcomatous mesotheliomas must be distinguished from fibrosarcoma, malignant fibrous histiocytoma, malignant schwannoma, and hemangiopericytoma. Synovial sarcoma and carcinosarcomas, which may also have mixed sarcomatous and epithelial components, usually present as a localized mass in the lung. In one series, of 82 malignant localized tumors, 45% were cured by simple excision. If the nature of a lesion was ambiguous, involvement of the pleura on random biopsy would establish a diagnosis of diffuse (malignant) disease.

Autopsy requires skilled performance and experienced interpretation to reliably exclude other occult primary carcinomas. Advanced malignant mesothelioma tends to form

[74] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

peripheral visceral masses mimicking primary carcinomas. Asbestos counts and postmortem examinations may have legal as well as epidemiologic value.[75]

Cytology

In one study of 21 cases of epithelial malignant mesothelioma (15 pleural, 6 peritoneal) diagnosed by effusion cytology, 13 were of the cohesive cell type and 8 were of the noncohesive cell type. Because of its resemblance to florid reactive mesothelial hyperplasia and the general lack of awareness of the existence of the single-cell pattern of mesothelioma, the noncohesive cell type can often be missed. For 29 patients with at least one cytologic pleural fluid examination, cytology was positive for mesothelioma in 32%. The median time from initial symptoms to the diagnosis of mesothelioma was 8 weeks (4 weeks for patients with positive or suspicious cytology results, and 12 weeks for those with negative cytology results). Cytogenetic analysis of pleural fluid had a sensitivity of 56% and was positive in one case in which results of cytologic examination were negative.[76]

Patients in whom the time from presentation to diagnosis was greater than 1 year all had negative cytologic results followed by long periods without further workup, despite a history of exposure to asbestos. Because the sensitivity of cytologic examination for mesothelioma is so low, patients in whom mesothelioma is suspected should undergo immediate pleural biopsy if the pleural fluid cytology result is negative.[77]

Below is a table of malignant pleural mesothelioma and adenocarcinoma of the lung.

[75] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[76] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[77] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

Comparison of Malignant Pleural Mesothelioma and Adenocarcinoma of the Lung

	MALIGNANT PLEURAL MESOTHELIOMA	ADENOCARCINOMA OF THE LUNG
Incidence, per year U.S.	2000 - 3000	66,000[78]
Sex, male:female	5:1	1.2:1 for lung cancer; adeno-common in women
Age, years (median)	60	60
Etiology, latency	Asbestos, 3 - 4 decades	Smoking, asbestos, asbestos + smoking
Pathology	Epithelial>mixed>sarcomatoid	Adenocarcinomas from primary lung, breast, ovary, stomach, kidney, or prostate cancer frequently metastasize to the pleura and can be extremely difficult to distinguish from epithelial mesothelioma cytologically or histologically. Metastatic adenocarcinoma with extensive pleural involvement may grossly resemble mesothelioma and has been called pseudo-mesothelioma. Synovial sarcoma and carcinosarcomas, which may also have mixed sarcomatous and epithelial components, usually present as a localized mass in the lung. Sarcomatous mesotheliomas must be distinguished from fibrosarcoma, malignant fibrous histiocytoma, malignant schwannoma, and hemangiopericytoma.
Immunohistochemistry	Positive: hyaluronic acid, keratin, vimentin	Positive: CEA, LeuM1, B72.3, BerEP4, D-PAS
Electron microscopy	Typical long microvilli on epithelial cells (the fibrosarcomatous cells	Microvilli are shorter and thicker than on mesothelioma cells

[78] Based on year 2000 numbers: 164,100 lung cancer cases x 40% adenocarcinoma: 65,640

	MALIGNANT PLEURAL MESOTHELIOMA	ADENOCARCINOMA OF THE LUNG
	lack them), as well as tonofilaments and cell junctions.	
Pleural effusion	Hyaluronic acid positive Increased IL-6 level (non-specific: also high with TB)	CEA positive
Staging Earliest stage with malignant pleural effusion/surgical candidate	T1 (median: 27 mo.)/yes	T4 (<10% 5-yr. Surv.)/no
Ipsilateral supraclavicular node	N3 (Stage IV)	N2 (Stage III)
Stage IV	T4, N3, or M1	M1
Natural history: metastatic disease pattern vs. locoregional disease	Local progression; rare hematogenous spread	Hematogenous spread common

Other Variants of Mesothelioma

Benign Fibrous Tumors of the Pleura

Benign fibrous tumors of the pleura are approximately one-third as common as diffuse malignant mesotheliomas and are most common from age 40 to 70 years. Because they appear to arise from subsurface fibrous tissue, rather than from the mesothelial lining, they have also been called submesothelial fibromas, localized fibrous mesothelioma, or solitary fibrous tumor of the pleura. Few patients have been exposed to asbestos, approximating the incidence of exposure in the general population. CT scan and MRI are useful but nonspecific. The differential diagnosis between benign and malignant lesions is based on histologic study. Lesions have ranged in size from 1 to 36 cm. Associated effusions can be serosanguineous. Hypertrophic pulmonary osteoarthropathy has occurred in approximately one-third of patients, particularly associated with lesions more than 10 cm in size. Hypoglycemia has also been associated with large lesions,

associated in some cases with tumor production of insulin-like growth factor. Mesotheliomas are often pedunculated and 80% arise from but usually do not invade the visceral pleura. Thus, benign pleural mesotheliomas usually have a sharp separation between tumor and compressed lung, and resection can be performed without pulmonary resection. Others may require a limited chest wall resection. While generally cured if completely resected, recurrences have occurred after several decades and 12% of patients eventually die of extensive local tumor. Localized malignant fibrous tumors of the pleura have also been described. Of 82 malignant localized tumors, 45% were cured by simple excision. If the nature of the lesion is ambiguous, involvement of the pleura on random biopsy would establish a diagnosis of diffuse (i.e., malignant) disease.[79]

Malignant Peritoneal Mesothelioma

Patients usually present with symptoms and signs of advanced disease including pain, ascites, weight loss, or an abdominal mass. A cake of tumor in the omentum may be palpable as an epigastric mass. No satisfactory staging system has been proposed for peritoneal mesotheliomas, which are usually confined to the abdomen at diagnosis. Chest radiography reveals pleural plaques in approximately 50% of patients with peritoneal primaries, compared with 20% in patients with pleural mesothelioma, reflecting the higher level of asbestos exposure in patients with peritoneal disease. Classic findings on CT scan include mesenteric thickening, peritoneal studding, hemorrhage within the tumor mass, and ascites; however, patients may have advanced disease with relatively normal CTs. MRI offers the possibility of improved resolution. Given the low incidence of bone, brain, or liver metastasis at presentation, extensive evaluation for metastatic disease is inappropriate in the absence of laboratory abnormalities. Adrenal, intrapulmonary, or bony metastasis should raise the possibility of an alternative diagnosis.[80]

Peritoneal fluid from malignant ascites may be a watery transudate or a viscous fluid rich in mucopolysaccharides. No diagnostic significance has been attached to the character of the fluid, although a viscous ascites (with high fluid hyaluronidase levels) may suggest the diagnosis. Massive ascites may result in confusion of mesothelioma with severe cirrhosis. Cytology establishes the diagnosis in only 5% to 10% of cases. Ultimately, definitive diagnosis requires adequate tissue sampling, preferably from peritoneoscopy or an open directed

[79] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[80] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

biopsy. A generous biopsy specimen is required to perform immunohistochemical stains, as well as electron microscopy. Open biopsy also permits inspection of the abdominal cavity for extent of disease with particular attention to the bowel and ovaries to distinguish mesothelioma from other more common causes of peritoneal carcinomatosis. Peritoneal mesotheliomas can be confused with adenocarcinomas arising from any abdominal organ, but the pattern of spread and tendency to accumulate in the pelvis readily leads to confusion with adenocarcinoma of the ovary or carcinoma arising from Mullerian duct remnants in the peritoneum. The tumor generally remains confined to the abdomen until late in the course and even then is more likely to spread to one or both pleural cavities than to disseminate hematogenously. Thrombocytosis is common and associated with high levels of IL-6 and a poor prognosis. Other common clotting abnormalities include phlebitis, emboli, hemolytic anemia, and disseminated intravascular coagulation. Most patients die without metastases or involvement of the chest. Esophageal achalasia, secondary amyloidosis, and dermatomyositis have been reported. The median survival of untreated patients in most series is short, 4 to 12 months.[81]

Well-Differentiated Papillary Mesothelioma or Cystic Mesotheliomas of the Peritoneum

Rare, well-differentiated papillary variants and a syndrome of recurrent peritoneal mesothelial cysts have both been found predominantly in younger women associated with a prolonged survival despite bulky disease. Rarely, the disease progresses over time to a typical malignant mesothelioma. Approximately 130 cases of multiloculated peritoneal inclusion cysts (also called benign cystic peritoneal mesotheliomas) have been described, mainly in the pathologic and surgical literature. Some authors have advocated classifying this lesion as reactive proliferation rather than as malignant. The radiologic differential diagnosis has been reviewed. Frequently associated with prior surgery, endometriosis, or pelvic inflammatory disease, they occur predominantly in women, but can occur in men. Treatment should be provided for palliation of symptoms or for clearly documented progression. Despite initial surgical resection, approximately one-half recur locally. Neither lesion size nor proliferation correlates with outcome. Tamoxifen resulted in a prolonged response in a 19-year-old woman. Permanent transvaginal catheter drainage in a patient with recurrent cysts resulted in infection and obliteration of the cyst. The potassium titanyl phosphate laser has also been used in treatment of benign multicystic peritoneal mesothelioma.[82]

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[81] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[82] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

Surgery for Peritoneal Mesothelioma

Surgical and autopsy series have shown that peritoneal mesothelioma involves all peritoneal surfaces, often with masses of 5 cm or more. Sites of local invasion included the liver, abdominal wall, diaphragm, retroperitoneum, gastrointestinal tract, and bladder. Seeding of laparotomy scars and biopsy tracts has also been observed. The tumor is most often confined to the peritoneal cavity at the time of initial diagnosis and remains there for much or all of the subsequent clinical course. Hence, effective local therapy may have a substantial effect on the survival of patients with this disease. Complete surgical resection is rarely, if ever, feasible, and has not been shown to afford survival benefit in the absence of additional therapy. Nevertheless, surgical intervention can provide palliation for small bowel obstruction and relief of massive ascites by peritovenous shunting or paracentesis via Tenckhoff's catheter.[83]

Prognostic Factors for Malignant Pleural Mesothelioma

Performance status has been one of the most reliable prognostic factors, in addition to the stage, which is discussed below. Epithelial cell type has been associated with a more favorable prognosis in most large series; the fibrosarcomatous type carries the worst prognosis, and the mixed type is intermediate. Younger age at diagnosis has also been reported as a favorable feature, whereas no prognostic differences were found between men and women, particularly after adjustment for cell type. Absence of weight loss, lack of involvement of the visceral pleura, early stage, and epithelial cell type were shown to be favorable prognostic factors in a large group of 188 patients with pleural mesothelioma. The negative prognostic impact of thrombocytosis first reported by Chahinian and colleagues has been confirmed in three other series. The prognostic role of other factors (asbestos exposure or not, duration of symptoms, side of pleural disease, and pleural versus peritoneal involvement) is more contradictory at this time. [84] The EORTC system of prognostic factors for malignant pleural mesothelioma defined high risk as: poor performance status, high WBC at diagnosis, probable or possible (uncertain) histology, male sex, and sarcomatous cell type;[85] in their experience in 204 adults with malignant pleural mesothelioma on five consecutive phase II clinical trials, the median survival was 13 months from diagnosis and 8 months from trial entry. [86] Epidermal

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[83] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.
[84] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine. Edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London
[85] Steele JPC, Rudd RM. Thorax 2000;55:725-726
[86] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943

growth factor-positive cells have been found in 68% of mesotheliomas examined and correlate with improved survival.[87]

The table below summarizes specific articles, which analyzed data for prognostic factors in malignant pleural mesothelioma.

AUTHOR JOURNAL DATE	DATES OF DATA	POPULATION	FACTORS	RESULTS OF PROGNOSTIC FACTORS
Curran J Clin Oncol 1998[88]	1984-1994	204 patients from 5 European Phase II trials drugs studied: mitoxantrone, epidoxirubicin, VP-16, taxol	Poor prognosis: Poor performance (PS) status High WBC Probable/possible histological dx Male Sarcomatous subtype	Good prognosis group: 1 yr. surv. 40% (95% CI:30%, 50%) Bad prognosis: 1 yr. Surv. 20% (95% CI:4%, 20%
Herndon Chest 1998[89]	1984-1994	337 Patients from CALGB trials Drugs studied: MMC, adriamycin, carboplatin, DHAC, trimetrexate, edatrexate, taxol	**Median survival in bold** PS=0, age<49 yr Or PS=0, age≥49 yrs, Hgb ≥14.6: **13.9 mo.** PS=1/2, WBC < 8.7, no chest pain: **9.5 mo.** PS=0, age ≥ 49 yrs, Hgb < 14.6 Or P/S=1/2, WBC < 15.6, chest pain, no weight loss, Hgb ≥ 12.3 Or	Best median survival, 13.9 months: PS=0 & age < 49 yrs and PS=0, age > 49 yrs., Hbgf ≥ 14.6 Worse median survival, 1.4 months: PS=1/2 and WBC ≥ 15.6 uL

Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[87] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[88] J Clin Oncol. 1998;16:145-152

[89] Chest 1998; 113:723-731

AUTHOR JOURNAL DATE	DATES OF DATA	POPULATION	FACTORS	RESULTS OF PROGNOSTIC FACTORS
			PS=1/2, 9.8 ≤ WBC<15.6, chest pain, weight loss, Hgb ≥ 11.2: **9.2 mo.** PS=1/2, 8.7 ≤ WBC<15.6, no chest pain: **6.5 mo.** PS=1/2, WBC <15.6, chest pain, no weight loss, Hgb<12.3 Or PS=1/2, 9.8 ≤ WBC<15.6, chest pain, weight loss, Hgb < 11.2 Or PS=1/2, WBC<9.8, chest pain, weight loss: **4.4 mo.** PS=1/2, WBC≥15.6:**1.4 mo.**	
Pass J Thorac Cardiovasc Surg 1998[90]	1993-1996	Analysis of impact of preoperative and postresection solid tumor volumes 47 of 48 malignant pleural mesothelioma patients resected and randomized to +/- photodynamic therapy @ the NCI		**Preoperative volume** < 100 cc: median, 22 months >100 cc: 11 months; p =0.03 **Postoperative volume** < 9 cc: median, 25 months > 9 cc: 9 months; p=0.0002

[90] Pass HI, Temeck BK, Kranda K, Steinberg SM, Feuerstein IR. J Thorac Cardiovasc Surg 1998; 115:310-318

AUTHOR JOURNAL DATE	DATES OF DATA	POPULATION	FACTORS	RESULTS OF PROGNOSTIC FACTORS
				Extrapleural pneumonectomy: median, 11 months **Pleurectomy/decortication**: 22 months; p = 0.07

Stage and Staging

Accurate staging and identifying significant prognostic factors is important and accepted in the study and treatment of other malignancies.[91] As an example, in another thorax tumor, precise staging of NSCLC has defined homogenous groups of patients according to prognosis;[92] a large surgical-pathological database supports the TNM staging system for NSCLC.[93] The International Mesothelioma Interest Group (IMIG) is a collection of pulmonary medicine physicians, thoracic surgeons, medical and radiation oncologists, epidemiologists, radiologists, pathologists, and laboratory scientists interested in research in malignant pleural mesothelioma.[94] The data to devise this staging system can be applied to radiographic, surgical, and pathological staging of this disease; it is the latter two that are primarily the basis of the staging system.[95]

Before the IMIG staging system, there were five other staging systems--three with stages I through IV and two with TNM stages; there was little prospective data to support these staging systems as derived from meticulously staged patients based on surgical-pathological data.[96],[97] None of these staging sysems have been fully validated or consistently used for survival analyses.[98]

The IMIG is a surgically-based TNM staging system that takes into consideration information about the impact of T and N status on survival. The IMIG staging system

[91] Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.
[92] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)
[93] Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)
[94] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)
[95] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)
[96] Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)
[97] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)
[98] Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.

improves upon other staging systems and provides precise TNM descriptors that can be used for radiographic, surgical, and pathologic staging.[99]

> The staging system differentiates between T1a and T1b; based on thoracoscopy data, T1a tumors had a median survival of 32.7 months and T1b tumors had a median survival of 7 months; this degree of differentiation between tumors is difficult noninvasively. This is also true about differentiating T1b and T2 tumors--i.e., diaphragmatic muscle involvement or tumor penetrating the pulmonary parenchyma is obvious at thoracotomy but not as obvious at thoracoscopy.[100] In one series, T3 tumors had a median survival of 13 months and T4 tumors had a median survival of 6.5 months.[101] Nodal staging in the IMIG is virtually identical to the staging system for NSCLC. N1 is involvement of the ipsilateral bronchopulmonary and hilar lymph nodes. N2 is subcarinal or ipsilateral mediastinal lymph nodes and ipsilateral internal internal mammary nodes. N3 is metastasis to nodes in the contralateral mediastinal, contralateral internal mammary, or the ipsilateral or contralateral supraclivicular areas;[102] in general, N3 is nodal involvement outside same hemithorax as the primary tumor. One study demonstrates a median survival of 18.3 months for N0 and 9.4 months for any nodal involvement.[103]

The IMIG staging system has been validated in two series of patients; it has not been prospectively evaluated with regard to clinical vs. operative stage.[104,105]

In one validation study,[106] from October 1983 to July 1994, 131 consecutive patients with malignant pleural mesothelioma underwent exploratory thoracotomy (108 men; 23 women; median age 63 years [range 32-80 years]). In this series, the pathological diagnosis was always based on both histologic tumor type and immunohistochemistry; when necessary, electron microscopy was added to confirm the diagnosis. There were 101 resections (71%), including 50 extrapleural pneumonectomies and 51 pleurectomy/decortications. The IMIG staging system was applied retrospectively to each patient to determine the TN status and corresponding tumor stage. Staging was based on precise information about tumor extent in the operative summary dictated by the surgeon

[99] Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.
[100] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)
[101] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)
[102] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)
[103] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)
[104] Pass HI, Temeck BK, Kranda K, Steinberg SM, Feuerstein IR. J Thorac Cardiovasc Surg 1998; 115:310-318
[105] Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.
[106] Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.

and on nodal involvement as recorded in the pathology report. The figure and table below summarizes much of the data.

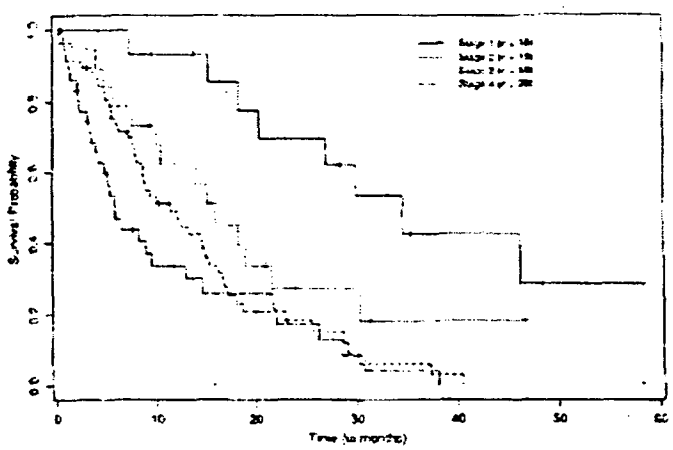

Fig. 5. Univariate analysis of overall survival by stage. When stage I/II was compared with stage III/IV, p was 0.0001. When all four stage groups were compared simultaneously, p was also 0.0001.

Table III. *Median survival for all 131 patients according to TN status, stage, and histologic type*

	Median survival (mo)
Operation	
Extrapleural pneumonectomy	9.9
Pleurectomy/decortication	18.3
T status	
T1	27
T2	12
T3	13
T4	6.5
N status	
N0	18.3
N1-3	5.4
Stage	
I	35
II	16
III	11.5
IV	5.9
Histologic type	
Epithelial	15.1
Nonepithelial	6

The median survival for the 101 patients who had either a pleurectomy/decortication or extrapleural pneumonectomy is shown according to which operation was performed

As shown in the table above, this surgical series correlated survival with stage, type of surgical resection, and histological type of cancer.

Based on this data, surgical decisions may be made. The primary tumor is considered potentially resectable if preoperative CT scans of the chest and abdomen did not show extrathoracic disease, clear invasion of the mediastinal organs or chest wall, or extension through the diaphragm. The decision to perform an extrapleural pneumoectomy as opposed to a pleurectomy/decortication for resection was based on the extent of visceral pleural tumor at thracotomy. Extrapleural pneumonectomy, defined as an en-bloc resection of the pleura, lung, ipsilateral diaphragm, and pericardium was performed for locally advanced disease, usually in patients with confluent visceral pleural tumor not separable from the lung and a partially or totally fused pleural space. Pleuroectomy/decortication, which removed all gross tumor without removing the underlying lung, was performed in patients who had minimal visceral pleural tumor. Partial parietal pleurectomy was sometimes performed for control of a pleural effusion if incompletely resectable tumor was found at exploration, but all pleurectomy/decortications and extrapleural pneumoectomies were performed only if it was thought thall all gross tumor could be removed. Resection was defined as incomplete if any visible gross tumor remained at the completion of thoractomy, even if only a few scattered tumor foci < 5 mm in size were present. [107]

Below is the IMIG staging system.

International Mesothelioma Interest Group Staging Criteria for Mesothelioma

Primary Tumor (T):

T1

[107] Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.

T1a Tumor limited to the ipsilateral parietal including mediastinal and diaphragmatic pleura, no involvement of the visceral pleura 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 pulmonary 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; on-transmural involvement of the pericardium

T4

Describes locally advanced technically unresectable tumor: 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

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, AnyN_1M_0, AnyN_2M_0
Stage IV AnyT_4, AnyN_3, AnyM_1

Evaluation of the Patient for Staging

Noninvasive Studies to Determine Stage

Although CT scans and MRIs are important in the staging of malignant pleural mesothelioma, these noninvasive techniques are not as accurate as surgical and pathologic staging.[108] For example, Rusch and Venkatramen report in their surgical series that more than 50% of malignant pleural mesothelioma cases are clinically understaged in comparison to their surgically documented pathologic nodal status.[109]

The major role of noninvasive procedures is to determine isolated hemithorax disease. Despite a history of asbestos contact in 50% to 70% of patients, pleural plaques or interstitial fibrosis are apparent on chest radiography in only approximately 20%, but pleural calcifications are evident on almost one-half of computed tomographic (CT) scans and in up to 87% at autopsy. Scoliosis with contracture of the ipsilateral hemithorax is visible even on chest radiography with advanced disease. A CT scan or magnetic resonance imaging (MRI) of the primary tumor to assess the extent of disease is indicated if treatment is contemplated. Characteristic CT findings in almost 100 patients are pleural thickening in 92% (and of the intralobar fissures in 86%), effusions in 74%, and pleural calcifications in 20% to 50%. CT scan is helpful in differentiating benign from malignant pleural thickening, but does not reliably distinguish primary from metastatic malignancy. Coronal MRI is particularly helpful to evaluate the diaphragm. In a study of 26 mesothelioma patients evaluated with sequential paired CT and MRI scans, MRI showed tumor spread into the interlobar fissures, tumor invasion of and through the diaphragm, and invasion of bony structures better than CT. Invasion of the chest wall and mediastinal soft tissue and tumor growth into the lung parenchyma were equally well seen on both imaging methods. CT was better for detecting pleural calcifications. Twenty-eight consecutive patients referred for the evaluation of suspected malignant

[108] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

[109] Rusch VW, Venkatraman, E. J Thorac Cardiovasc Sug 1996; 111:815-826.

mesothelioma were evaluated by positron emission tomography (PET) with 2-fluoro-2-deoxy-d-glucose (FDG) imaging. Video-assisted thoracoscopy or surgical biopsies provided a malignant diagnosis in 24 patients (22 with mesothelioma) and benign processes in the remaining four. The uptake of FDG was significantly higher in malignant than in benign lesions (P = .0001). FDG-PET images identified active tumor sites. Hypermetabolic lymph nodes were noted on FDG-PET images in 12 patients, 9 of which appeared normal on CT scans. Histologic examination in six patients confirmed malignant nodal disease in five cases and granulomatous lymphadenitis in one. Standardized uptake values were inversely correlated with duration of survival after the PET study (P = .05). These data could be useful in deciding which patient may be a candidate for an aggressive approach since a high FDG uptake in these tumors may indicate a shorter patient survival. Mesotheliomas are reported to take up gallium 67. Gallium 67 scans in seven cases obtained before resection were compared with pathology. When the involved pleural thickness was over 6 mm, gallium 67 uptake correlated with the macroscopic thickness of mesothelioma in resected specimens. Thickness of the pleura on CT images was only reliable for thick involvement. No definite correlation was found between gallium 67 uptake and the histologc type, extent of tumor parenchyma, interstitial volume, and tumor vascularity. Planar **201Tl scintigraphy in a single mesothelioma patient revealed diffuse pleural tumor accumulation. Single photon emission CT demonstrated exact tumor location. Brain, bone, and liver metastases or extension into other serosal surfaces, although present in more than one-half of patients at autopsy, are sufficiently uncommon at presentation to obviate the need for extensive baseline studies in the absence of symptoms or laboratory abnormalities. However, such studies may identify an occult adenocarcinoma of the lung, a pattern of widespread metastases, or a markedly elevated serum or pleural fluid carcinoembryonic antigen suggesting a diagnosis other than mesothelioma. Although there are no definitive biomarkers for mesothelioma, future studies investigating serial serum levels of tissue polypeptide antigen or thrombomodulin may be of interest.[110]

Invasive Studies to Determine Stage

Although obtaining an accurate histologic confirmation of mesothelioma from pleural fluid cytology or needle biopsy specimens is often difficult, the diagnosis of mesothelioma has such a poor prognosis that an unequivocal tissue diagnosis is mandatory. Surgical intervention is usually required, either a thoracoscopy or thoracotomy, despite the risk of seeding the biopsy site or surgical scar with tumor. In any evaluation for the patient with mesothelioma, careful attention must be paid to the diaphragmatic extent of the tumor with suspicious scans

[110] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

confirmed by laparoscopic evaluation for transdiaphragmatic extension. For patients who are not candidates for radical surgery, thoracoscopy usually obtains sufficient tissue for histochemical analysis. The later development of chest wall masses from seeding of the biopsy site or surgical scar is an uncommon complication approximately 10%) of any diagnostic procedure, but can usually be avoided by radiotherapy to the scar if appropriate. Tumor nodules seeded from fluids rich in tumor cells may develop in the subcutaneous tissue surrounding Denver shunts and intrapleural ports. If preoperative studies suggest stage I mesothelioma in good-risk patients with asbestos exposure, most surgeons combine the diagnostic and therapeutic surgical interventions in one stage. Generous biopsies can be performed at the inception of the exploration, using frozen sections to differentiate mesothelioma from adenocarcinoma. A sample of uninvaded lung should be obtained for counting asbestos fibers. Bronchoscopy should be performed in all patients suspected of mesothelioma to rule out endobronchial disease, rare in mesothelioma. The role of mediastinoscopy in patients with suspected mesothelioma is undefined. Some surgeons believe it is unnecessary because nodes can be removed with the lung. Other surgeons believe that, because positive nodes indicate stage III disease, surgery would be contraindicated. Nevertheless, if radical extrapleural pneumonectomy (EPP) is contemplated, mediastinoscopy is recommended, because 20% of patients with mesothelioma have mediastinal lymph node involvement.[111]

Natural History

The natural history of malignant mesothelioma is important because it provides insights into the development of treatment strategies. Investigators have described the initial presentation as variable in symptoms and duration, and disease progression as initially being local. Systemic disease has been underemphasized. At least 50% of all patients have distant metastatic disease at autopsy and systemic disease is the most common form of relapse in patients who have achieved local control of their disease via extrapleural pneumonectomy.[112]

Before the 1990s, with few exceptions, there was little effort to precisely stage malignant pleural mesothelioma. The disease was thought of as a tumor that involved all the pleural surfaces, encased the lung, and led to death within 2 years of diagnosis due to cardiopulmonary failure from local progression of disease.[113]

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[111] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[112] Rusch VW. Oncology 1999;13:931-932

[113] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

Mesotheliomas spread over the parietal and visceral serosal surfaces. Pleural mesothelioma extends over the diaphragm, mediastinum, pericardium, and, eventually, the peritoneum. It also extends into the interlobar fissures and into the lung itself by contiguity or by interstitial and alveolar spread. Seeding along the track of needle biopsy channels occurs in 10 to 20% of cases. Lymphatic dissemination is common and mediastinal nodes are involved in about 50% of cases of pleural mesothelioma.[114] Distant blood-borne metastases are more common than was previously thought and are seen at autopsy in 50 to 80% of cases. They can occur in any organ, including the brain. A peculiar pattern of massive hepatic calcifications, attributed to degenerative and necrotic liver metastases, has been described.[115]

Based on thorascopic studies, investigators suggest that malignant pleural mesothelioma arise in the parietal and diaphramatic pleura, and then spreads to the visceral pleura. Patients with T1 disease usually have a free pleural space and present with a large pleural effusion.[116] T2 disease has confluent involvement of the visceral pleura and/or extension of the pulmonary parenchyma; the pleural tumor cannot be fully removed without resecting the underlying lung. In T2 disease, there is still free pleural space with an effusion but the parietal and visceral pledural surfaces have begun to fuse; the pleural effusion may have resolved or become loculated.[117] T3 disease is an advanced tumor that has the potential for resection. In T3 disease there is involvement of all the pleural surfaces; there may be tumor extension into the endothoracic fascia or the mediastinal fat; the surface of the pericardium may be involved; a focus of resectable tumor invading the chest wall is also considered T3.[118] T4 disease is locally advanced and not amenable to resection; there is involvement of all the pleural surfaces, diffuse extension into the chest wall, direct extension through the diaphragm to the underlying peritoneum; there may also be direct extension to the contralateral pleura, mediastinal organs, the spine, the myocardium, or the internal surface of the pericardium. Interestingly, malignant pleural mesothelioma may progress to T4 disease before distant metastasis is present.[119]

Shortness of breath and chest pain can be controlled initially by repeated thoracenteses and minor narcotics. Although chest tube drainage and sclerosis is

[114] Note for comparison:Peritoneal mesothelioma involves mainly the parietal and visceral serosal surfaces, the omentum, and the mesentery with tumor nodules and/or infiltration causing thickening. Involvement of the serosa overlying the small and large bowel, the liver, the spleen, and other organs leads to encasement of these organs in tumor tissue.

[115] Chahinian AP, Pass HI. MALIGNANT MESOTHELIOMA. In: Cancer Medicine, edited by Holland & Frei, 2000. B.C. Decker Inc. Hamilton • London

[116] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

[117] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

[118] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

[119] The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest. 1995;108:1122-1128)

generally unsuccessful, pleural fluid eventually becomes loculated as the tumor obliterates the pleural space. With advanced disease, fatigue and dyspnea increase out of proportion to radiographic findings or pulmonary function values. Because hypoxia results from shunting of desaturated blood through a poorly aerated lung, therapeutic oxygen provides little symptomatic relief.[120]

Mesothelioma tends to be locally invasive. Chest wall masses develop in approximately 10% of patients, generally over thoracentesis, chest tube drainage, or thoracotomy tracts. Direct involvement of esophagus, ribs, vertebrae, nerves, and the superior vena cava cause dysphagia, pain, cord compression, brachial plexopathy, Horner's syndrome, or superior vena cava syndromes, respectively. Fevers and sweats with no documented source of infection are common and often accompanied by significant weight loss, poor performance status, and an early death. Thrombocytosis and other clotting abnormalities occur in 10% to 20% (more frequently in peritoneal mesothelioma). Disseminated intravascular coagulation, thrombophlebitis, pulmonary emboli, and Coombs' positive hemolytic anemia have been reported, as well as hypercalcemia associated with elevated levels of a parathyroid hormone-like peptide.[121]

Patients generally die of respiratory failure or pneumonia. Small bowel obstruction from direct extension through the diaphragm develops in approximately one-third, and 10% die of pericardial or myocardial involvement.[122]

Surgical Treatment

According to one group of authors, the role of surgery in managing diffuse pleural mesothelioma remains controversial, but there are an increasing number of thoracic oncologic surgeons who are operating for this disease. Nevertheless, overwhelming pessimism for curative surgical options continues in most centers that do not routinely deal with the disease since the combination of effusive disease and bulky tumor renders surgical eradication virtually impossible. The disappointing long-term overall survival results, the historically high morbidity and mortality, as well as the propensity for local recurrences have forced many centers to abandon radical operations except for the rare localized situation. The arguments regarding appropriate management of mesothelioma can have geographic differences. In a United Kingdom poll of chest physicians, only 46% of the physicians surveyed would consider referral to a thoracic surgeon for radical resection. The French approach to the disease has been a concentration on detection of

[120] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.
[121] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.
[122] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

early stage I disease that is treated with intrapleural therapy, including interferon-gamma with or without cisplatin. Surgery is performed after this therapy only to improve local control, either by pleurectomy or extra pleural pneumonectomy (EPP). In patients with stage II or III mesothelioma, one group of authors recommend surgery and postoperative radiation therapy. In the United States a cohort of specialized cancer centers have evolved that have maintained an interest in the surgical management of the disease. As a new cohort of aggressively trained, specialized thoracic oncologists enters practice, the necessity for such referrals may be diminished. At the present time, however, the evolution of the use of surgery with or without intraoperative, postoperative innovative adjuvant therapies is being defined by these centers. In general, innovative, multimodality protocols that incorporate surgery as part of the package are being explored in larger numbers of patients.[123]

Rationale for Surgical Management

Diffuse pleural mesotheliomas are rarely amenable to en bloc removal. A small proportion of tumors called mesotheliomas may present as an encapsulated mass, not associated with pleural effusion, and these may be amenable to surgical extirpation with negative margins of resection. The majority of diffuse malignant mesotheliomas, however, cannot be surgically removed en bloc with truly negative histologic margins because many of the patients have had a previous biopsy and there is invasion of the endothoracic fascia and intercostal muscles at that site, or pleural effusion, which, although cytologically negative, may be breached, or both leading to local permeation of tumor cells either into the residual cavity or into the abdomen. Nevertheless, in the largest series of EPP performed for mesothelioma from the Boston group, 66 of 183 patients were defined as having negative resection margins after EPP. Patients with this finding who had epithelial mesothelioma were found to have 2- and 5-year survival rates of 68% and 46%, if the node dissection did not reveal tumor.[124]

The operation of choice, especially for early pleural mesothelioma, has yet to be defined. There is no doubt that EPP is a more extensive dissection and may serve to remove more bulk disease than a pleurectomy, chiefly in the diaphragmatic and visceral pleural surfaces. Some surgeons, however, include diaphragmatic resection and pericardial resection with their pleurectomies to accomplish removal of "all gross disease." For EPP, it is almost a necessity to include pericardiotomy with or without resection, for the maneuver aids in the exposure of the vessels and allows intrapericardial control to prevent a surgical catastrophe.

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[123] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[124] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

There are no real guidelines preoperatively that one can use to assure the patient which operation will accomplish tumor removal. The presence of irregular, bulky disease that on the CT infiltrates into the fissures probably dictates the necessity for EPP; a large effusion with minimal bulk disease may call for pleurectomy decortication. Moreover, the philosophy of the surgeon regarding the operation may affect his or her choice, because some surgeons reserve EPP for those patients with bulk disease that presents simple pleurectomy, whereas others believe that the greatest chance for complete gross excision is via EPP performed in the patient with minimal disease. This important factor, preoperative quantitative bulk of disease, may not only influence the choice of resection, but may be an important preoperative prognostic factor in any patient with malignant pleural mesothelioma.[125]

Indications for Surgical Management

As described above, surgery is involved in the management of pleural mesothelioma either for diagnosis, palliative therapy, or as part of a multimodal therapeutic plan. The operations involved in this management include thoracoscopy, pleurectomy and decortication, or EPP. The indications for each of these operations depend on the extent of disease, performance and functional status of the patient, and the philosophy of the treating institution. Basically, operative intervention in mesothelioma is for primary effusion control, cytoreduction before multimodal therapy, or to deliver and monitor innovative intrapleural therapies.[126]

[125] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

[126] Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943 Epidemiology In: Cancer. Principles and Practice of Oncology, 6th Edition, edited by VT DeVita, S Hellman, SA Rosenberg. Lippincott, Williams, and Wilkins. Philadelphia, 2001; p. 1943.

Chemotherapy

There are a multitude of off-label chemotherapy treatments used in practice for mesothelioma. The table below provides a list of patients and their prior treatments. These patients were entered on a Phase II trial of ranprinase (primary endpoint→median survival: 6 months; RR: 4 of 81 assessable patients; median survival: 6 months).[127]

Patients Who Had Prior Chemotherapy

SITE NO.	PATIENT NO.	GROUP	AGE (YEARS)	REGIMEN
1	5	2	72	Mit C + CDDP
1	6	5	28	DOX + CDDP
1	7	3	42	DOX + CDDP; DOX + CBCDA
1	12	3	50	CDDP + TMX + IFN-alpha
1	13	2	53	Mit C + CDDP + VLB + IL-3; CBCDA + MTX + VLB
1	15	5	58	CTX + DOX + CDDP
1	18	2	47	MTX + VCR + leucovorin
1	20	4	69	CDDP + VLB + MTX
1	26	1	41	CDDP + TMX + IFN-alpha
1	28	3	61	CDDP + TMX + IFN-alpha
1	30	5	66	CDDP + MTX + VLB; CBCDA + Mit C
1	31	3	56	CTX + DOX + CDDP
2	1	5	78	Unknown
2	2	4	74	Unknown
2	3	2	68	Mit C + CBCDA
2	7	3	66	DOX + CDDP
2	9	2	67	DOX
2	12	3	52	CTX + DOX + CDDP
2	13	2	64	DOX
3	3	1	67	PTX
3	5	2	34	IUDR + folinic acid
3	6	1	43	DOX + CDDP + IFS + VP-16; PTX + MXN
3	9	2	76	BLM
3	12	6	48	DOX + CDDP; PTX + CBCDA; NVB
3	13	3	60	DOX + CDDP
3	14	3	49	Doxil; TMX + CDDP

[127] Stanislaw M. Mikulski, John J. Costanzi, Nicholas J. Vogelzang, Spence McCachren, Robert N. Taub, Hoo Chun, Abraham Mittelman, Timothy Panella, Carmelo Puccio, Robert Fine, Kuslima Shogen. Phase II Trial of a Single Weekly Intravenous Dose of Ranpirnase in Patients With Unresectable Malignant Mesothelioma *Journal of Clinical Oncology*, Vol 20, Issue 1 (January), 2002: 274-281

SITE NO.	PATIENT NO.	GROUP	AGE (YEARS)	REGIMEN
3	16	2	51	Unknown
3	17	3	66	Mit C + VCR + 5-FU
3	18	3	58	DOX + CBCDA
3	22	6	57	CDDP – TMX
3	23	5	64	Mit C + CDDP; IFN-gamma + IFN-alpha + TNF-alpha
3	25	4	57	PTX + CBCDA
3	26	3	60	CDDP – VP-16
3	28	5	52	DOX + MTX + VLB + CDDP
3	31	4	66	DOX + CDDP + CTX; doxil
4	4	3	41	High-dose MTX + leucovorin
4	15	5	50	Mit C + CDDP
4	19	3	49	CTX + DOX + CDDP
4	23	3	50	CTX + DOX + CDDP

Abbreviations: Mit C, mitomycin; CDDP, cisplatin; DOX, doxorubicin; CBCDA, carboplatin; TMX, tamoxifen; IFN-alpha, interferon-alpha; VLB, vinblastine; IL-3, interleukin-3; MTX, methotrexate; CTX, cyclophosphamide; VCR, vincristine; PTX, paclitaxel; IUDR, 5-iododeoxyuridine; IFS, ifosfamide; VP-16, etoposide; MXN, mitoxantrone; BLM, bleomycin; NVB, navelbine; 5-FU, 5 fluorouracil; IFN-gamma, interferon-gamma; TNF-alpha, tumor necrosis factor alpha.

Below are two tables which summarize the results (response rates only) of single and combination chemotherapy regimens in mesothelioma. None of the regimens provide a survival benefit.

Table 1. Series of ≥ 15 Patients With Malignant Mesothelioma Treated With Single-Agent Chemotherapy

Agent	First Author/Year	No. of Patients	Responders		95% Confidence Interval* (%)
			No.	%	
Doxorubicin	Lerner[7]/1983	51	7	14	7-26
Doxorubicin	Sorenson[8]/1985	15	0	0	0-20
Detorubicin	Colbert[11]/1985	35	9	26	14-42
Pirarubicin	Koukel[12]/1987	35	8	22	11-38
Epirubicin	Magri[15]/1991	21	1	5	1-23
Epirubicin	Mattson[16]/1992	48	7	15	6-28
Mitoxantrone	Eisenhauer[17]/1986	28	2	7	2-22
Mitoxantrone	van Breukelen[18]/1991	34	1	3	0-27
Cisplatin	Mintzer[19]/1985	24	3	13	4-31
Cisplatin	Zidar[20]/1988	35	5	14	6-29
Carboplatin	Mbidde[22]/1986	17	2	12	0-27
Carboplatin	Raghavan[24]/1990	31	5	16	5-34
Carboplatin	Vogelzang[25]/1990	40	3	7	2-21
Vindesine	Kelsen[26]/1983	17	1	6	0-17
Vindesine	Boutin[27]/1987	21	0	0	0-15
Vincristine	Martensson[28]/1989	23	0	0	0-14
Vinblastine	Cowan[29]/1988	20	0	0	0-16
Paclitaxel	Vogelzang[30]/1994	15	2	13	4-38
Cyclophosphamide	Sorenson[8]/1985	16	0	0	0-19
Ifosfamide	Alberts[33]/1988	17	4	24	10-48
Ifosfamide	Zidar[34]/1992	26	2	8	1-25
Ifosfamide	Falkson[35]/1992	40	1	3	1-14
Mitomycin	Bajorin[36]/1987	19	4	21	8-43
Methotrexate	Solheim[37]/1992	60	22	37	26-50
Trimetrexate	Vogelzang[40]/1994	51	6	12	2-33
Edatrexate	Belani[41]/1994	20	5	25	9-49
Edatrexate + leucovorin	Belani[42]/1995	17	3	18	6-41
CB3717	Cantwell[43]/1986	18	1	6	0-27
5-FU	Harvey[9]/1984	20	1	5	1-24
DHAC	Harmon[44]/1991	42	7	17	9-31
Amsacrine	Falkson[47]/1980	19	1	5	1-24
Diaziquone	Eagan[48]/1986	20	0	0	0-17
BCG	Webster[49]/1982	30	NA	NA	NA
Acivcin	Alberts[50]/1988	19	0	0	0-17
Interferon alfa-2a	Christmas[51]/1993	25	3	12	4-30
Interleukin-2†	Eggermont[73]/1991	17	4	24	10-48
Interferon gamma†	Boutin[74]/1991	22	5	23	10-44

NOTE. Modified and reprinted with premission.[79]

Abbreviations: CB3717, dideazafolic acid; 5-FU, fluorouracil; DHAC, 5-dihydroazocytidine; BCG, bacillus Calmette-Guérin; NA, not assessable.

*If confidence intervals were not cited in original reports, they were calculated according to the Wilson quadratic formula.

†Intrapleural therapy for early-stage disease.

Table 2. Series of ≥ 15 Patients With Malignant Mesothelioma Treated With Combination Chemotherapy

Agent	First Author/Year	No. of Patients	Responders		95% Confidence Interval (%)
			No.	%	
Doxorubicin + cyclophosphamide	Samson[57]/1987	36	4	11	6-21
Doxorubicin + DTIC + cyclophosphamide	Samson[57]/1987	40	5	13	6-21
Doxorubicin + cyclophosphamide + DTIC	Dhingra[58]/1983	20	5	25	11-47
Doxorubicin + ifosfamide	Carmichael[59]/1989	16	2	12.5	1-38
Doxorubicin + cisplatin	Ardizzoni[62]/1991	24	6	25	10-47
Doxorubicin + cisplatin	Chahinian[63]/1993	35	5	14	5-30
Mitomycin + cisplatin	Chahinian[63]/1983	35	9	26	12-43
Doxorubicin + cisplatin + cyclophosphamide	Shin[61]/1993	23	6	26	12-46
Epirubicin + ifosfamide	Magri[64]/1992	17	1	6	1-27
Rubidazone + DTIC	Zidar[65]/1983	23	0	0	0-14
DHAC + cisplatin	Samuels[66]/1994	30	4	13	5-29
Mitomycin + bleomycin + cisplatin + doxorubicin	Breau[67]/1991	25	11	44	27-63
Cisplatin + etoposide	Eisenhauer[68]/1988	26	3	12	4-30
Pirarubicin + cisplatin	Koschel[14]/1991	39	6	15	7-29
Doxorubicin + 5-azacytidine	Chahinian[66]/1982	36	8	22	12-38
Doxorubicin + interferon alfa	Upham[52]/1993	25	4	16	6-35
Mitomycin + cisplatin + interferon alfa	Tanson[54]/1994	20	2	11	3-30
Cisplatin + interferon alfa	Trondafir[55]/1994				
	Low-dose interferon	22	8	36	19-57
	High-dose interferon	15	3 + 1 CR	27	11-52

NOTE. Modified and reprinted with permission.[79]
Abbreviation: CR, complete response.

The following is a summary of results from the Solheim et al study of methotrexate in mesothelioma. High-dose methotrexate (MTX), 3 g (infused over 16 hours) with leucovorin rescue q 10 days x 4 courses, was administered and then (if response or SD + symptomatic improvement) q 21 days. There were 63 patients (61 males with diffuse, malignant mesothelioma. The results: 37% response rate; median survival was 11 months (12 months for 42 patients with epithelial histology [68%]; 5 months for 20 patients with sarcomatous [6]% or mixed histology[26%]). There was no evidence of differences in response rates between the different histological subtypes; response rate was not correlated to the extent of disease. It was noted that some patients with epithelial histology were known to have a slow natural history; i.e., in one study of untreated patients, 10-15% of patients had prolonged survival. Interestingly, the high-MTX study stable disease had a median survival of 10 months vs. 7.5 months for patients with an objective response. The article supports, regarding evaluation of mesothelioma, the FDA stand on: 1) difficulty in evaluating disease by tumor measurement; 2) need for randomized controlled trials; 3) survival as the primary endpoint.

V. Clinical Review Methods

1. How the Review was Conducted

The safety and efficacy review included detailed analyses of study JMCH:

Protocol H3E-MC-JMCH(g): A Single-blind Randomized Phase 3 Trial of MTA[128] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma (Pivotal trial; reviewed by FDA)

Enrolled: 226 alimta plus cisplatin arm (168 folic acid + Vitamin B12 supplemented 168; 58 partially supplemented or never supplemented); 222 cisplatin alone arm (163 folic acid + Vitamin B12 supplemented, 59 partially supplemented or never supplemented).

The safety review included analyses from the studies listed below.

Study	Phase	Design	Status	Indication	No. Patients	Treatment[a]	Vitamin Suppl.	Dexamethasone Prophylaxis
LY231514 plus Cisplatin								
JMCH	3	Single-blind, randomized	Completed	MPM	Enrolled=456 Safety evaluable=448	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2 vs cisplatin, 75 mg/m^2	Yes. 331 patients (both arms)	primary
JMAY	2	Open-label, nonrandomized	Completed	NSCLC	Enrolled=36 Safety evaluable=36	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2	No	primary
JMBZ[b]	2	Open-label, nonrandomized	Completed	NSCLC	Enrolled=31 Safety evaluable=31	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2	No	primary
JMAP	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=51 Safety evaluable=51	LY231514, 300 to 600 mg/m^2 plus Cisplatin, 60 to 100 mg/m^2	No	secondary
LY231514 Single-Agent Studies								
Integrated data on supplemented patients[c]	2	Open-label, nonrandomized	Completed	Breast and MPM	Enrolled=207 Safety evaluable=207	LY231514, 500 mg/m^2	Yes	primary
Integrated data on nonsupplemented patients[d]	2/3[b]	Open-label, randomized (JMBQ) and nonrandomized	Completed	Various cancers	Enrolled=608 Safety evaluable=608	LY231514, 500 and 600 mg/m^2, presented by starting dose	No	primary and secondary (specified per study in Table ISS.5.1)

[128] alimta

Integrated JMAN and JMAO[b]	2	Open-label, nonrandomized	Completed	NSCLC Colorectal cancer	Enrolled=66 Safety evaluable=65	LY231514, 500 and 600 mg/m^2	No	primary
Integrated JMAM and JMAF[c]	2	Open-label, nonrandomized	Completed	Cervical cancer Gastric cancer	Enrolled=73 Safety evaluable=73	LY231514, 500 and 600 mg/m^2	Yes; 43 patients	primary (JMAF) secondary (JMAM)
JMAW	1	Open-label, dose-finding	Completed	Renal dysfunction Concomitant NSAIDs	Enrolled=106 Safety evaluable=106	LY231514, 150 to 600 mg/m^2	Yes; 72 patients	primary
Other – LY231514 plus Carboplatin								
JMAU	1	Open-label, dose-finding	Completed	MPM	Enrolled=27 Safety evaluable=27	LY231514, 300 to 600 mg/m^2 plus Carboplatin, AUC 4 to 6.	No	primary
Other – LY231514 Dose- and Schedule-Finding Studies								
JMAA	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=37 Safety evaluable=37	LY231514, 50 to 700 mg/m^2	No	none recommended
BP-001[f]	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=38 Safety evaluable=38	LY231514, 0.2 to 5.2 mg/m^2	No	none recommended
JMAB[g]	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=25 Safety evaluable=25	LY231514, 10 to 40 mg/m^2	No	none recommended

Abbreviations: AUC = area under the curve; MPM = malignant pleural mesothelioma; NSAIDs = nonsteroidal anti-inflammatory drugs; NSCLC = non-small cell lung cancer.

[a] One dose of the study drug(s) administered once every 21 days defined one cycle of therapy, unless otherwise noted.

[b] Studies conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Data cannot be integrated with studies conducted by Lilly.

[c] Data from supplemented patients in studies JMBT, JMDM, JMDR, and JMDS.

[d] Data from nonsupplemented patients in studies JMAC, JMAD, JMAG, JMAH, JMAI, JMAJ, JMAK, JMAL, JMBB, JMBM, JMBP, JMBQ, JMBR, JMBT, JMDM, and JMDR.

[e] Supplementation regimen: 5 mg folic acid daily for 5 days beginning 2 days before each cycle; no vitamin B_{12} was given.

[f] A cycle was defined as LY231514 given daily for 5 days every 21 days.

[g] A cycle was defined as LY231514 given once per week for 28 days followed by a 14-day rest period.

[h] Three patients from a prematurely terminated Phase 3 study are included.

2. Overview of Materials Consulted in Review

The NDA was electronic. No other INDs, except for IND#40,061, were consulted.

3. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI was consulted to audit four sites from study JMCH.

Sites for DSI Audit

SITE #	PLACE	# OF PATIENTS (ALIMTA/CISPLATIN + CISPLATIN ALONE)	MEDIAN SURVIVAL (MO.)		PTS. WITH PROTOCOL VIOLATION/# OF PTS.	# CONSENTED, UNQUALIFIED BUT ENTERED
			ALIMTA/CISPLATIN	CISPLATIN		
130	Chicago	4 + 7	16.7	9.1	9/16	5
131	Dallas	10 + 8	11.65	8.1	5/28	10
409	Hamburg, Germany	9 + 13	10.9	6.5	15/25	3
502	\Milano, Italy	6 + 4	11.05	5.55	6/15	5

4. Were Trials Conducted in Accordance with Accepted Ethical Standards?

The DSI consult reported no deviations from ethical standards.

5. Evaluation of Financial Disclosure

5.1 Financial Disclosure Review

Financial disclosure was submitted 3/24/2003. For study JMCH, there were 95 Primary Investigators and 344 Subinvestigators/Co-investigators. The last patient on-study visit was November 7, 2001. In the 3/24/2003 submission, source documents were not provided, except for the one investigator with financial information to disclose. The overall information was provided to FDA as illustrated in the sample below.

7/133	2	Dr. David R Gandara	PI	5/21/01	A	None
			SI	8/23/01	A	None
			SI	12/18/01	D	None
			SI	9/19/01	A	None
			SI	10/15/01	D	None
			SI	10/3/01	A	None
			SI	10/17/01	A	None
			SI	8/8/01	A	None
			SI	7/12/01	A	None
			SI	10/15/01	D	None
			SI	7/11/01	A	None
			SI	10/15/01	D	None
			SI	7/12/01	A	None
			SI	10/4/01	A	None
			SI	10/15/01	D	None
			SI	10/15/01	D	None
			SI	10/4/01	A	None
			SI	10/4/01	A	None
8/107	4	Dr David S. Ettinger	PI	7/6/01	B	None
			SI			None
			SI	6/12/01	A	None
12/128	1	Dr. Karen Kelly	PI	6/8/01	A	None
			SI	6/4/01	A	None
15/129	1	Dr. Harvey I Pass	PI	6/7/01	A	None
			SI	6/5/01	A	None
			SI	6/5/01	A	None
16/130	16	Dr. Nick J Vogelzang	PI	6/8/01	A	None
			SI	11/16/01	D	None
			SI	6/7/01	A	None
			SI	6/8/01	A	None
			SI	6/8/01	A	None
			SI	11/16/01	D	None
			SI	11/16/01	D	None
			SI	6/8/01	A	None
			SI	11/16/01	D	None
			SI	6/8/01	A	None

Below is the key for the above table.

[1]In some cases, patients were consented but not enrolled in the trial
[2]PI = Primary Investigator; SI = Subinvestigator; CI = Co-Investigator
[3]A = Nothing to disclose; B = Disclosure provided; C = Refused to disclose;
D = Disclosure not obtained, due diligence performed; E = Did not participate in study (Submitted on Form FDA 1572 to Regulatory, did not enroll patients)
[4]Family member name listed if information disclosed
* Incomplete documentation on financial disclosure: A note to the reviewer will be included in the submission indicating what is missing and stating the information will be available upon request. The ALIMTA Team will obtain the missing information or document due diligence in attempting to obtain the missing information.
**Disclosure not available at the time of submission. A note to the reviewer will be included in the submission indicating what is missing and stating the information will be available upon request. The ALIMTA Team will obtain the missing information or document due diligence in attempting to obtain the missing information.

H3E-MC-JMCH-Form 3454 attachment.doc

An abstract of JMCH was submitted to the ASCO annual meeting (2002; Abstract #5). Although there was no data in the abstract, the final results were presented at the Plenary Session at ASCO in May 2002. The abstract presentation at the Plenary Session was one of five out of 3500 abstracts submitted. Below is a financial disclosure analysis of the authors of the abstract.

CO-AUTHOR INVESTIGATOR U.S CITY OR COUNTRY		LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003	[129]DATE SIGNED FINANCIAL DISCLOSURE DATE LAST PATIENT @ SITE RANDOMIZED TO STUDY
Vogelzang Chicago	Nothing to disclose 9 of 21 subinvestigators: disclosure not obtained; due diligence performed	1 of 9 delinquent financial disclosure information now on file	6/8/2001 3/28/2001 alimta/cisplatin — 5/22/2003 3/28/2001 alimta/cisplatin
Denham Dallas	Nothing to disclose 20 of 95 subinvestigators: disclosure not obtained; due diligence performed 1 did not participate in study	5 of 20 delinquent financial disclosure information now on file	6/22/2001 2/8/2001 alimta/cisplatin — 11/2/2001 — 11/30/2001 — 10/22/2001 — , 10/22/2001 10/24/2001 2/8/2001 alimta/cisplatin
Gatzemeier Germany	Nothing to disclose		2/19/2001 12/1/2000

[129] LILLY response to FDA deficiencies dated 12/10/2003

CO-AUTHOR INVESTIGATOR U.S CITY OR COUNTRY		LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003	[12y]DATE SIGNED FINANCIAL DISCLOSURE DATE LAST PATIENT @ SITE RANDOMIZED TO STUDY
			cisplatin alone
Kaukel Germany	Nothing to disclose		2/19/2001 2/5/2001 cisplatin alone
Ruffie France	Nothing to disclose		11/6/2001 3/1/2001 cisplatin alone
Boyer Australia	Nothing to disclose		8/23/2001 2/20/2001 alimta/cisplatin
Emri Turkey	Nothing to disclose		Not dated; fax date 9/1/2001 3/22/2001 cisplatin alone

All the authors had "nothing to disclose"; all the authors signed financial disclosure before the last patient on-study visit (range: 1 day-9 months; median: approximately 5 months). 8 of 21 of the subinvestigators, who worked with the author, did not comply with the financial disclosure requirements at the Chicago site; one of the delinquent financial disclosure subinvestigators, who had information now on file, signed the financial disclosure form 2 months after the submission of Financial Disclosure to the FDA. 15 of 20 of the subinvestigators, who worked with the author, did not comply with the financial disclosure requirements at the Dallas site; five of the delinquent financial disclosure subinvestigators, who had information now on file, signed the financial disclosure form *16 months prior to the submission* of Financial Disclosure to the FDA (all five signed the financial disclosure form close to the last patient on-study visit. The non-U.S., co-authors and sites had no financial disclosure issues.

The results of review of financial disclosure for the entire JMCH study are in the table below; also, in the far right column are answers from Lilly in response to a FDA query, regarding deficiencies in reporting financial disclosure. The table only contains investigator-sites that had problems with regard to financial disclosure.

In summary, financial disclosure documentation for study JMCH, provided 3/24/2003, was incomplete.

- There were four investigators who were indicated as "disclosure provided". Lilly has provided disclosure from one of these investigators.
- Financial disclosure for the seven U.S. investigators, who were identified as having missing information, was incomplete.
- It was noted that 48 investigators did not comply with financial disclosure (i.e., this was the group indicated as "disclosure not obtained; due diligence performed").
- The financial disclosure for the two investigators, whose information was not available at the time of the submission, was incomplete.

PRINCIPAL INVESTIGATOR(S) COUNTRY OR U.S. CITY	SUBMITTED 3/24/2003 DISCLOSURE BY PI PROBLEM WITH DISCLOSURE WITH SUB-INVESTIGATORS OR CO-INVESTIGATORS	NUMBER OF PATIENTS CONSENTED AT THE SITE	LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003
Fein Argentina	Nothing to disclose 1 sub-investigator: disclosure not obtained; due diligence performed	1	
Shapiro Australia	Nothing to disclose 1 of 4 subinvestigators: disclosure not obtained; due diligence performed	5	
Humblet Belgium	Nothing to disclose 1 of 4 subinvestigators: disclosure not obtained; due diligence performed	2	
Butts Canada	Disclosure provided (absent in submission)	2	Disclosure provided
Vetcha Coupkova Czech Republic	Nothing to disclose Nothing to disclose 1 of 2 co-investigators: disclosure not obtained; due diligence performed	2	
Shah India	Nothing to disclose 1 of 3 co-investigators: disclosure not obtained; due diligence performed	10	
Botta Italy	Did not participate in study	1	
Pazares Barragan Spain	Nothing to disclose Did not participate in study	15	

PRINCIPAL INVESTIGATOR(S) COUNTRY OR U.S. CITY	SUBMITTED 3/24/2003 DISCLOSURE BY PI PROBLEM WITH DISCLOSURE WITH SUB-INVESTIGATORS OR CO-INVESTIGATORS	NUMBER OF PATIENTS CONSENTED AT THE SITE	LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003
	1 co-investigator: Did not participate in study		
Obyrne United Kingdom	Disclosure provided (absent in submission)	3	Disclosure provided
Price United Kingdom	Disclosure provided (not in submission) 1 of 6 sub-investigators: disclosure not obtained; due diligence performed	15	Disclosure provided
Aisner NJ	Disclosure not obtained; due diligence performed 1 of 3 sub-investigators: no information provided in column for type of disclosure, i.e., the space was blank	4	Financial disclosure information now on file Not identified as having participated in financial arrangements or had financial interest that require disclosure
Gandara California	Nothing to disclose 6 of 17 sub-investigators: disclosure not obtained; due diligence performed	2	1 of 6 delinquent financial disclosure information now on file
Eittinger Baltimore	Disclosure provided 1 of 2 sub-investigators: no information provided in column for type of disclosure, i.e., the space was blank	4	Not identified as having participated in financial arrangements or had financial interest that require disclosure
Vogelzang Chicago	Nothing to disclose 9 of 21 sub-investigators: disclosure not obtained; due diligence performed	16	1 of 9 delinquent financial disclosure information now on file
J. Kessler New Port News	Nothing to disclose 2 out of 18 sub-investigators: no information provided in column for type of disclosure, i.e., the space was blank	3	Not identified as having participated in financial arrangements or had financial interest that require disclosure
Sridar Miami	Nothing to disclose	4	

PRINCIPAL INVESTIGATOR(S) COUNTRY OR U.S. CITY	SUBMITTED 3/24/2003 DISCLOSURE BY PI PROBLEM WITH DISCLOSURE WITH SUB-INVESTIGATORS OR CO-INVESTIGATORS	NUMBER OF PATIENTS CONSENTED AT THE SITE	LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003
	1 of 3 sub-investigators: disclosure not obtained; due diligence performed		
Yeung Clinton, MD	Nothing to disclose 1 out of 3 sub-investigators: no information provided in column for type of disclosure, i.e., the space was blank	1	Not identified as having participated in financial arrangements or had financial interest that require disclosure
Lu Shin Houston	Nothing to disclose Disclosure not obtained; due diligence performed 1 out of 14 sub-investigators: no information provided in column for type of disclosure, i.e., the space was blank	2	For the one sub-investigator, disclosure not obtained; due diligence performed
Denham Dallas	Nothing to disclose 20 of 95 sub-investigators: disclosure not obtained; due diligence performed 1 did not participate in study	36	5 of 20 delinquent financial disclosure information now on file
Ilson New York	Disclosure not obtained; due diligence performed 4 out of 9 sub-investigators: disclosure not obtained; due diligence performed	2	Financial disclosure information now on file 3 of 4 delinquent financial disclosure information now on file
R. Kessler Marrero, LA	Nothing to disclose 1 out of 14 subinvestigators: disclosure not obtained; due diligence performed 1 did not participate in study	5	
Stark Portsmouth, VA	Nothing to disclose 1 out of 3 subinvestigators: disclosure not obtained; due diligence performed	1	

PRINCIPAL INVESTIGATOR(S) COUNTRY OR U.S. CITY	SUBMITTED 3/24/2003 DISCLOSURE BY PI PROBLEM WITH DISCLOSURE WITH SUB-INVESTIGATORS OR CO-INVESTIGATORS	NUMBER OF PATIENTS CONSENTED AT THE SITE	LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003
Gitlitz Los Angeles	no information provided in column for type of disclosure, i.e., the space was blank	4	disclosure not obtained; due diligence performed

Financial disclosure for JMCH submitted 3/24/2003:

H3E-MC-JMCH

Country/Inv Number/Site Number	Number of Patients Consented per Site[1]	Study Investigators	Title[1]	Response Received[1]	Disclosure[2]	Family Member Name[3,4]
UNITED STATES						
8/107	4	David S. Ellinger	PI	11/18/01	B	None

Disclosure of Financial Information (USD)

H3E-MC-JMCH

Country/Inv Number/Site Number	Number of Patients Consented per Site[1]	Study Investigators	Title[1]	Response Received[1]	Disclosure[2]	Family Member Name[3,4]
CANADA						
3/252	2	Dr. C A Bulls	PI	12/18/01	B	None

Disclosure of Financial Information

Financial disclosure for JMCH submitted 12/4/2003 in response to FDA query:

H3E-MC-JMCH

Country/Inv Number/Site Number	Number of Patients Consented per Site[1]	Study Investigators	Title[2]	Response Received[3]	Disclosure[3]	Family Member Name[3,4]
UNITED KINGDOM						
2/802	3	Dr. Kenneth Obyrne	PI	11/12/01	B	None

Disclosure of Financial Information

[redacted]

H3E-MC-JMCH

Country/Inv Number/Site Number	Number of Patients Consented per Site[1]	Study Investigators	Title[2]	Response Received[3]	Disclosure[3]	Family Member Name[3,4]
UNITED KINGDOM						
4/804	16	A Price	PI	11/19/01	B	None

Disclosure of Financial Information

[redacted]

The table for financial disclosure for the entire JMCH study is duplicated below minus the "NUMBER OF PATIENTS CONSENTED AT THE SITE" column, deletion of the rows with no further information from a Lilly response dated 12/10/2003, and a new column with additional information from Lilly's 12/10/2003 response (**bold**: far right column). The table only contains investigator-sites that had problems with regard to financial disclosure.

PRINCIPAL INVESTIGATOR(S) COUNTRY OR U.S. CITY	SUBMITTED 3/24/2003 DISCLOSURE BY PI PROBLEM WITH DISCLOSURE WITH SUB-INVESTIGATORS OR CO-INVESTIGATORS	LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003	[130]**DATE SIGNED FINANCIAL DISCLOSURE** **DATE LAST PATIENT @ SITE RANDOMIZED TO STUDY**
Aisner NJ	Disclosure not obtained; due diligence performed 1 of 3 sub-investigators: no information provided in column for type of disclosure, i.e., the space was blank	Financial disclosure information now on file Not identified as having participated in financial arrangements or had financial interest that require disclosure	**10/6/2002** **10/20/2000 cisplatin alone** **—— , 2/6/2002** **10/20/2000 cisplatin alone**
Gandara California	Nothing to disclose 6 of 17 sub-investigators: disclosure not obtained; due diligence performed	1 of 6 delinquent financial disclosure information now on file	**—— 11/19/2001** **No patients enrolled; last of 2 patients entered 12/12/2000**
Eittinger Baltimore	Disclosure provided 1 of 2 sub-investigators: no information provided	Not identified as having participated in financial arrangements or had financial interest that require disclosure	**—— 10/2/2003** **3/27/2001 alimta/cisplatin**
Vogelzang Chicago	Nothing to disclose 9 of 21 sub-investigators: disclosure not obtained; due diligence performed	1 of 9 delinquent financial disclosure information now on file	**—— 5/22/2003** **3/28/2001 alimta/cisplatin**
J. Kessler New Port News	Nothing to disclose 2 out of 18 sub-investigators: no information provided in	Not identified as having participated in financial	**—— , fax date 3/18/2003**

[130] LILLY response to FDA deficiencies dated 12/10/2003

PRINCIPAL INVESTIGATOR(S) COUNTRY OR U.S. CITY	SUBMITTED 3/24/2003 DISCLOSURE BY PI PROBLEM WITH DISCLOSURE WITH SUB-INVESTIGATORS OR CO-INVESTIGATORS	LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003	[130]DATE SIGNED FINANCIAL DISCLOSURE DATE LAST PATIENT @ SITE RANDOMIZED TO STUDY
	column for type of disclosure, i.e., the space was blank	arrangements or had financial interest that require disclosure	— 3/31/2003 10/18/1999 alimta/cisplatin
Yeung Clinton, MD	Nothing to disclose 1 out of 3 sub-investigators: no information provided in column for type of disclosure, i.e., the space was blank	Not identified as having participated in financial arrangements or had financial interest that require disclosure	— 3/17/2003 no patients enrolled; one patient entered 1/11/2000
Denham Dallas	Nothing to disclose 20 of 95 sub-investigators: disclosure not obtained; due diligence performed 1 did not participate in study	5 of 20 delinquent financial disclosure information now on file	, 11/2/2001 , 11/30/2001 10/22/2001 , 10/22/2001 , 10/24/2001 2/8/2001 alimta/cisplatin
Ilson New York	Disclosure not obtained; due diligence performed 4 out of 9 sub-investigators: disclosure not obtained; due diligence performed	financial disclosure information now on file 3 of 4 delinquent financial disclosure information now on file	4/16/2002 1/5/2000 cisplatin alone — 10/20/2001 — , 10/22/2001 — 10/12/2001 1/5/2000 cisplatin alone

The Chicago and Dallas sites were analyzed previously with regard to the far right column. With regard to the other investigator sites, 7 of the subinvestigators, who were listed as not complying with the financial disclosure requirements, signed the financial disclosure form *prior to the submission* of Financial Disclosure to the FDA (range: ~5.5-17 months; median: ~15.5 months); one primary investigator listed as " Disclosure not obtained; due diligence performed", signed the financial disclosure form 5.5 months *prior to the submission* of Financial Disclosure to the FDA

All the financial disclosure forms (Form FDA 3455) for the above cases were signed-off by Lilly 3/13/2003.

5.2 Summary Statements About Financial Disclosure

Preliminary review: 3/24/2003 submission

None of the authors on an ASCO abstract of JMCH had financial disclosure issues. At two of the sites in the US, 23 of 41 subinvestigators did not comply with the financial disclosure requirements. The non-US sub-investigators had no financial disclosure problems.

Among the Primary Investigators (PIs) only 4 of 95 had financial information to disclose and they disclosed it; 3 PIs were listed as "disclosure not obtained; due diligence performed" (all US investigators); one PI was listed as "no information provided in column for type of disclosure, i.e., the space was blank."

Among the Sub-Investigators and Co-Investigators, none had financial information to disclose; 48 were listed as "disclosure not obtained; due diligence performed" (6 foreign investigators; 42 US investigators); 6 were listed as "no information provided in column for type of disclosure, i.e., the space was blank."

In response to FDA queries:

Out of the 7 investigators (1 PI and 6 SIs/CIs) previously identified as "no information provided in column for type of disclosure, i.e., the space was blank," Lilly now has financial information on file for 5 of these investigators (5 SIs).

Out of 51 investigators (3 PIs and 48 SIs/CIs) previously identified as not complying with financial disclosure, Lilly now has financial disclosure information on file for 12 of these investigators (2 PIs and 10 SIs).

Eleven investigators, who were listed as "disclosure not obtained; due diligence performed", signed the financial disclosure forms months *prior to the submission* of Financial Disclosure to the FDA. It is unknown why these investigators were listed as "disclosure not obtained; due diligence performed", in view that the financial disclosure forms were signed months *prior to the submission* of Financial Disclosure to the FDA.

IN CONCLUSION, the FDA analysis of financial disclosure does not rule in or rule out that bias affected the results of the JMCH study--a single-blinded study.

VI. Integrated Review of Efficacy

1. Brief Statement of Conclusions

1.1 Lilly's Summary of Efficacy--Study JMCH

1) Treatment with LY231514/cisplatin was superior to cisplatin monotherapy in the randomized and treated population in terms of the following endpoints:

- longer survival
- longer time to disease progression
- higher tumor response rates
- improvement in pulmonary function

2) The superiority of LY231514/cisplatin over cisplatin monotherapy was maintained even when clinically relevant prognostic factors were taken into account.

3) The superiority of LY231514/cisplatin over cisplatin monotherapy was maintained in the fully supplemented subgroup.

4) Folic acid and vitamin B12 supplementation also improved the clinical outcome regardless of the treatment arm. The advantage was associated with more cycles delivered in the fully supplemented subgroups.

1.2 FDA's Summary of Efficacy--Study JMCH

Survival

The overall survival analyses of the randomized and treated and the intent-to-treat populations demonstrated a statistically significant improvement in survival in favor of the alimta/cisplatin arm. In the fully folic acid/vitamin B12 supplemented group, the alimta/cisplatin arm was favored and was marginally statistically significant. Sixty-seven percent of the patients enrolled on study had pathologically confirmed mesothelioma; in the confirmed mesothelioma subset, survival analyses of the randomized and treated and the fully folic acid/vitamin B12 supplemented groups demonstrated a marginally significant survival advantage in favor of the alimta/cisplatin arm. The under-powered female subgroup demonstrated in randomized and treated and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm. The white subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-

powered non-white group demonstrated a trend in favor of alimta/cisplatin in the randomized and treated group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age ≥ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

IN CONCLUSION, alimta/cisplatin has satisfactorily demonstrated a consistent survival advantage compared to cisplatin alone in patients with pleural malignant mesothelioma in one randomized, single-blinded study.

Tumor Response

Based on FDA review of the images alimta + cisplatin responders and the — database, response rate and time to progression should not be included in the label.

A summary of the problems found during the FDA with review of images follows.

- Patients who were screening failures were entered on study.
- CT scans were not performed in some patients as required by protocol, i.e., upper abdomen scans.
- There were missing images (NRs > RRs) from the imaging database; for some of these patients the reasons included: no baseline scans, baseline scans incomplete, or scans not available
- Not all patients had independent review of their images.
- The independent reviewers did not record disease measurements in all patients. Specifically, there was non-agreement of measurability of disease (inclusion criteria for entry in the study; stratification factor) between the investigators and independent readers and between independent readers.
- Patients were listed as responders by Lilly who were scored as a non-responder by the independent reviewers. Specifically, there was non-agreement of response between the investigators and independent readers, i.e., SD, PD, and UK for cases listed by Lilly as PR.
- Patients were listed as responders who were later called non-responders by Lilly.
- Patients who were scored a responder by the independent reviewers but a non-responder by the investigator were not on the Lilly responder list.

- There was non-agreement in some patients of sites of disease between investigators and independent readers at baseline and at time of progressive disease.
- There was dissociation of response in the chest and non-response in the "liver" in some patients, i.e., response in the chest (unidimensional disease) and non-response in the "liver" (bidimensional disease).
- There was dissociation of overall response scoring and calculation of response by independent readers, i.e., patients were scored as PR but calculations of measurements indicated NR or PD.
- FDA review of imaging studies confirmed only 47 of 94 responses listed by Lilly in the alimta/cisplatin group.

Also, according to Lilly:

- In patients with "extensive lobulated disease", it was difficult to select the appropriate lesions to follow and the tumor burden may not be accurately represented by the lesions chosen at baseline.[131]
- When the disease is "extensive and lobulated" or has "irregular contours", it makes it difficult to measure.[132]

Patient Benefit Response

[ ]

Pulmonary Function Tests

Although changes in pulmonary function evaluations are statistically significant, the changes are within the variability range for these tests (i.e., FVC) allowed by the American Thoracic Society and thus, the changes are not clinically significant. Also, over 20% of the patients did not contribute data to the pulmonary function evaluations; in a single-blinded study, this may suggest bias in testing and reporting. Therefore, it is not believed that this information should be included in the label.

[131] Lilly correspondence dated 11/26/2003
[132] Lilly correspondence dated 12/4/2003

2. General Approach to Review of the Efficacy of the Drug

The efficacy review included a detailed analyses of study JMCH. The regimen tested in this clinical trial was consistent with the proposed regimen of alimta in combination with cisplatin.

Protocol H3E-MC-JMCH(g): A Single-blind Randomized Phase 3 Trial of MTA[133] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma (Pivotal trial; reviewed by FDA)

Enrolled: 226 alimta plus cisplatin arm (168 folic acid + Vitamin B12 supplemented 168; 58 partially supplemented or never supplemented); 222 cisplatin alone arm (163 folic acid + Vitamin B12 supplemented, 59 partially supplemented or never supplemented).

[133] alimta

- pulmonary function test scores (ie, forced vital capacity, vital capacity, forced expiratory volume).
- lung density determinations in approximately 170 patients (total number of patients in both treatment arms).
- relative toxicities.

Additional secondary objectives of this study were:

- To assess toxicity experienced in cycles in which patients did receive folic acid and vitamin B12 supplementation and toxicity experienced in cycles in which patients did not receive folic acid and vitamin B12 supplementation.
- To assess pharmacokinetics.
- To collect information regarding vitamin metabolite status in this patient population.

It was anticipated that a total of up to 430 qualified patients would be randomized in this study. The study would include approximately 150 qualified patients without study vitamin supplementation (initial study cohort) and the anticipated 280 patients with vitamin supplementation treated on the revised protocol.

Entry Procedures

An informed consent was to be obtained from each patient after the nature of the study was explained. The investigator was responsible to see that informed consent was 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" included all consent and/or assent
given by subjects, patients, or their legal representatives.

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 were 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 were *enrolled* in the study were those who have been assigned to a treatment group.

A person who has been *entered* into the study was 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 were *entered* into the study but fail to meet the criteria for enrollment were *not* eligible to participate in the study and would not be *enrolled.*

SITE	PATIENT #	ARM
131	1285	MTA/Cisplatin
131	1286	Saline/Cisplatin
131	1287	
131	1288	Saline/Cisplatin
131	1289	
131	1381	
131	1382	
131	1383	
131	1384	Saline/Cisplatin
131	1385	Saline/Cisplatin
131	1386	MTA/Cisplatin
131	1387	Saline/Cisplatin
131	1389	MTA/Cisplatin

SITE	PATIENT#	ARM
502	5011	
502	5012	
502	5013	
502	5014	MTA/Cisplatin
502	5015	MTA/Cisplatin
502	5016	
502	5017	Saline/Cisplatin
502	5018	MTA/Cisplatin
502	5019	
502	5020	Saline/Cisplatin
502	5051	MTA/Cisplatin
502	5052	MTA/Cisplatin
502	5053	Saline/Cisplatin
502	5054	MTA/Cisplatin
502	5055	Saline/Cisplatin

It appears that patients entered and consented were also given a patient number.

Violation of Criteria for Enrollment

The criteria for enrollment were to be followed explicitly. Patients were not to be enrolled (assigned to a treatment group) until they were stable on an analgesic regimen, have taken folic acid on at least 5 of the 7 days immediately preceding treatment, and have had a vitamin B12 injection. If there was inadvertent enrollment of individuals who did not meet enrollment criteria, these individuals were to be discontinued from the study. Such individuals could remain in the study only if there were ethical reasons to have them continue. In these cases, the investigator was to obtain approval from the Lilly clinical research physician for the study participant to continue in the study.

Patients must have a histologic diagnosis of pleural mesothelioma. Study entry was not to be restricted to patients with a particular stage of disease, but for the purposes of analysis, all patients were to be staged prior to enrollment according to the International Mesothelioma Interest Group staging criteria. Below is the staging criteria described in the protocol.

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 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 pulmonary 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; on-transmural involvement of the pericardium

T4

Describes locally advanced technically unresectable tumor: 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

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, AnyN_1M_0, AnyN_2M_0
Stage IV Any T_4, AnyN_3, AnyM_1

MEDICAL OFFICER NOTE: Stage IV can be determined by disease that is T4, N3, or M1. On the case report form, the TNM stage is not provided. There is a box to check-off for Stage Ia, Stage Ib, Stage II, Stage III, and Stage IV. The contribution of T, N, and M to the stage is not provided.

Inclusion Criteria

Patients were included in the study only if they met all of the following criteria:

- Histologically proven diagnosis of mesothelioma of the pleura in patients not candidates for curative surgery. Patients were to be clinically staged using the IMIG TNM staging criteria (see above). Patients were to be entered and randomized based on local pathology; however, independent centralized pathology review was to be carried out on all patients if feasible.

- Disease status was to be that of unidimensionally and/or bidimensionally measurable disease defined as:

  Measurable disease. Bidimensionally and unidimensionally measurable lesions with clearly defined margins by computerized tomography (CT) or MRI. Examples of measurable disease would include a mediastinal or hilar node, or a discrete pleural mass. A CT scan was also required for any palpable masses. For metastatic disease, this would include a clearly defined mass on CT.

  NOTE: Neither pleural effusions nor positive bone scans are considered measurable.

- Patients who have undergone pleurodesis. If pleurodesis was performed, there must be at least a 2-week delay before MTA or cisplatin is administered. If the original CT scan

occurred prior to the pleurodesis, an additional CT scan was required 2 weeks or longer after the pleurodesis, which will then be considered the baseline scan.

NOTE: For patients with clinically significant pleural effusions, consideration was given to draining the effusion.

- Performance status of 70 or higher on the Karnofsky Scale (after any palliative measures including pleural drainage have occurred).
- Estimated life expectancy of at least 12 weeks.
- Patient compliance and geographic proximity that allow adequate follow-up.
- 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 ≥ 9 g/dL.

  Hepatic: bilirubin ≤ 1.5 times the upper limit of normal, alkaline phosphatase, aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times upper limit of normal (alkaline phosphatase, AST, ALT ≤ 5 times upper limit of normal is acceptable if liver has tumor involvement).
- Albumin ≥ 2.5 g/dL.
- Renal: calculated creatinine clearance (CrCl) ≥ 45 mL/min using the lean body mass formula only (see Protocol Attachment JMCH.3). If both local and central lab — CrCl are ≥ 45 mL/min investigators could have chosen which value to follow for the duration of the study. If investigators had chosen to follow the local CrCl, the serum creatinine must be assayed at the same local lab each time for that patient. If the local CrCl was <45 mL/min and the — CrCl was ≥ 45 mL/min the patient could be enrolled based on the — result. If the patient was enrolled based on the — result, — CrCl was to be used for all future dosing decisions. If the localCrCl was ≥ 45 mL/min and the — CrCl was <45 mL/min, the Lilly physician responsible for the study was to be contacted before the patient is enrolled.
- Signed informed consent from patient.
- Males or females at least 18 years of age.
- Male and female patients with reproductive potential were to use an approved contraceptive method if appropriate (eg, intrauterine device [IUD], birth control pills, or barrier device) during and for 3 months after the study.

Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

- Prior systemic chemotherapy. Prior intracavitary cytotoxic drugs or immunomodulators were not permitted, unless given for the purpose of pleurodesis.
- Prior radiation therapy to the target lesion, unless the lesion was clearly progressing and the interval between the most recent radiation therapy and enrollment was at least 4 weeks.
- Active infection (at the discretion of the investigator). Patients previously treated with a nephrotoxic antibiotic were at risk of further toxicity due to cisplatin and should be very carefully monitored.
- Pregnancy or breast feeding.
- Serious concomitant systemic disorders (including oncologic emergencies) incompatible with the study (at the discretion of the investigator).
- 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).
- Use of any investigational agent within 4 weeks before enrollment into the study.
- Inability to interrupt aspirin or other nonsteroidal anti-inflammatory agents 2 days before, the day of, and 2 days after the dose of MTA plus cisplatin or cisplatin alone. If a patient is taking a NSAID (Cox-2 inhibitors included) or salicylate with a long half-life (eg, naproxen, piroxicam, diflunisal, nabumetone, rofecoxib, or celecoxib) it should not be taken 5 days before the dose of MTA, the day of, and 2 days after the dose of MTA plus cisplatin or cisplatin alone.
- Disease which cannot be radiologically imaged.
- Known or suspected brain metastases.
- Any patient who was obviously malnourished or who has experienced a greater than 10% weight loss in the preceding 6 weeks.
- Inability to take folic acid or vitamin B12 administration.

The Randomized Treatments:

A. MTA or alimta, 500 mg/m2, was to be administered intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/m2, administered intravenously over approximately 2 hours on Day 1 of each 21-day cycle. Because pharmacokinetic samples were to be collected, infusion start and stop times, as well as hydration schedules were to be accurately recorded in those cycles which included pharmacokinetic sampling. Patients were to be pre- and post-hydrated according to local practice. Decadron 4 mg, or equivalent corticosteroid was to be taken orally twice per day on the day before, the day of, and the day after each dose of MTA plus cisplatin. Folic acid supplementation, 350 –600 • g or equivalent, was to be taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of MTA plus cisplatin and continued daily until the patient was discontinued from study therapy. A vitamin B12 injection, 1000 • g, was to be given intramuscularly approximately 1 to 3 weeks prior to the first dose of MTA plus cisplatin and should be repeated approximately every 9 weeks until the patient was discontinued from study therapy.

B. Normal saline which did not contain MTA was to be administered intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/m2, administered intravenously over approximately 2 hours on Day 1 of each 21-day cycle. Because pharmacokinetic samples were to be collected, all infusion start and stop times, as well as hydration schedules were to be accurately recorded in those cycles which included pharmacokinetic sampling. Patients were to be pre- and post-hydrated according to local practice. Decadron 4 mg, or equivalent corticosteroid were to be taken orally twice per day on the day before, the day of, and the day after each dose of cisplatin. Folic acid supplementation, 350 – 600 • g or equivalent were to be taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of cisplatin and continue daily until the patient discontinued from study therapy. A vitamin B12 injection, 1000 • g, was to be given intramuscularly approximately 1 to 3 weeks prior to the first dose of cisplatin and was to be repeated approximately every 9 weeks until the patient was discontinued from study therapy.

For the purposes of treating this patient population, a regimen of MTA plus cisplatin or single agent cisplatin was to be defined as six cycles of therapy. A patient who was receiving benefit from treatment may have received additional cycles based on the discretion of the investigator. Cycles were to be repeated until there was evidence of disease progression, unacceptable toxicity, the patient requested therapy to be discontinued, the investigator felt that it was not in the patient's best interest, or if Lilly, after consultation with the investigator, decided to discontinue the patient.

Drugs other than MTA

- Cisplatin
  Cisplatin was be obtained locally. A total dose of 75 mg/m2 of cisplatin was to be diluted to a volume of 1000 mL with 0.9% sodium chloride prior to infusion. The cisplatin solution was

not to be refrigerated. Prior to the administration of cisplatin the patient was to be adequately hydrated according to local practice.

- Decadron
  Decadron was one of a variety of corticosteroids available in tablets ranging from 0.25 mg to 6 mg. For purposes of this study, patients were be given decadron 4 mg orally (or an equivalent corticosteroid and dose) twice per day on the day before, the day of, and the day after each dose of MTA plus cisplatin or cisplatin alone.

- Folic Acid
  Folic acid was to be supplied by Lilly in one of the following forms, with preference in order from option #1 to option #3:
  1. 350 - 600 • g folic acid.
  2. A multivitamin containing folic acid in the range of 350 • g to 600 • g was acceptable if option #1 was not available.
  3. A dose of folic acid between 350 • g and 1000 • g was acceptable only if neither option #1 or option # 2 was available.

  For purposes of this study, patients were to take oral folic acid daily beginning approximately 1 to 3 weeks before treatment with MTA plus cisplatin or cisplatin alone and continued daily until 3 weeks after discontinuation from study therapy.

- Vitamin B12
  Vitamin B12 was to be prescribed by the investigator and administered as a 1000 • g intramuscular injection. A vitamin B12 injection were to be administered approximately 1 to 3 weeks before treatment with MTA plus cisplatin or cisplatin alone and were to be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Dose Adjustments or Delays for Subsequent Cycles
Any patient who required a dose reduction was not eligible for any dose escalations for the remainder of the study. Treatment could be delayed for up to 42 days to allow a patient sufficient time for recovery from study drug related toxicity. A patient who could not be administered study drug for 42 days from the time of last treatment must be discontinued from the study unless continuation is approved by Lilly.

Table. Dose Adjustments for MTA and Cisplatin Based on Nadir Hematologic Values for Preceding Cycle

PLATELETS (× 10⁹/L) NADIR		ANC (× 10⁹/L) NADIR	PERCENT OF PREVIOUS Dose (both drugs)
≥50	and	≥0.5	100%
≥50	and	<0.5	75%

PLATELETS (× 10^9/L) NADIR		ANC (× 10^9/L) NADIR	PERCENT OF PREVIOUS Dose (both drugs)
<50	and	any	50%
Recurrence of Grade 3 or 4 after 2 dose reductions		Recurrence of Grade 3 or 4 after 2 dose reductions	Discontinue patient from study

Table. Dose Modifications for Mucositis

CTC GRADE	DOSE FOR NEXT CYCLE	
	MTA or normal saline without MTA	Cisplatin
Grade 0-2	100% of previous dose	100% of previous dose
Grade 3-4	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

Diarrhea or Other Non-Hematologic Toxicity

In the event of diarrhea requiring hospitalization, the drug was to be held until diarrhea has resolved before proceeding. Treatment was to be restarted at a 25% dose reduction. For other nonhematologic effects greater than or equal to Grade 3 (with the exception of Grade 3 transaminase elevations), the drug was to be held until resolution to less than or equal to the patient's baseline value before proceeding. Treatment was to restart at a 25% dose reduction if deemed appropriate by the treating physician.

Table. Neurosensory Toxicity

CTC GRADE	DOSE FOR CISPLATIN (MG/M^2)	DOSE FOR MTA OR NORMAL saline without MTA (mg/m^2)
0 - 1	100% of previous dose	100% of previous dose
2	50% of previous dose	100% of previous dose
3 - 4	Discontinue patient from Study	Discontinue patient from study

Tinnitus or Significant Clinical Hearing Loss

In case of tinnitus or significant clinical hearing loss, cisplatin therapy was to be reduced or stopped, at the discretion of the investigator.

Creatinine Clearance

The modified Cockcroft and Gault formula was to be used to calculate local creatinine clearance (CrCl) for enrollment or dosing. If a patient who was being followed by local CrCl develops a CrCl <45 mL/min, it was strongly recommended, if possible, that a —— CrCl be obtained. If the —— value was ≥45 mL/min (as reported by ——) the next cycle can continue

without delay and the patient was to be followed with — CrCl for the remainder of the study. If it was not possible to perform — CrCl then the next cycle was to not begin until the local CrCl was ≥45 mL/min. Re-testing was recommended at weekly intervals but was to be conducted at the investigator's discretion. If a patient's CrCl had not returned to ≥45 mL/min within 42 days, the patient was tobe discontinued from the study unless continuation was approved by Lilly.

If a patient who was being followed by — results develops a CrCl <45 mL/min using the modified Cockcroft and Gault formula for lean body weight, then the next cycle was not to begin until the — CrCl was ≥45 mL/min. Re-testing was recommended at weekly intervals but was to be conducted at the investigator's discretion. If a patient's CrCl had not returned to ≥45 mL/min within 42 days, the patient was to be discontinued from the study unless continuation was approved by Lilly.

Treatment Delays Due to Insufficient Folic Acid or Vitamin B12 Supplementation
There were four situations in which treatment might be delayed due to insufficient folic acid or vitamin B12 supplementation. These were represented in the following table.

	FIRST DOSE OF STUDY THERAPY AFTER INITIATION OF FOLIC ACID AND B12 SUPPLEMENTATION	SECOND AND SUBSEQUENT DOSES OF STUDY THERAPY AFTER INITIATION OF FOLIC ACID AND B12 SUPPLEMENTATION
Patient was enrolled ON Amendment (c) or later	Delay until patient has taken folic acid for at least 5 of the 7 days before the first dose of MTA plus cisplatin or cisplatin alone and until the B12 Injection has been administered.	Delay until the patient has taken folic acid for at least 14 of the 21 days before the dose of MTA or cisplatin.
Patient was enrolled PRIOR TO Amendment (c)	Delay until patient has taken folic acid for at least 2 Consecutive days immediately Preceding the first dose of MTA plus cisplatin or cisplatin alone and until the B12 injection has been administered.	Delay until the patient has taken folic acid for at least 14 of the 21 days before the dose of MTA or cisplatin.

Concomitant Therapy
Patients were allowed to receive full supportive care therapies concomitantly during the study. Because of the emetogenic potential of cisplatin alone and in combination with MTA the protocol strongly recommend the use of a 5-HT3 antagonist and dexamethasone at standard recommended doses as a premedication on the day that chemotherapy was given and the continuation of dexamethasone as an antiemetic for the next 24-48 hours after chemotherapy was given. No other chemotherapy, immunotherapy, hormonal cancer therapy, radiation therapy, surgery for cancer, or experimental medications was to be permitted while the patients were participating in this study. Any disease progression requiring other forms of specific antitumor therapy was be cause for early discontinuation in this study. The following concomitant therapies were permitted.

Colony Stimulating Factors
Routine use of granulocyte colony stimulating factors (G-CSFs) was not permitted during this study. Patients were not to receive G-CSFs prophylactically in any cycle. G-CSFs could be used only for patients who have ANC <0.5 · 10^9/L for at least 5 days, neutropenic fever, or documented infections while neutropenic. G-CSFs were to be discontinued at least 24 hours prior to the start of the next cycle of chemotherapy.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
Patients taking NSAIDs or salicylates were not to take the NSAID 2 days before, the day of, or 2 days after receiving MTA plus cisplatin or cisplatin alone. If a patient was taking a NSAID or salicylate with a long half-life (eg, naproxen, piroxicam, diflunisal, or nabumetone), it was not to be taken 5 days before, the day of, or 2 days after receiving MTA plus cisplatin or cisplatin alone.

Because pain intensity was a component of the clinical benefit measurements, any modifications of treatment for the purposes of pain stabilization was to have taken place at least 3 days prior to the first dose of MTA, normal saline without MTA, or cisplatin.
After this time, patients who were taking NSAIDS for pain management were not to switch to a different NSAID if at all possible. Pain was considered stable if there was a <50% variability in the daily analgesic consumption compared to the average daily analgesic consumption at baseline.

Leucovorin
Leucovorin rescue was allowed for CTC Grade 4 neutropenia lasting ≥5 days, CTC Grade 4 thrombocytopenia, and mucositis ≥ Grade 3. If given for myelosuppression as described above, leucovorin was to be started on the fifth day of the Grade 4 myelosuppressive event. Leucovorin was to be started immediately if a patient developed CTC Grade 3 or 4 mucositis. The following doses and schedules were recommended:
Leucovorin 100 mg/m2 intravenously times one; then Leucovorin 50 mg/m2 intravenously every 6 hours for 8 days.

> **Note:** The primary mode of cytotoxicity of MTA was proposed to be inhibition of thymidylate synthase and it may have been more appropriate to provide the end product

of TS inhibition as a rescue agent, namely thymidine. Thymidine was proposed as a reversal agent for severe toxicity from either 5-fluorouracil (5-FU) or methotrexate, but overall the clinical experience was limited. Thymidine was been reported to reverse the severe toxicity associated with 5-FU in a patient with dihydropyrimidine dehydrogenase deficiency. Reversal of methotrexate toxicity has also been reported in patients with normal as well as impaired renal function. 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 was an expected toxicity of MTA, but severe neurotoxicity was 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/m2/day. Partial resolution of the neurotoxicity was noted after the first day of infusion and by the third day the patient had fully recovered.

Statistical Design

Approximately 215 qualified patients were to be enrolled into each arm of the study. An interim analysis comparing clinical benefit response between the two vitamin supplemented treatment arms was to be conducted on 75 qualified vitamin supplemented patients per arm. Clinical benefit response was to be measured using pain intensity, dyspnea, analgesic consumption, and performance status scores. Pooled analysis of survival with supplemented and non-supplemented patients (N=300) was also to be performed.

Additional analyses were to be done on the other efficacy and safety endpoints of the study.

Patient randomization to treatment arms were to be balanced for the following baseline factors: performance status, pain intensity at entry, analgesic consumption at entry, dyspnea at entry, homocysteine levels, gender, degree of measurability of disease, white blood cell count, histological subtype, treatment center, and country.

According to data examined in a multivariate analysis across a variety of MTA studies (n = 267 patients), elevated baseline homocysteine levels (≥12 • mol/L) strongly correlated with severe hematologic and nonhematologic toxicities following treatment with MTA. Because of these correlations, this study was to provide for balancing the numbers of patients with baseline homocysteine levels <12 • mol/L or ≥12 • mol/L equally across all treatment groups. Additional prognostic factors to be balanced for between the two treatment arms included performance status, histological subtype, white blood cell count, and gender[135]. Because both unidimensionally and bidimensionally measurable disease were to be permitted, treatment arms were also to be balanced for degree of measurability of disease.

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[135] Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, Giaccone G. 1998. Prognostic factors in patients with pleural mesothelioma: The European organization for research and treatment of cancer experience. J Clin Oncol 16(1):145-152.

MEDICAL OFFICER COMMENT:

A description of the informed consent process (p. 972):

> "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."

From the informed consent:

> "In this study you will either receive LY231514 given with a widely used drug called cisplatin or you will receive a salt water solution and the widely used drugn. Your participation in this study will last until your disease gets worse, you don't want to continue the study anymore, the drug(s) make you sick, or your doctor and/or the Sponsor feels that it is in your best interest to stop taking the drug. There is nomaximum time you can take this drug. At least 430 patients will be participating in this study. (p. 1733)"

Below are two examples of entered and enrolled patients at one U.S. site and one foreign site, respectively:

SITE	PATIENT #	ARM
131	1044	MTA/Cisplatin
131	1271	Saline/Cisplatin
131	1272	MTA/Cisplatin
131	1273	
131	1274	MTA/Cisplatin
131	1275	MTA/Cisplatin
131	1276	
131	1277	MTA/Cisplatin
131	1278	MTA/Cisplatin
131	1279	
131	1280	Saline/Cisplatin
131	1281	Saline/Cisplatin
131	1282	
131	1283	MTA/Cisplatin
131	1284	

The 280 qualified patients receiving vitamin supplementation during every cycle of their study therapy were to be equally randomized between the treatment arms (ie, 140 patients per arm). A treatment was to be judged superior if it is associated with a 33% reduction in the hazard ratio of the two treatments by median survival time period of the least efficacious therapy. Assuming an exponential survival, 15 month patient accrual, and an additional minimum 9 month follow-up for all patients and a censoring rate of 30% or less after the 24 month accrual and follow-up period, the procedure described above gives at least an 81% chance (power) to detect a 33% shift in hazard ratio as reflected by a 63% survival probability on the best treatment arm by the time only 50% of patients are still alive (median time) on the least efficacious treatment arm. These calculations used a twosided logrank test with a 0.05 chance of rejecting the null hypothesis H0 of no difference in survival between the two treatment arms when H0 was actually true.

Patient Assignment

This was a competitive enrollment study. All patients were to be randomized to receive the specified regimen of either MTA plus cisplatin or cisplatin alone. Randomization was to be controlled by a computerized voice response unit at a central location. Each patient's treatment assignment was to be unknown until time of randomization. Randomization was to be stratified as to treatment center, country, pain at entry, analgesic consumption at entry, dyspnea at entry, performance status, degree of measurability of disease, histologic subtype, gender, baseline homocysteine levels, and baseline white blood cell count. For each of these factors, the following stratification was to be performed:

- Performance status was to have two strata:
  - High: Baseline score = 90 or 100
  - Low: Baseline score = 70 or 80

- Degree of measurability of disease was to have two strata:
  - Bidimensionally measurable disease only or both bidimensionally measurable and unidimensionally measurable disease
  - Unidimensionally measurable disease only

- Histological subtype was to have two strata:
  - Epithelial
  - All others

- Baseline white blood cell count was to have two strata:
  - High: WBC $\geq 8.3 \cdot 10^9/L$
  - Low: WBC $< 8.3 \cdot 10^9/L$

- Pain intensity at entry was to have two strata:
  - Low: baseline score <20 mm on the visual analog scale (VAS) of Question 6 in the Lung Cancer Symptom Scale (LCSS) patient scale.
  - High: baseline score ≥20 mm on the VAS of Question 6 in the LCSS

patient scale.

- Analgesic consumption at entry was to have two strata:
  Low: baseline score <60 mg morphine equivalents per day, only NSAIDS, or no analgesic consumption.
  High: baseline score ≥60 mg morphine equivalents per day.

- Dyspnea at entry was to have two strata:
  Low: Baseline score <20 mm on the VAS of Question 4 in the LCSS patient scale.
  High: Baseline score ≥20 mm on the VAS of Question 4 in the LCSS patient scale.

- Baseline homocysteine (pre-folic acid supplementation) was to have two strata:
  High: Baseline homocysteine ≥12 • mol/L
  Low: Baseline homocysteine <12 • mol/L

- Each gender was to be a stratum.

- Each country was to be a stratum.

- Each treatment center was to be a stratum.

Patients were to be balanced with respect to the study drug in each stratum for each prognostic factor, using the algorithm outlined in Pocock and Simon.[136] The randomization probability parameter P will be set at 1.0.

Blinding

This was a randomized single-blind study. Patients who were assigned to Treatment Arm B received normal saline in place of the MTA infusion. In order to protect the blinding of the patients, the MTA solution and normal saline was to be visually indistinguishable. While every effort was made to blind the patients to the identity of the treatment, it could occur that a patient became inadvertently unblinded. This was not to be sufficient cause (in and of itself) for that patient to be removed from the study or excluded from any safety or efficacy analysis. Efficacy information was not to be shared between sites until the study was completed.

[136] Pocock S, Simon R. 1975. Sequential treatment assignment with balancing of prognostic factors in controlled clinical trials. Biometrics 31:103-115.

Clinical Benefit Response

A secondary efficacy endpoint for each patient was clinical benefit response. Each patient was to be classified as positive, negative, or stable on the basis of the following measures:

- Change in pain (as reflected by change in pain intensity and change in analgesic consumption)
- Change in performance status
- Change in dyspnea

Each of a patient's measures of clinical benefit was to be categorized as positive, stable, or negative. A patient was to have experienced positive clinical benefit if none of the measures was negative and at least one of the measures was positive. In order for a patient to have been classified as a positive clinical benefit responder, these criteria were to be met, and at least the minimal criteria for positive change (as defined below) was to be maintained for at least one cycle beyond the initial documentation on the CRF of positivechange. A patient was to have experienced negative clinical benefit if any one of the measures was negative. In order for a patient to have been classified as a negative clinical benefit responder, these criteria were to be met, and at least the minimal criteria for negative change (as defined below) must be maintained for at least one cycle beyond the initial documentation on the CRF of negative change. A patient was to have experienced stable clinical benefit if all of the measures were stable.

MEDICAL OFFICER COMMENT: The study was single-blind. Lilly declined performing a double-blinded study.

Pain intensity:

Pain intensity was to be recorded by each patient using Question 6 on the LCSS, on a visual analog scale measuring 100 mm in length, with a score of 0 mm representing no pain, and a score of 100 mm representing as much pain as there could be.

The baseline measurement of pain intensity was the mean of the pain intensity score assessed 4 to 6 days before the start of study drug therapy and the pain intensity score assessed 1 to 2 days before the start of study drug therapy. Once the patient was randomized and began to receive study drug, he or she was to record pain intensity once weekly by filling out the LCSS. These weekly scores were to then be averaged by Lilly to obtain one pain intensity score per cycle.

- A positive change in pain intensity was to be defined as a lessening of pain intensity as demonstrated by a decrease of at least 10 mm from the baseline score on the VAS. (Average over at least one treatment cycle.)

- A negative change in pain intensity was to be defined as a worsening of pain intensity as demonstrated by an increase of at least 10 mm from the baseline score on the VAS. (Average over at least one treatment cycle.)

- No change in pain intensity (or stable pain intensity) was to be defined as a difference in pain intensity as demonstrated by a change of less than 10 mm from the baseline score on the VAS. (Average over at least one treatment cycle.)

Dyspnea:
Dyspnea was to be recorded by each patient using Question 4 on the LCSS, on a visual analog scale measuring 100 mm in length, with a score of 0 mm representing no shortness of breath, and a score of 100 mm representing as much shortness of breath as there could be. The baseline measurement of dyspnea was the mean of the dyspnea score assessed 4 to 6 days before the start of study drug therapy and the dyspnea score assessed 1 to 2 days before the start of study drug therapy. Once the patient was randomized and began to receive study drug, he or she was to record dyspnea once weekly by completing the LCSS. These weekly scores were to then be averaged by Lilly to obtain one dyspnea score per cycle.

- A positive change in dyspnea was to be defined as a lessening of dyspnea as demonstrated by a decrease of at least 10 mm from the baseline score on the VAS. (Average over at least one treatment cycle.)

- A negative change in dyspnea was to be defined as a worsening of dyspnea as demonstrated by an increase of at least 10 mm from the baseline score on the VAS. (Average over at least one treatment cycle.)

- No change in dyspnea (or stable dyspnea) was to be defined as a difference in dyspnea as demonstrated by either a positive or negative change of less than 10 mm from the baseline score on the VAS. (Average over at least one treatment cycle.)

Analgesic consumption:
Patients were to be stable on an analgesic regimen. Analgesic consumption was to be recorded by each patient daily using a patient diary. Each medication was to be converted by Lilly to milligrams morphine equivalents per day. The baseline measurement of analgesic consumption was the mean of the milligrams of morphine equivalents per day of the analgesics recorded starting 4 to 6 days before the start of study drug therapy. Once the patient began to receive study drug, he or she was to continue to record daily analgesic use with a patient diary. The cycle measurement of analgesic consumption was the mean of the milligrams of morphine equivalents per day from the patient diary for that cycle.

- A positive change in analgesic consumption was to be defined as a decrease in analgesic consumption in milligrams of morphine equivalents per day per week of at least 50%. (Average over at least one treatment cycle.)

- A negative change in analgesic consumption was to be defined as an increase in analgesic consumption in milligrams of morphine equivalents per day per week or at least 50%. (Average over at least one treatment cycle.)

- No change in analgesic consumption (stable analgesic consumption) was to be defined as an increase or decrease in analgesic consumption of less than 50%. (Over at least one treatment cycle.)

Karnofsky Performance Status:
Performance status was to be assessed by an independent observer. The baseline performance status was to be assessed at the time of study entry. Once the patient was randomized and begins to receive study drug, the independent observer will assess performance status at the beginning of each cycle.

- A positive change in performance status was to be defined as an increase in performance status of at least 20 points. (Over at least one treatment cycle.)

- A negative change in performance status was to be defined as a decrease in performance status of at least 20 points. (Over at least one treatment cycle.)

- No change in performance status (stable performance status) was to be defined as an increase or decrease in performance status of less than 20 points. (Over at least one treatment cycle.)

Lung Cancer Symptom Scales (LCSS):
Included in the protocol as an attachment.

Pulmonary Function Tests:
Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and slow vital capacity (SVC), were to be measured using standard apparatus and following American Thoracic Society or European Respiratory guidelines (American Thoracic Society 1995; Quanjer et al. 1993). Because each patient was to act as his own control, lung function was to be measured using the same apparatus and in the same laboratory at each measurement.

Tumor Response

Assessment Intervals
Within 4 weeks of study enrollment each patient was to have been assessed by computerized tomography of the chest and upper abdomen.

MEDICAL OFFICER NOTE: If the upper abdomen was assessed, the liver was also assessed at baseline.

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
- Collection of information on habits
- Evaluation of performance status (Karnofsky scale)
- Measurement of pulmonary function using the following tests:
  Forced vital capacity (FVC).

Slow vital capacity (SVC).

Forced expiratory volume in one second (FEV1).

- Measurement of lung density by inspiratory expiratory CT scan images (patients enrolled on JMCH(a)-(d)).

Four to six days prior to the start of drug therapy (dexamethasone), patients were to:

- Begin completing a daily diary of analgesic consumption.
- Complete the LCSS patient scale.

One to two days prior to the start of drug therapy (dexamethasone), patients were to:

- Complete the LCSS patient scale.

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

- Weekly (Days 8 (±1 day), 15 (±1 day), and 19 of each cycle):

  Complete the LCSS patient scale.
- Prior to each cycle of treatment:

  Weight measurements.

  Performance status evaluation (should be done by an independent observer).

  Limited medical history and physical examination.

  LCSS observer scale administered prior to consultation with physician and other procedures (should be done by an independent observer).
- Prior to every other treatment cycle:

  Pulmonary function tests.

  Lung density measurements (patients on JMCH(a)-(d) only.

  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 were to take place at the stated intervals:

- Approximately 4 weeks after a patient has received his or her last dose of MTA or cisplatin:

  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).

  LCSS patient and observer scales completed, unless the patient has received post study chemotherapy, radiotherapy, or surgical intervention for cancer.
- Approximately every 6 weeks after a patient without demonstrated progressive disease has received their last CT scan:

  - CT scan for the purpose of evaluating disease status. If patients had progressive disease during this time or had not progressed after 6 months off study, CT scans only were to be done if there was clinical suspicion of progression.

- Clinical assessment to evaluate disease status. If patients had progressive disease during this time or had not progressed after 6 months off study, these clinical assessments were to be changed in frequency to every 12 weeks.

• Approximately every 3 months after the patient has received their last dose of MTA or cisplatin:

- Information were to be collected regarding date of death, and any poststudy chemotherapy, radiotherapy, or surgical intervention.
- LCSS patient and observer scales were to be completed, unless the patienthas received post-study chemotherapy, radiotherapy, or surgical intervention for cancer.

Efficacy Criteria for Tumor Response

The response status of each patient was to be reviewed by a panel of independent investigators and was to be reviewed by Lilly. In case of a discrepancy between the assessment of the independent panel and that of the investigator, the independent panel's assessment was to take precedence.

MEDICAL OFFICER NOTE: The assessment by the independent panel's assessment of response was to take precedence in determination of response.

The measurability of a tumor was defined as follows:

Disease Status

• Measurable disease: Bidimensionally measurable lesions with clearly defined margins by 1) 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 or equal to 1.0 cm and at least one image with both diameters greater than or equal to 1.5 cm or 3) palpation, with both diameters 2 cm or greater. Unidimensionally measurable lesions with clearly defined margins by 1) plain x-ray measuring at least 0.5 cm or greater (bone lesions not included); or 2) CT or MRI with the length greater than or equal to 1.0 cm and at least one image with the length greater than or equal to 1.5 cm.

• Evaluable disease: Lesions measured by x-ray with both diameter(s) less than 0.5 cm, lesions on scan with either diameter(s) smaller than 1.0 cm, palpable lesions with either diameter less than 2 cm, or bone disease.

• Nonevaluable disease: Pleural effusions, ascites, disease documented by indirect evidence only (e.g., by lab values). Scan only bone disease.

MEDICAL OFFICER NOTE: measurability of disease is also discussed in the inclusion criteria and as stratification factor and below in the response criteria and as a qualifier for response analysis.

Lesion Measurement

All responses were to be documented using appropriate diagnostic tests which were to be

repeated approximately every 6 weeks to continue evaluation. The same assessment method used to determine disease status at baseline was to be used consistently for efficacy evaluation throughout the study.

CT scan measurement of tumor response:
Within 4 weeks of study enrollment each patient was to have been assessed by computerized tomography of the chest and upper abdomen. Contrast medium was to be used consistently throughout the study unless clinically contraindicated. The sections (cuts) should be 10 mm and should include the apex through the base of the lung. This method was to be used consistently for tumor assessment and was to be repeated every 6 weeks (prior to every other cycle) and every 6 weeks off study until documentation of progressive disease. For each patient, every CT image was to 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 was to be used during the CT scanning procedure. The thickness of the tumorous parietal, visceral, diaphragmatic, and mediastinal pleura was to be measured together with any enlarged lymph nodes in the mediastinum, retrocural space, or axillae.

CT images from each patient was to be assessed for tumor response by a panel of independent reviewers. In case of a discrepancy between the assessment of the independent panel and that of the investigator, the independent panel's assessment was to take precedence.

In all patients with measurable disease in the pleural cavity the thickness of the pleural rind were to be measured, if possible, at three separate levels on transverse cuts on the thoracic CT scan at study entry. The levels chosen were to be those with the greatest volume of disease and with anatomical landmarks which were to make the level reproducible. Levels were to be at least 2 cm apart to ensure reproducible discrimination of levels on subsequent CT scans. Where feasible, up to 3 areas of pleural rind were to be measured at each level. At least one level were to have at least one rind measurement $\geq$1.5 cm. Measures were not to be made of pleural thickening that was less than 1 cm. Any of the three levels chosen were to be the same as those used for lung density measurement but only if the distribution of disease warranted choosing these levels for disease measurement.

- In patients with unidimensional disease only (including pleural rind disease only), measure all unidimensional lesions outside of the pleural rind and follow the directions above for all pleural rind disease.
- In patients with bidimensional disease only, all bidimensional disease were to be measured. If too many lesions were present in a given organ system, 3 lesions were to be chosen, and then the directions were to be followed for measuring pleural rind disease (see above).
- In patients with both bidimensional and unidimensional disease, an attempt was to be made to measure 1) all bidimensional lesions at all levels where present, 2) all unidimensional lesions outside of the pleural rind and 3) directions should be followed as above for measuring pleural rind disease. All bidimensionally measurable lesions and up to three unidimensional lesions at each rind level were to be chosen for measurement and

follow-up evaluation. When fewer than three bidimensionally measurable lesions were present, the remaining lesion(s) could be unidimensional lesions.

All documented lesions were to be followed. If an organ had too many lesions to measure at each evaluation, choose three target lesions at baseline were to be followed for repeated measure before the patient was entered on study. If an area of pleural rind was considered for measurement but, when measured, was less than 1.0 cm, it was not to be included in the baseline measurements. If an area of pleural rind that was less than 1.0 cm at baseline assessment became greater than 1.0 cm after the patient has began study therapy, this lesion should be measured at the visit in which it becomes greater than 1.0 cm. It could be retrospectively measured on the baseline scan in order to calculate response or progression. This lesion was to be followed from this point on as any other lesion until response or progression occurred. This lesion was not to be considered a new lesion.

Included in the evaluations were 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 were be assessed using the same technique as baseline.

  Refers to clinical CR. When restaging surgery was required, a separate pathologic response variable was incorporated in the response data.

- Partial response (PR): Applied only to patients with at least one unidimensionally or bidimensionally measurable lesion. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.
- Patients with bidimensionally measurable disease only: Greater than or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of bidimensionally measurable disease. No new lesions. Nonmeasurable lesions must remain stable or regress for this category.
- Patients with unidimensionally measurable disease only: Greater than or equal to a 30% decrease under baseline in the sum of the greatest diameters of unidimensionally measurable lesions. No new lesions. Nonmeasurable lesions must remain stable or regress for this category.
- Patients with bidimensionally and unidimensionally measurable disease: Greater than or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of bidimensionally measurable disease (and no progression in the sum of the unidimensionally measurable lesions) **or** a 30% decrease under baseline in the sum of the greatest diameters of unidimensionally measurable lesions (and no progression in the sum of bidimensionally measurable lesions). No new lesions. Nonmeasurable lesions must remain stable or regress for this category.

MEDICAL OFFICER NOTE: **Although unidimensional or bidimensional response may be interchangeable and appropriate for the same lesion, it may not be appropriate in the case of different lesions in the same organ (e.g., in the lung, a**

unidimensional RUL lesion and a bidimensional RML lesion) or lesions in different organs (e.g., a unidimensional lung lesion and a bidimensional liver lesion). From the RECIST criteria article, the interchangablity of unidimensional and bidimensional response appeared to be with the same lesion and not lesions in a different part of an organ or lesions in different organs.[137]

- Stable/No response: Did not qualify for CR, PR, or progression. All measurable and evaluable sites was to be assessed using the same techniques as baseline.
- Progression: All measurable and evaluable sites was to be assessed using the same techniques as baseline.
- Patients with bidimensionally measurable disease only: 50% increase or an increase of 10 cm2 (whichever was smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease).
- Patients with unidimensionally measurable disease only: greater than or equal to a 25% increase in the sum of the longest dimension of unidimensional measurable lesions over the smallest sum observed (over baseline if no decrease).
- Patients with bidimensionally and unidimensionally measurable disease: a 50% increase or an increase of 10 cm2 (whichever is smaller) in the sum of the products of all bidimensionally measurable lesions over the smallest sum observed (over baseline if no decrease) **or** 25% increase in the sum of the measurements for unidimensional lesions over the smallest sum observed (over baseline if no decrease).
- **OR** reappearance of any lesion which had disappeared,
- **OR** appearance of any new lesion/site,
- **OR** clear worsening of evaluable disease
- **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 was to not constitute progression.
- Exceptions: In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms were to persist beyond 4 weeks or there was to be additional evidence of progression. Lesions which appeared to increase in size due to presence of necrotic tissue were to not be considered to have progressed.
- Unknown: Progression had not been documented and one or more measurable or evaluable sites had not been assessed.

Notes

[137] Therasse et al. J Natl Cancer Inst 2000; 92:205–16.

1) Nonevaluable disease was not to affect objective status except in determination of CR (all disease was to be absent -- a patient who otherwise had a CR, but who had 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 could not be assessed for response.
2) For evaluable disease other than types specified in partial response, the only objective statuses which apply were CR, stable/no response, progression, and unknown.
3) Objective statuses was to stay the same or improve over time until progression (unknown excepted).

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

• Disease assessment every 3 to 4 weeks: Two objective status determinations of CR before progression were required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, were required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR were required for a best response of stable/no response; if the first objective status was unknown, only one such determination was required. Patients with an objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) were to have a best response of increasing disease. Best response was unknown if the patient did not qualify for a best response of increasing disease and if all objective statuses after the first determination and before progression were unknown.

For CR or PR, response must be confirmed; a second assessment was to be scheduled for 4 weeks after the first documentation of response.

Definition of Efficacy Measures

A responder was defined as any patient who exhibited a CR or PR. The duration of a CR or PR was 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 was 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 was defined as the time from study enrollment to time of death due to any cause.**

All responses were to be documented using appropriate diagnostic tests which were to be repeated approximately every 6 weeks to continue evaluation. The same assessment method used to determine disease status at baseline was to be used consistently for

efficacy evaluation throughout the study.

Clinical Laboratory Tests and Procedures

Prestudy

Prior to study enrollment each patient was to have the following assessments.

Approximately 1 to 3 weeks prior to study enrollment:

- Homocysteine (assayed by ——). The homocysteine result from this assay was to be used for randomization.
- Vitamin metabolites : homocysteine, cystathionine, methylmalonic acid, methylcitrate (total, I and II). (To be assayed by ———)
- Begin completing a daily diary of folic acid consumption (diary was to be used up until the first dose of MTA plus cisplatin or cisplatin alone).

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 (segmented and bands), lymphocytes, monocytes, eosinophils, and basophils.
- Blood chemistries: bilirubin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, calcium, glucose (non-fasting), total protein, albumin, and electrolytes (sodium, potassium, magnesium, bicarbonate, and chloride)
- Calculated creatinine clearance (see Protocol Attachment JMCH.3).
- Homocysteine (assayed by ——). Because the purpose of measuring homocysteine a second time was to assess the effect of folic acid supplementation on homocysteine levels, this sample was to not be drawn until the patient has taken folic acid for at least 5 days.
- Vitamin metabolites: homocysteine, cystathionine, methylmalonic acid, methylcitrate (total, I and II) (assayed by ———)

During the Study

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

- Measurement of vital signs were to be repeated as clinically indicated.
- Concomitant medication (including any non-study vitamin supplementation) 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
- Calculated creatinine clearance up to 4 days prior to each cycle.
- Vitamin metabolites (assayed by [redacted] up to 4 days prior to each cycle beginning with Cycle 2.
- 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)
- Pharmacokinetic sampling from patients at selected centers during Cycles 1 and 3.

Note: [redacted] was to assay the blood chemistries, homocysteine, and calculated creatinine clearance (CrCl) and was to manage the centralized independent pathology review and pharmacokinetic samples. The local laboratory was to assay the hematology and CrCl if used for enrollment or dosing decisions. Vitamin metabolites were to be assayed at [redacted] Patients were to be enrolled on the basis of local chemistries and CrCl. as described in above.

Investigators must have signed or initial each laboratory report to indicate that they have read the report. Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values had to be evaluated by the investigator. Any clinically significant laboratory values that were outside a clinically acceptable range or differ importantly from a previous value had to be further commented on in the CRF comments page.

Schedule of Events

CYCLE/VISIT	0	1				2				3*				PS
Day Within a Cycle		1	8	15	19	1	8	15	19	1	8	15	19	
Informed consent	X													
Treatment Arm A														
MTA/cisplatin therapy		X				X				X				
Treatment Arm B														
cisplatin therapy		X				X				X				
All patients														
Folic acid[n]	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	
Vitamin B12[o]	X[o]												X	
Physical examination[a]	X					X				X				
Medical history[a]	X					X				X				
Habits[a] (PK pts only)	X													
Weight[a]	X					X				X				
Height	X													
KPS	X[q]					X				X				
CT scan or MRI for tumor measurement[a,b]	X[r]									X				X[r]
CT scan for lung density measurement[a,b,p]	X									X				
Pulmonary function tests[j]	X									X				
LCSS patient scale	X[k]		X[g]	X[g]	X[c]		X[g]	X[g]	X[c]		X[g]	X[g]	X[c]	X
LCSS observer scale	X					X[a]				X[a]				X

CYCLE/VISIT	0	1				2				3*				PS
Analgesic Consumption[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[e]	X													
Concom meds notation	X					X				X				
Homocysteine	X[m,f]													
Chemistry	X[f]		X[i]			X	X[i]			X	X[i]			X
Hematology	X[f]		X[i]	X[i]		X	X[i]	X[i]		X	X[i]	X[i]		X
Calc creatinine clearance	X[f]					X				X				
Vitamin metabolites	X[m,f]					X[i]				X[i]				
PK sampling		X[h]								X[h]				
Toxicity rating						X[a]				X[a]				

* Cycles 4-6 are the same as cycles 1-3.

a - Obtain prior to infusion.

b - Repeat prior to every other cycle; after documentation of tumor response; confirm tumor response with studies 4 weeks later.

c - LCSS patient scale scheduled for Day 19 should be completed before dexamethasone administration begins for the following cycle.

d - Will be documented daily by each patient.

e - Repeat as clinically indicated.

f –Collect up to 7 days prior to enrollment. The second homocysteine sample must not be drawn until the patient has taken folic acid for at least 5 days.

g - Obtain +/ 1 days of the designated day

h - 60 patients per arm at selected centers (Protocol Attachment JMCH.9.)

i – Collect +/ 3 days of the designated day and up to 4 days prior to each cycle.

j - Forced vital capacity, slow vital capacity, and forced expiratory volume.

k - See Section 3.9.1.1 for an explanation of baseline measurement of pain and dyspnea.

l - every 6 weeks until progressive disease

m – Approximately 1 - 3 weeks prior to enrollment.

n – Daily beginning approximately 1 - 3 weeks prior to enrollment and continuing daily while patient remains on study. To be documented via patient diary and medical interview as entered into the patient chart until the first dose of MTA plus cisplatin or cisplatin alone.

o – Given as an intramuscular injection approximately 1 - 3 weeks prior to enrollment and repeated approximately every 9 weeks while patient remains on study.

p-Patients enrolled on JMCH(a)-(d) only

q – First done at entry (informed consent) by the investigator. Next two done prior to randomization or chemotherapy. Done by the investigator and used for randomization and done by an indpendent observer.

r – Within 4 weeks of enrollment.

Follow-Up

After each patient discontinued the study, the investigator was to make every effort to continue to evaluate the patient for delayed toxicity by clinical and laboratory evaluations as clinically indicated. Every attempt was to be made to obtain hematology, and chemistry approximately 30 days after the last dose of MTA or cisplatin. The patient had to be followed every 30 days until toxicity resolves.

Appropriateness and Consistency of Measurements

At the time the protocol was written, there was no tumor-specific quality of life (QoL) instrument or symptom scale which had been validated for patients with mesothelioma. Therefore, a validated, lung cancer-specific QoL instrument, the Lung Cancer Symptom Scale (LCSS) had been included in this study. The LCSS was comprised of a patient scale and an optional observer scale. The patient scale included six symptom questions and three summation questions, while the observer scale included the same six symptom questions. With the permission of the developers, references to lung cancer were to be removed from the patient scale as follows:
In the directions, "cancer" was to be replaced with "illness."
In Question #7, "lung cancer" was to be replaced with "your lung illness."
The patient scale had been translated into English, Dutch, Finnish, Flemish, French, German, Italian, Polish, Portuguese, Spanish, Slovak, Czech, Turkish, Hindi, Gujarati, and Chinese and has been tested for discriminant validity, reliability, and cross-cultural validity. Only patients for whom there was a validated translation in a language in which they were fluent will be required to complete the LCSS. Collection of LCSS data was to not interfere with the routine collection of adverse event data reported by the patient, nor were the two sources of data required to agree. These data will be analyzed with the same rigor as the study objectives relating to safety and efficacy.

Pharmacokinetics and Pharmacodynamics
Pharmacokinetic data was to be collected on 60 patients per arm (with or without folic acid supplementation) at selected centers. Blood samples were to be collected for the analysis of MTA and total platinum (MTA plus cisplatin arm) and for total platinum (cisplatin alone arm) in plasma. Blood samples were to be collected during Cycles 1 and 3 (see Protocol Attachment JMCH.9). In order to maintain the blinding, the same series of MTA or saline samples were to be collected from all patients and sorted by ——— according to treatment arm. Samples was to be collected at specified times in order to provide a characterization of the MTA and cisplatin concentration-time profiles in this patient population. Pharmacokinetic analysis was to be performed by mixed-effect modeling methods using the NONMEM program. Total plasma clearance values for each patient was to be used to calculate the area under the plasma concentration-time curve (AUC). Patient specific AUC values was to be used as a measure of drug exposure in a multivariate analysis.

Discontinuations

A patient was to be discontinued from the study under the following circumstances.

- If there was evidence of progressive disease.
- If the patient had received 6 cycles of therapy (if the patient had shown tumor response and/or clinical benefit and the investigator felt the patient would benefit from more than 6 cycles, the Lilly CRP was to be consulted and was to grant approval).
- If the attending physician thought a change of therapy would be in the best interest of the patient.
- If the patient requested discontinuation.
- If the patient experienced unacceptable toxicity due to study drug administration.

- If a patient became pregnant or failed to use adequate birth control (for those patients who were able to conceive).
- If the patient was noncompliant with study procedures, at the discretion of the investigator.
- If, in consultation with the investigator, Lilly was to use its discretion as the sponsor to discontinue the patient.

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) were be evaluated for safety.

All randomized patients were to be evaluated for survival and secondary time to event efficacy measures.

All enrolled patients meeting the following criteria were be evaluated for tumor response:

- Histologic diagnosis of malignant pleural mesothelioma.
- No prior systemic chemotherapy.
- No concurrent systemic chemotherapy or radiotherapy.
- Presence of unidimensionally and/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 discontinued from the study due to unacceptable drug toxicity prior to receiving one complete cycle of therapy was to be included in the efficacy analysis.

Additionally, all enrolled patients meeting at least one of the following criteria, and who had at least one post-baseline observation will be included in the analysis of clinical benefit:

- Presence of mesothelioma-related pain intensity at baseline as reflected by a score of $\geq$10 mm on the VAS.
- Presence of mesothelioma-related dyspnea at baseline as reflected by a score of $\geq$10 mm on the VAS.
- Baseline analgesic consumption $\geq$10 mg morphine equivalents per day for mesothelioma-related pain, and daily consumption within 50% of average baseline consumption.

Each patient who had a baseline observation and at least one post-baseline observation was to be included in the analysis of LCSS, pulmonary function tests, and lung density measurements. Because there may have been a discrepancy between the pathological diagnosis assessment of the independent reviewer and the investigator, data analysis was also to be performed on all patients whose diagnoses were confirmed by the independent reviewer.

Post Study Follow-Up

Responding patients were to have a follow-up CT scan approximately 1 month after the last dose of study drug. The LCSS patient and observer scales were to be completed approximately 1 month and three months after the last dose of study drug for those patients who had not received post-study chemotherapy, radiotherapy, or surgical intervention. All patients who had not progressed were to be followed every 6 weeks (+/- 3 days) for clinical assessment and lesion evaluation. Thereafter, patients were to be followed approximately every 3 months in order to record the date of death, and any post-study chemotherapy, radiotherapy, or surgical intervention. All patients were to be followed until death or they are lost to follow-up. If alternative anti-cancer therapy was given, details of this therapy was to be collected and patients may have been censored at that point.

Folic Acid Supplementation Compliance

In the pre-randomization period, compliance with folic acid supplementation requirements were to be monitored through the use of a patient diary and medical interview documented in the patient chart. A patient was to be considered to be fully compliant if at least five doses of folic acid had been taken in the 7 days immediately preceding the first dose of study drug. While on study therapy, compliance with folic acid supplementation requirements was to be monitored through medical interviews and pill counts. A patient was to be considered to be fully compliant if at least fourteen doses of folic acid had been taken in the 3 weeks preceding the study drug dose in question.

Data Analysis Methods

General Considerations

All confidence intervals for parameters to be estimated were to be constructed with a significance level of • =0.05 (i.e., a 95% confidence interval). Additional exploratory analyses, including an assessment of the effect of folic acid and vitamin B12 supplementation on the safety and efficacy of study therapies, were to be conducted as deemed appropriate. The interpretation of study results was to be the responsibility of the Lilly clinical research physician and the statistician. The Lilly clinical research physician and the statistician were also to 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.

Data to Be Analyzed

The efficacy and safety analyses were be performed on data from qualified patients as described above, regardless of whether or not they were treated with vitamin supplementation.

Patient Disposition

A detailed description of patient disposition was to be provided for each study treatment arm. 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 for the study.
- An account of all identified protocol violations.

All patients entered in the study were to be accounted for in the summation. The number of patients who did not qualify for analysis, who die, or who discontinue before treatment begins was to be specified.

Clinical Benefit Response Criteria

	FDA Recommendations for Mesothelioma trial	Lilly Mesothelioma MTA Trial	Most Conservative Evaluation Method
Change in Pain Intensity	≥ 50% reduction	≥ 10 mm decrease on a 100 mm visual analog scale	≥ 50% reduction together with a > 10 mm decrease on a 100 mm visual analog scale
Change in Analgesic Consumption	≥ 50% reduction	≥ 50% reduction	≥ 50% reduction
Change in Performance Status (Karnofsky)	≥ 20 point improvement	≥ 20 point improvement	≥ 20 point improvement
Dyspnea	≥ 50% reduction	≥ 10 mm decrease on a 100 mm visual analog scale	≥ 50% reduction together with a > 10 mm decrease on a 100 mm visual analog scale

The algorithm used for the determination of clinical benefit response was to be implemented in three different ways with three different criteria: the FDA recommended criteria, the Lilly mesothelioma trial criteria, and finally a set of criteria that use the most conservative between the FDA and Lilly criteria on each of the clinical benefit components of change in pain intensity, change in analgesic consumption, change in performance status (Karnofsky), and dyspnea as described in Table above. In each analysis, the clinical benefit response rates from the two treatment arms were to be compared. The analysis based on the conservative approach from the FDA and Lilly criteria was to serve as the primary analysis for assessing clinical benefit response. Additional secondary efficacy analyses was also to be performed regarding comparisons between the two treatment arms in changes from baseline of the following:

- LCSS scores.
- Pulmonary function tests.
- Lung density measurements.

Treatment groups were to be compared for individual components of clinical benefit response using a distribution-free approach in which each patient's clinical benefit response data were characterized by a single summary statistic. The two summary statistics chosen for each of the four components were the slopes of least squares regression lines fit through each subject's data and the change from baseline to the best value of the clinical benefit response variable. For pain intensity, analgesic consumption, and dyspnea, the best value was to

be the nadir, and for KPS, the best value was to be the peak. The next step was to stratify the subjects according to time to treatment failure. For
these analyses, the following four-strata stratification scheme was to be chosen: the first strata was to include patients who were on study less than 3 weeks; the second strata, patients who were on study from 3 to 9 weeks; the third strata, patients who were on study from 9 to 18 weeks; and the fourth strata, patients who were on study for 18 weeks or longer. A standardized Wilcoxon rank-sum statistic, Z_g, where g represented stratum, was to be computed for each stratum.

Safety Analyses

Adverse events were reported for all individuals who received MTA or cisplatin. An adverse event was not to be collected prior to receiving study drug unless the investigator felt that the event may have been caused by a protocol procedure (such as pre-treatment with dexamethasone). For the purposes of this study, "study drug" was to be defined as any of the following: MTA or alimta, cisplatin, or dexamethasone (or equivalent corticosteroid) administered as described in the protocol.

All patients who met the safety criteria for qualification were to be evaluated for safety. Safety analyses were to include a comparison between the two treatment arms:

- Number of blood transfusions required.
- Incidence of adverse events as well as laboratory changes.
- Listings and frequency tables categorizing laboratory and nonlaboratory adverse events by maximum CTC toxicity grade and relationship to study drug.

In each treatment arm a comparison of incidence of adverse events were to be done between patients with and without vitamin supplementation. To account for those patients supplemented with vitamins sometime after the first cycle of therapy, the same comparison of incidence of adverse events were to be done between patients with and without supplementation on a cycle of therapy basis. These comparisons were to be done within and between study treatment arms on an exploratory basis.

Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic data was to be collected on 60 patients per arm at selected centers. Plasma concentration-time data for MTA and total platinum in the MTA plus cisplatin arm and for total platinum in the cisplatin-only arm was to be pooled and analyzed using population pharmacokinetic methods. Pharmacokinetic parameters were to be estimated by Non-Linear Mixed Effects Modeling using the NONMEM program. The effects of patient specific factors (age, weight, gender, smoking, etc) on pharmacokinetic parameters were to be evaluated. The effects of MTA concentrations on measures of hematologic toxicity (absolute neutrophil and platelet counts) were to be evaluated. The effect of cisplatin administration on the pharmacokinetics of MTA was to be assessed after pooling plasma concentration time data for MTA previously collected in a series of Phase 2

studies with data collected in this study using the NONMEM program. The effect of MTA on total platinum were to be assessed by pooling the platinum data from both arms of this study.

Interim Analysis

Rationale for Interim Analysis

The primary endpoint of this study was patient overall survival. However, patients with malignant pleural mesothelioma presented with a number of disease-specific symptoms, mainly pain and dyspnea. As the trial proceded to evaluate the primary endpoint of survival, Lilly believed it was appropriate to evaluate how well the disease specific symptoms were controlled with study treatment. The first goal of this interim analysis was to compare the survival of patients between the two treatment arms by pooling patients with study vitamin supplementation and patients without study vitamin supplementation. At this point, the study could have been stopped upon recommendation by a data monitoring board due to significant difference in survival between the two study arms. This interim analysis was to assess in addition the clinical benefit from treatment as reflected primarily by pain intensity, analgesic consumption, dyspnea, and performance status. Other supportive efficacy endpoints as well as the safety endpoints were also to be assessed.

Proposed Interim Analysis Plan

An interim analysis on the primary endpoint of survival was to be conducted on approximately 300 qualified patients by pooling the 150 patients with study vitamin supplementation with the 150 patients without study vitamin supplementation. The proposed interim analysis was to be conducted under the auspices of a data monitoring board assigned specifically to Study JMCH. The study was to have been stopped at this time upon recommendation by the Data Monitoring Board if significant survival difference between the two treatment arms were observed from this pooled survival analysis. Because of the possibility to stop the study early based on study primary endpoint of survival, an adjustment of the significance level α was to be made. A log rank-based adjustment of the significance level α for the interim analysis was appropriate because of the possibility to stop the trial if significant survival difference between the two treatment arms was observed from this pooled analysis from a total of 300 patients. The adjustment of the significance level α, based on log rank statistic, were to be done by testing the null hypothesis of no difference in survival between the treatment arms at a nominal significance level $\alpha = 0.01$. To ensure an overall significance level $\alpha = 0.05$, the final analysis on the 430 patients was to be undertaken with a nominal significance level 0.0476, thereby taking a statistical penalty on α equal to 0.0024.

As for the secondary endpoints of clinical benefit response rate, tumor response rate, time to progressive disease and time to treatment failure, the interim analysis was to be performed first on the subset of the first 150 patients treated in the revised protocol with vitamin supplementation. Then the same analysis was to be performed using data from the pooled 300 patients with and without vitamin supplementation treated up to that time.

No adjustment for significance level α was to be performed for looking at any other study endpoint during the interim analysis beside the primary endpoint of survival.

Implications of the Planned Interim Study Results

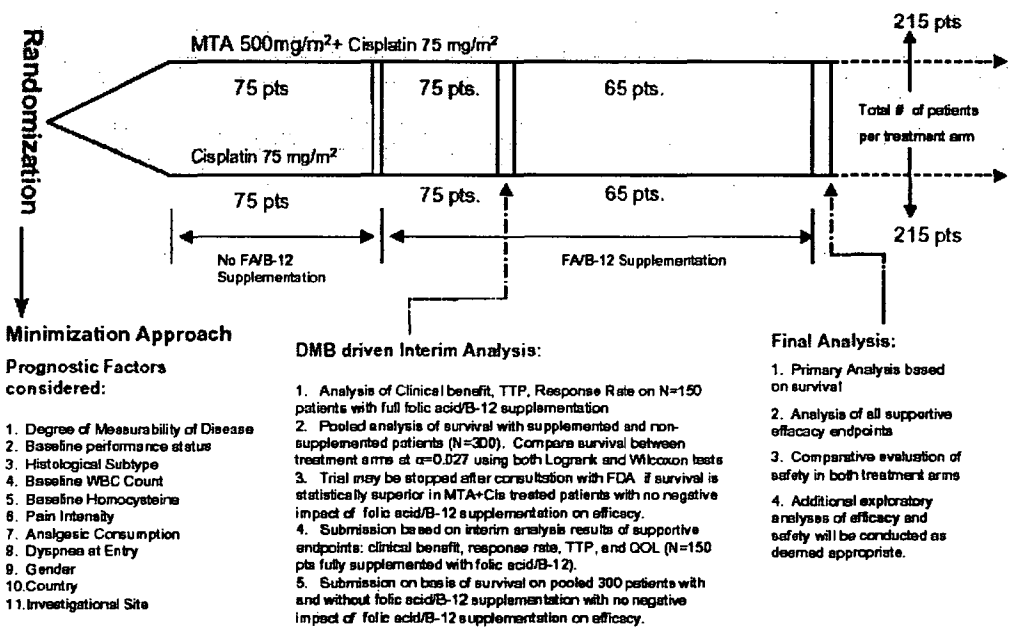
A data monitoring board was to be established to conduct the interim analysis. Only the data monitoring board was authorized to review completely unblinded interim efficacy and safety analysis and, if necessary, to disseminate the results. The data monitoring board was to disseminate interim results in a manner that would minimize bias. Study sites were not to receive information about interim results unless they needed to know for the safety of their patients or if the results show overwhelming evidence of efficacy such that data monitoring board recommended that the study should be closed and Lilly as a result agreed to close the trial. As a result of preparation and presentation of interim results before the FDA and the Oncology Drug Advisory Committee (ODAC), a study investigator may have become aware of the interim results. The investigator may have then considered opting out of the study or changing patient disease management. The following are what Lilly believed would be the implications of this interim analysis.

1) If there was no conclusive difference in the primary study endpoint of survival between the two study arms, then the study should continue as originally planned.

2) The first anticipated public review of the interim results was to be at an ODAC meeting. If one treatment arm proved to be superior, then investigators might have been inclined to cross patients over to the superior arm. This could confound the final patient survival analysis results.

Brief Schematic of Protocol and the Amendments

9.8.2.1.1. Protocol Amendment (A)



Protocol Amendment (A) was approved on 11 January 1999. Based on recommendations from the FDA, the following changes to the protocol were made:

- the primary endpoint was changed from tumor response rate to survival
- a planned interim analysis was added
- the study design was modified from open-label to single-blind
- unidimensional measurement was allowed, which aided the investigator in measuring a disease that is difficult to measure bidimensionally. This change occurred before RECIST allowed unidimensional lesions to code to measurable disease versus evaluable disease.
- pain intensity, analgesic consumption, and dyspnea were added to the randomization factors to help balance the treatment arms for the CB response analysis

9.8.2. Amendments to the Protocol

Table JMCH.9.14. Timeline of Amendment Approval H3E-MC-JMCH

Clinical Document	Date of Approval	Time Elapsed (months)	Primary Reason(s) for Amendment
Original protocol	16 July 1998	NA	NA
Amendment (A)	11 January 1999	6	Study design became single-blind and survival became the primary endpoint
Amendment (B)	06 August 1999	13	Inclusion criterion for albumin laboratory level changed from 3.0 to 2.5 g/dl and changes to algorithm for CB response
Amendment (C)	10 December 1999	17	Addition of folic acid and vitamin B_{12} supplementation
Amendment (D)	21 January 2000	18	Corrections made to wording errors
Amendment (E)	19 June 2000	23	Increased sample size for the FS subpopulation
Amendment (F)	24 January 2001	30	Changed the primary objective of the interim analysis from a CB comparison to a survival comparison
Amendment (G)	02 August 2001	38	LY231514 lyophilized formulation

3.2 The Sponsor's Assessment of JMCH Results

Introduction

On 13 February 2002 the final reporting database was created. The reporting database included data from all 574 patients who entered the trial. Of the 574 patients who signed informed consent, 456 patients were randomly assigned a treatment arm (enrolled). Tumor response data from the independent peer review are presented as of 13 February 2002 and as of 10 June 2002. The latter was done to facilitate a more complete evaluation of the independent peer review data.

The primary analyses of this study were performed on a *RT* basis. The RT population was defined as all patients randomly assigned to a treatment arm who received study drug (LY231514 plus cisplatin or cisplatin alone). Of the 456 patients randomly assigned to a treatment arm, 448 (98.2%) received alimta/cisplatin or cisplatin monotherapy. These patients constituted the RT population for this study. Prior to randomization patients were stratified by prognostic factors using the Pocock-Simon method. See Applicant's table below taken from the protocol.

STRATIFICATION VARIABLE	ABBREVIATION	LEVELS
Baseline Performance Status	KPS	Low (70-80) and High (90-100)
Baseline Homocysteine	Hcys	Low (<12μmol/L) and High (≥12μmol/L)
Disease Measurability	DM	Bidimensional and Unidimensional
Histology Subtype	HS	Epithelial and Others
Baseline WBC	WBC	Low (<8.3×10^9/L) and High (≥8.3×10^9/L)
Gender	Gender	M and F
Pain Intensity	PI	Low (<20mm) and High (≥20mm)
Analgesic Consumption	AC	Low (<60 morphine equivalents per day,
		only NSAIDS, or no analgesic consumption)
		High (≥60 morphine equivalents per day)
Dyspnea	Dyspnea	Low (<20mm) and High (≥20mm)
Country	C	C1, C2, C3
Investigation Center	IC	IC1, IC2, IC3, IC4, IC5, IC6, IC7, and IC8

The table below lists the primary reasons for discontinuation before study drug administration for the 8 (1.8%) patients, who were randomized and not treated.

Table JMCH.12.1. Patients Randomly Assigned Treatment But Not Treated H3E-MC-JMCH

Investigator Site / Patient Number	Treatment Arm	Reason
111-1342	Cisplatin	Inclusion criteria not met
136-1634	Cisplatin	Patient decision
142-1472	Cisplatin	Patient decision
201-2200	Cisplatin	Patient decision
213-2133	Cisplatin	Inclusion criteria not met
301-3161	LY/cis	Discontinued because of hypertension[1]
510-5109	LY/cis	Death (from study disease)
601-6014	Cisplatin	Patient decision

[1] This patient received hydration, experienced an SAE, and discontinued. Study drug was not administered.

MEDICAL OFFICER NOTE: 456 patients should compose the intent-to-treat population.

This was a multicenter trial that entered patients at 88 investigational sites (see the table below). Nineteen percent of the patients randomized (n=456) were from the United States; 81% of the patients randomized were from outside the United States. Among the 88 investigational sites, four centers (numbers 120, 133, 504, and 952) did not randomly allocate any patients to a

Table JMCH.10.1. Distribution of All Patients by Country H3E-MC-JMCH

	Number of Investigational Sites	Number of Patients Entered	Number of Patients Enrolled (Randomized)	Percent of Patients Enrolled in the Entire Study
United States	24	122	87	19.1%
Germany	9	90	80	17.5
France	6	55	48	10.5
Argentina	6	15	11	2.4
Australia	5	34	33	7.2
Belgium	5	26	18	3.9
Italy	5	39	30	6.6
United Kingdom	4	31	20	4.4
Canada	3	7	6	1.3
Czech Republic	3	6	6	1.3
Finland	3	22	19	4.2
India	3	16	12	2.6
Poland	3	38	31	6.8
Spain	2	16	14	3.1
Taiwan	2	2	2	0.4
Chile	1	7	5	1.1
Mexico	1	25	16	3.5
Slovakia	1	3	2	0.4
Singapore	1	1	0	0
Turkey	1	19	16	3.5
Total	88	574	456	100%

treatment arm. The majority of patients enrolled into this study were from the United States, Germany, France, and Australia. Mexico and Turkey enrolled a large number of patients at single investigational sites. The investigators included 69 oncologists, 16 pneumologists, and 3 thoracic surgeons.

574 patients signed the informed consent for study JMCH and were entered on the study; 456 patients were randomized; 118 patients were not randomized; 448 patients were randomized and treated. The schematic below illustrates the disposition of the patients entered on study JMCH.

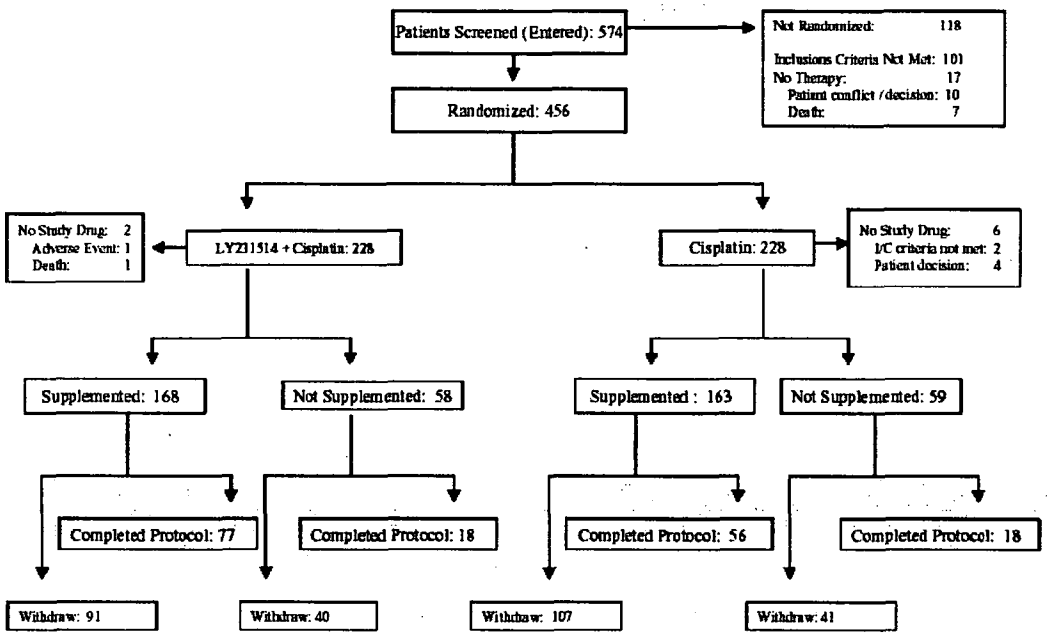


Figure JMCH.10.1. Disposition of patients while on-study[1].

1 On-study refers to the period when the patient started study drug therapy until 30 days after the last dose.

The study was originally designed to enroll a total of 280 patients (140 patients per treatment arm). During the trial, unexpected toxicities in patients receiving LY231514 in this and other trials resulted in Lilly's decision to add folic acid and vitamin B12 supplementation to therapy. *Supplementation was added to both treatment arms to preserve blinding at the patient level.* Mandatory supplementation was implemented after 118 patients had been randomized, of these 117 were treated. After supplementation was implemented, enrollment was extended to ensure that at least 280 fully supplemented (FS) patients were included. The increased sample size allowed for a fully powered statistical analysis in the FS subgroup.

One group of patients was classified as FS if they were randomized to a treatment group on or after *December 2, 1999*. The intent was that these patients would begin supplementation during the baseline period and continue during their entire course of treatment. The second group included patients who were partially supplemented (PS) and who were never supplemented (NS); this group was classified as nonsupplemented (PS+NS) if they were randomized to a treatment group before *December 2 1999*. The table below illustrates the definitions.

SUBPOPULATION	ABBRV.	DESCRIPTION
Fully supplemented[1]	FS	Patients randomly assigned to a treatment arm on or after 02 December 1999. These patients would begin supplementation during the baseline period and continue during their entire course of treatment.
Partially supplemented	PS	Patients randomly assigned to a treatment arm before 02 December 1999 and had at least 1 dose of study drug on or after 02 December 1999 and therefore received supplementation some time during the course of chemotherapy.

SUBPOPULATION	ABBRV.	DESCRIPTION
Never supplemented	NS	Patients randomly assigned to a treatment arm before 02 December 1999 and received all doses of study drug before 02 December 1999.
Nonsupplemented	PS+NS	Patients randomly assigned to a treatment arm before 02 December 1999. This group is the pool of all partially and never supplemented patients.
Fully + Partially Supplemented	FS+PS	This group is the pool of all fully and partially supplemented patients.
[1]Fully supplemented subpopulation = supplemented subpopulation in the statistical analysis plan.		

When the programmatic change to implement vitamin supplementation occurred on December 2 1999, 117 patients (representing nearly 50% of the targeted enrollment) were already randomly assigned to a treatment arm.

Protocol Violations

Of the 88 study sites that entered patients, 52 study sites (59.1%) reported a total of 270 protocol violations (PVs) that were considered significant. The most common type of PV was related to hematology or chemistry evaluations not being performed according to protocol specifications.

> **MEDICAL OFFICER NOTE: These protocol violations are minor with regard to impact on the study results. In the FDA analysis of efficacy, major protocol violations will be provided.**

Folic Acid Compliance

Although *the protocol did not indicate the reporting of folic acid compliance*, Lilly determined that this was an important parameter to summarize. The percentage of folic acid compliant patients was calculated for each cycle separately.

The numerator and denominator for the baseline period compliance was calculated as follows:

- Denominator = number of patients in the supplemented group who received their first dose of study therapy
- Numerator = number of patients in the supplemented group who received their first dose of study therapy and who received folic acid on at least 5 of the 7 days preceding their first dose of study therapy.

The numerator and denominator for Cycle N ($N \geq 1$) compliance was calculated as follows:

- Denominator = number of patients in the supplemented group who received their Cycle N + 1 study therapy
- Numerator = number of patients in the supplemented group who received their Cycle N + 1 study therapy and who received folic acid on at least 14 of the 21 days preceding their Cycle N + 1 study therapy

In the *prerandomization period, compliance* with folic acid supplementation requirements was *monitored through the use of a patient diary and medical interview documented in the patient chart.* A patient was considered to be fully compliant if at least five doses of folic acid were taken in the 7 days immediately preceding the first dose of study drug. While *on study therapy, compliance* with folic acid supplementation requirements was *monitored through medical interviews and pill counts.* A patient was considered to be fully compliant if at least 14 doses of folic acid were taken in the 3 weeks preceding the study drug dose in question.

Patients were allowed to take folic acid in the range of 350 to 1000 µg daily. Among the 331 FS patients, a total of 289 (87%) patients took initial doses between 350 and 600 µg. A total of 238 (72%) took initial doses of 400 µg and 49 (15%) patients took an initial dose of 500 µg. The remaining 42 (13%) patients took initial doses higher than 600 µg. The table below summarizes folic acid compliance.

Table JMCH.11.18. Summary of Folic Acid Compliance RT Population for FS Patients H3E-MC-JMCH

	LY/cis (N=168)		Cisplatin (N=163)	
Cycle Number	FS Patients / cycle	Compliant Patients	FS Patients / cycle	Compliant Patients
0	168	158 (94.0%)	163	154 (94.5%)
1	155	147 (94.8)	148	143 (96.6)
2	134	128 (95.5)	98	97 (99.0)
3	123	118 (95.9)	90	89 (98.9)
4	107	103 (96.3)	74	74 (100)
5	97	96 (99.0)	66	65 (98.5)
6	15	14 (93.3)	5	4 (80.0)
7	12	12 (100)	5	5 (100)
8	5	4 (80.0)	1	1 (100)
9	4	4 (100)	0	--
10	3	3 (100)	0	--
11	2	2 (100)	0	--

Demographics

In the RT population, 81% were men; 90% were white; and the median age was 61 years. These parameters were balanced on both arms. The gender and age incidences were consistent with the literature.

Table JMCH.11.2. Summary of Patient Characteristics RT Population H3E-MC-JMCH

	LY/cis (N=226)	Cisplatin (N=222)
Sex		
Male	184 (81.4%)	181 (81.5%)
Female	42 (18.6)	41 (18.5)
Origin		
Caucasian	204 (90.3)	206 (92.8)
Hispanic	11 (4.9)	12 (5.4)
Asian[1]	10 (4.4)	4 (1.9)
African	1 (0.4)	0
Age		
Median	61	60
Minimum	29	19
Maximum	85	84

[1] Western and East/Southeast Asian have been combined.

The table below divided the study populations by supplementation status (i.e., FS vs. PS+NS). These parameters were balanced on both arms.

Table JMCH.11.3. Summary of Patient Characteristics RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Sex				
Male	136 (81.0%)	48 (82.8%)	134 (82.2%)	47 (79.7%)
Female	32 (19.0)	10 (17.2)	29 (17.8)	12 (20.3)
Origin				
Caucasian	150 (89.3)	54 (93.1)	153 (93.9)	53 (89.8)
Hispanic	10 (6.0)	1 (1.7)	7 (4.3)	5 (8.5)
Asian[1]	7 (4.2)	3 (5.2)	3 (1.8)	1 (0.7)
African	1 (0.6)	0	0	0
Age				
Median	60	62	60	61
Minimum	29	32	19	35
Maximum	85	77	82	84

[1] Western and East/Southeast Asian have been combined.

Sixty-eight percent of the population had an epithelial histology, about 8% had a sarcomatoid histology, and 16% had a mixed histology; between 4 and 8.5 % had an *other* histology. Seventy-five percent of the population was Stage III/IV. Over 50% of the population were Karnofsky performance status 90/100. These parameters were balanced on both arms. The histology proportions (except for *other*) were consistent with the literature. The table is below.

Table JMCH.11.6. Summary of Baseline Disease Characteristics RT Population H3E-MC-JMCH

	LY/cis (N=226)	Cisplatin (N=222)
Diagnosis / Histology		
Epithelial	154 (68.1%)	152 (68.5%)
Mixed	37 (16.4)	36 (16.2)
Sarcomatoid	18 (8.0)	25 (11.3)
Other	17 (7.5)	9 (4.1)
Stage at Entry		
Ia	9 (4.0)	8 (3.6)
Ib	7 (3.1)	6 (2.7)
II	35 (15.6)	33 (15.0)
III	73 (32.4)	68 (30.9)
IV	101 (44.9)	105 (47.7)
Unspecified	1 (0.4)	2 (0.9)
Performance Status		
70	37 (16.4)	31 (14.0)
80	72 (31.9)	66 (29.7)
90	93 (41.2)	94 (42.3)
100	24 (10.6)	31 (14.0)

The table below divides the study populations by supplementation status (i.e., FS vs. PS+NS). These parameters were balanced on both arms.

Table JMCH.11.7. Summary of Baseline Disease Characteristics RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Diagnosis / Histology				
Epithelial	117 (69.6%)	37 (63.8%)	113 (69.3%)	39 (66.1%)
Mixed	25 (14.9)	12 (20.7)	25 (15.3)	11 (18.6)
Sarcomatoid	14 (8.3)	4 (6.9)	17 (10.4)	8 (13.6)
Other	12 (7.1)	5 (8.6)	8 (4.9)	1 (1.7)
Stage at Entry				
Ia	8 (4.8)	1 (1.7)	7 (4.3)	1 (1.7)
Ib	7 (4.2)	0	5 (3.1)	1 (1.7)
II	27 (16.2)	8 (13.8)	27 (16.8)	6 (10.2)
III	51 (30.5)	22 (37.9)	49 (30.4)	19 (32.2)
IV	74 (44.3)	27 (46.6)	73 (45.3)	32 (54.2)
Unspecified	1 (0.6)	0	2 (1.2)	0
Performance Status				
70	25 (14.9)	12 (20.7)	22 (13.5)	9 (15.3)
80	58 (34.5)	14 (24.1)	47 (28.8)	19 (32.2)
90	67 (39.9)	26 (44.8)	69 (42.3)	25 (42.4)
100	18 (10.7)	6 (10.3)	25 (15.3)	6 (10.2)

MEDICAL OFFICER NOTE: Stage is a check-off box on the CRF. There is no data on TNM parameters.

Sixty-eight percent of patients on the alimta/cisplatin arm had prior surgery; 57% of the patients on the cisplatin arm had prior surgery (table below). Division of patients by supplementation status maintained similar proportions.

Table JMCH.11.14. Reported Prior Therapies RT Population H3E-MC-JMCH

	LY/cis (N=226)	Cisplatin (N=222)
Prior surgery	144 (63.7%)	127 (57.2%)
Prior radiotherapy	22 (9.7)	31 (14.0)
Prior chemotherapy	17 (7.5)	11 (5.0)
Prior immunotherapy[1]	1 (0.4)	0
Unknown classification[2]	1 (0.4)	0

1 Patient 502-5052 received IL-2.

2 Patient 501-5001 received an unknown drug for the purpose of pleurodesis.

Table JMCH.11.15. Reported Prior Therapies RT Population by Treatment Arm and Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Prior surgery	107 (63.7%)	37 (63.8%)	93 (57.1%)	34 (57.6%)
Prior radiotherapy	18 (10.7)	4 (6.9)	23 (14.1)	8 (13.6)
Prior chemotherapy	8 (4.8)	9 (15.5)	7 (4.3)	4 (6.8)
Prior immunotherapy	1 (0.6)	0	0	0
Unknown classification[1]	1 (0.6)	0	0	0

1 Patient 501-5001 received an unknown drug for the purpose of pleurodesis.

Ninety-eight percent of patients had pleural rind disease; 20% had mediastinal lymph node disease; 20% had pleural disease; 7.5 to 10.4% of patients had chest wall involvement. These parameters were balanced between treatment groups. Division of patients by supplemental status maintained similar proportions, except for mediastinal lymph node for NS cisplatin..

Table JMCH.11.8. Summary of Sites of Disease Occurring >10% at Baseline RT Population H3E-MC-JMCH

Disease Site[1]	LY/cis (N=226)	Cisplatin (N=222)
Pleural rind	222 (98.3%)	217 (97.8%)
Lymph node, mediastinal	46 (20.4)	48 (21.6)
Pleura	44 (19.5)	44 (19.8)
Lung, NOS	27 (11.9)	25 (11.3)
Chest wall	17 (7.5)	23 (10.4)

[1] Patients may have more than one disease site involved. Percentages are defined as the involvement of a given site among all patients in the group.

Table JMCH.11.9. Summary of Sites of Disease In >10% at Baseline RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
Disease Site[1]	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Pleural rind	168 (100%)	54 (93.0%)	160 (98.2%)	57 (96.6%)
Lymph node, mediastinal	34 (20.2)	12 (20.7)	32 (19.6)	16 (27.1)
Pleura	33 (19.6)	11 (19.0)	36 (22.1)	8 (13.6)
Lung, NOS	23 (13.7)	4 (6.9)	20 (12.3)	5 (8.5)
Chest wall	9 (5.4)	8 (13.8)	18 (11.0)	5 (8.5)

[1] Patients may have more than one disease site involved. Percentages are defined as the involvement of a given site among all patients in the group.

Nearly half of patients had one or more historical illness. The other parameters were balanced except for accidental injury and myocardial infarction that appeared more frequent in the cisplatin alone arm. Division of patients by supplementation status suggested that the two arms were balanced except for myocardial infarction that appeared more frequent in the cisplatin alone.

Table JMCH.11.10. Summary of Historical Illnesses in >2% of Patients RT Population H3E-MC-JMCH

Event[1]	LY/cis (N=226)	Cisplatin (N=222)
Patients with ≥1 diagnosis	104 (46.0%)	103 (46.4%)
Surgical procedure	51 (22.6)	57 (25.7)
Accidental injury	6 (2.7)	11 (5.0)
Hernia	6 (2.7)	6 (2.7)
Lung disorder	6 (2.7)	3 (1.4)
Kidney calculus	5 (2.2)	5 (2.3)
Myocardial infarction	5 (2.2)	14 (6.3)
Pleural disorder	5 (2.2)	1 (0.5)

1 Patients may have more than one historical illness. Percentages are defined as the involvement of a given illness among all patients in the group.

Table JMCH.11.11. Summary of Historical Illnesses in >2% of Patients RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
Event[1]	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Patients with ≥1 diagnosis	74 (44.0%)	30 (51.7%)	68 (41.7%)	35 (59.3%)
Surgical procedure	35 (20.8)	16 (27.6)	40 (24.5)	17 (28.8)
Accidental injury	5 (3.0)	1 (1.7)	7 (4.3)	4 (6.8)
Hernia	4 (2.4)	2 (3.4)	5 (3.1)	1 (1.7)
Lung disorder	2 (1.2)	4 (6.9)	2 (1.2)	1 (1.7)
Kidney calculus	4 (2.4)	1 (1.7)	2 (1.2)	3 (5.1)
Myocardial infarction	4 (2.4)	1 (1.7)	8 (4.9)	6 (10.2)
Pleural disorder	5 (3.0)	--	--	1 (1.7)

1 Patients may have more than one historical illness. Percentages are defined as the involvement of a given illness among all patients in the group.

Baseline stratification factors used for randomization were balanced between treatment groups. *It is noted that over 60% of patients had bidimensional disease at baseline.*

Table JMCH.11.5. Baseline Stratification Factors Used for Randomization RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
KPS				
Low (≤80)	83 (49.4%)	26 (44.8)	69 (42.3%)	28 (47.5)
High (≥90)	85 (50.6)	32 (55.2)	94 (57.7)	31 (52.5)
Degree of Meaurability[1]				
Unidimensional	61 (36.5)	12 (20.7)	62 (38.0)	11 (18.6)
Bidimensional	106 (63.5)	46 (79.3)	101 (62.0)	48 (81.4)
Histologic Subtype				
Epithelial	117 (69.6)	37 (63.8)	113 (69.3)	39 (66.1)
Mixed	25 (14.9)	12 (20.7)	25 (15.3)	11 (18.6)
Sarcomatoid	14 (8.3)	4 (6.9)	17 (10.4)	8 (13.6)
Other	12 (7.1)	5 (8.6)	8 (4.9)	1 (1.7)
WBC				
Low (<8.3 GI/L)	72 (42.9)	25 (43.1)	68 (41.7)	23 (39.0)
High (≥8.3 GI/L)	96 (57.1)	33 (56.9)	95 (58.3)	36 (61.0)
Pain Intensity[2]				
Low (<20 mm)	82 (49.4)	30 (51.7)	80 (49.1)	33 (55.9)
High (≥20 mm)	84 (50.6)	28 (48.3)	83 (50.9)	26 (44.1)
Analgesic Consumption				
Low (<60 mg morp eq/day)	129 (76.8)	44 (75.9)	124 (76.1)	46 (78.0)
High (≥60 mg morp eq/day)	39 (23.2)	14 (24.1)	39 (23.9)	13 (22.0)
Dyspnea[2]				
Low (<20 mm)	66 (39.8)	25 (43.1)	68 (41.7)	24 (40.7)
High (≥20 mm)	100 (60.2)	33 (56.9)	95 (58.3)	35 (59.3)
Homocysteine				
Low (<12 umol/L)	119 (70.8)	36 (62.1)	118 (72.4)	38 (64.4)
High (≥12 umol/L)	49 (29.2)	22 (37.9)	45 (27.6)	21 (35.6)
Sex				
Male	136 (81.0)	48 (82.8)	134 (82.2)	47 (79.7)
Female	32 (19.0)	10 (17.2)	29 (17.8)	12 (20.3)

1 A single patient was missing their evaluable disease measurement at baseline.

2 Patients 302-3025 and 720-7209 completed the patient LCSS at baseline, but outside of the protocol defined window; those data are not included in the reporting database.

MEDICAL OFFICER NOTE: The independent reviewers did not confirm that bidimensional disease was the predominant degree of measurability of disease. Over 50% of the patients who had measurements recorded by the independent reviewers had unidimensional disease. This proportion did not include the patients who the independent reviewers did not record measurable disease (see section "Subjects with No Disease Measured by Both Independent Reviewers" of this review). Degree of measurability of disease was a stratification factor.

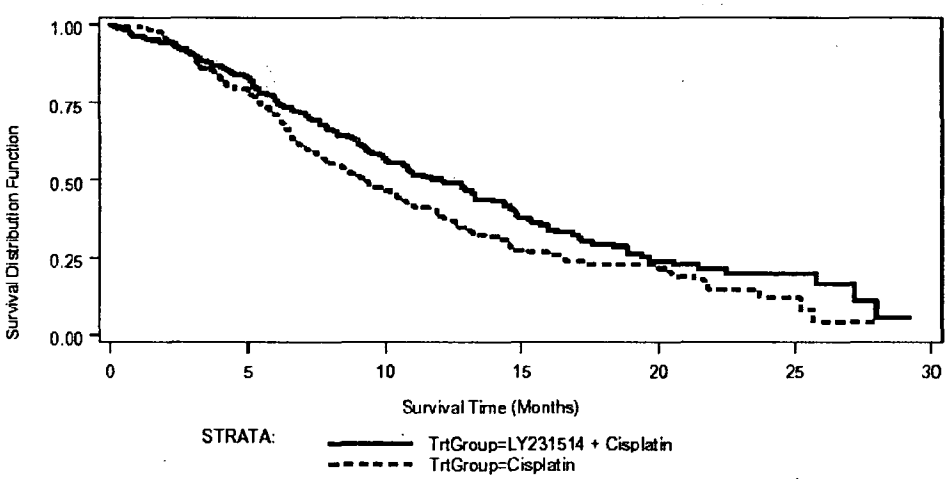
Survival: The Primary Endpoint

The overall median survivals in the randomized and treated groups were 12.1 months for alimta/cisplatin and 9.3 months for cisplatin alone (p = 0.02); the hazard ratio was 0.77. For the fully supplemented groups, the median survivals were 13.3 and 10 months for alimta/cisplatin and cisplatin alone, respectively (p = 0.051); the hazard ratio was 0.75. For the PS+NS groups, the median survivals were 9.5 and 7.2 months for alimta/cisplatin and cisplatin alone, respectively (p = 0.253); the hazard ratio was 0.76. *Interestingly, the addition of folic acid and B12 (supplementation) added approximately 4 months to the median survival of the alimta/cisplatin arm and approximately 3 months to the median survival of the cisplatin alone arm.* The table and figures below are provided for illustration.

Table JMCH.11.20. Summary of Survival Time (Months)
RT Population
H3E-MC-JMCH

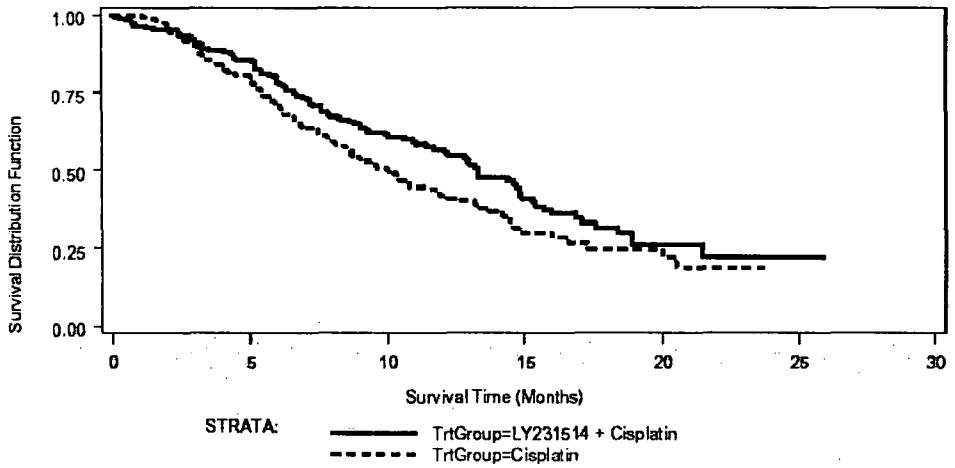
	RT Patients (N=448)		FS Patients (N=331)		PS+NS Patients (N=117)	
	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=168)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
Minimum						
25th percentile	6.1	5.5	6.6	5.4	5.1	5.7
Median	12.1	9.3	13.3	10.0	9.5	7.2
95% CI for Median	10.0 -14.4	7.8 -10.7	11.4 -14.9	8.4 -11.9	8.1 -10.8	6.5 -9.9
75th percentile	19.7	16.4	21.5	17.3	16.3	12.7
Maximum						
Hazard ratio	0.77		0.75		0.76	
95% CI for hazard ratio	0.61 – 0.96		0.57 – 1.00		0.54 – 1.17	
Log-rank p-value	0.020		0.051		0.253	
Wilcoxon p-value	0.028		0.039		0.440	
Probability of survival lasting at least (n[1]):						
6 months	0.76 (166)	0.71 (153)	0.78 (128)	0.71 (111)	0.68 (38)	0.71 (42)
9 months	0.61 (129)	0.51 (104)	0.63 (98)	0.53 (78)	0.56 (31)	0.44 (25)
12 months	0.50 (84)	0.38 (64)	0.57 (66)	0.42 (46)	0.34 (18)	0.29 (17)
18 months	0.30 (32)	0.23 (21)	0.32 (20)	0.25 (11)	0.23 (12)	0.17 (10)
24 months	0.20 (8)	0.12 (3)	0.22 (2)	0.19 (0)	0.15 (6)	0.08 (3)
Percent censored	35.8	28.4	43.5	36.8	13.8	5.1

[1]n = number of patients known alive at indicated time.



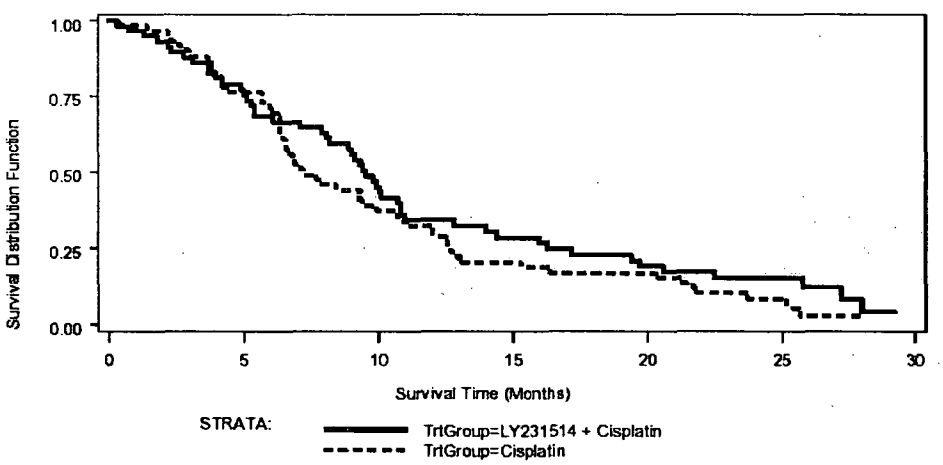
Program name: ttevent4.SAS. Variable name: survtime. Population: All.

Figure JMCH.11.1. K-M estimates of survival time for LY/cis and cisplatin alone, RT population.



Program name: ttevent4.SAS. Variable name: survtime. Population: Supplemented.

Figure JMCH.11.2. K-M estimates of survival for LY/cis and cisplatin alone, FS subpopulation.



Program name: ttevent4.SAS. Variable name: survtime. Population: Nonsupplemented.

Figure JMCH.11.3. K-M estimates of survival for LY/cis and cisplatin alone, PS+NS subpopulation.

Below is a table illustrating the subgroup analyses of the randomized and treated patients for survival. Note that for the supplementation analyses, Lilly grouped the patients as *FS + PS and NS* (above the groupings were FS and PS + NS). For the subgroups of supplementation status, performance status, epithelial, mixed, sarcomatoid, Stage III/IV WBC, post study chemotherapy, and pre-folate cystathionine) analyzed, the addition of alimta resulted in an increased median survival. Stage I/II and other histologies were trending in the direction of the cisplatin alone arm.

MEDICAL OFFICER NOTE: The label groups the data as RT and FS

Table JMCH.11.77. Summary of Results from Survival Time Subgroup Analyses H3E-MC-JMCH

	All RT				LY/Cis			Cis			
	N	Median (mo)	% Censored	HR[1]	N	Median (mo)	% Censored	N	Median (mo)	% Censored	HR[2]
Supplementation Group											
FS+PS	378	11.0	37.3	0.68	194	13.2	41.2	184	9.4	33.2	0.71
NS	70	7.45	4.3	--	32	8.0	3.1	38	7.15	5.3	0.89
KPS Group											
70, 80	206	7.3	19.9	--	109	8.6	26.6	97	6.5	12.4	0.76
90, 100	242	14.5	42.6	0.50	117	15.3	44.4	125	12.7	40.8	0.83
Disease Stage Group											
I, II	98	16.0	51.0	0.58	51	14.4	49.0	47	16.4	53.2	1.14
III, IV	347	9.3	26.5	--	174	10.9	32.2	173	7.9	20.8	0.72
Histological Subtype											
Epithelial	306	12.1	37.3	0.45	154	13.3	42.9	152	10.8	31.6	0.81
Sarcomatoid	43	5.4	23.3	--	18	7.0	38.9	25	5.4	12.0	0.77
Mixed	73	7.6	15.1	0.71	37	8.2	10.8	36	6.9	19.4	0.84
Other	26	9.55	34.6	0.57	17	9.0	23.5	9	11.6	55.6	1.29
WBC											
<8.2 Gl/L	176	13.2	41.5	0.67	92	14.4	43.5	84	12.7	39.3	0.88
≥8.2 Gl/L	272	8.9	26.1	--	134	10.6	30.6	138	7.5	21.7	0.71
Post study Chemo											
Y	190	13.3	35.3	0.65	85	14.9	38.8	105	12.5	32.4	0.84
N	258	8.7	29.8	--	141	9.8	34.0	117	6.8	24.8	0.69

Table JMCH.11.77. Summary of Results from Survival Time Subgroup Analyses (concluded) H3E-MC-JMCH

Pre-FA Cystathionine											
<301 µmol/L	298	12.0	36.2	0.62	146	14.4	40.4	152	10.8	32.2	0.75
≥301 µmol/L	139	7.4	25.2	--	71	10.0	29.6	68	6.3	20.6	0.63

1 Hazard ratio for subgroup relative to complementary subgroup. For Histological subtype, hazard ratio relative to sarcomatoid subgroup.
2 Hazard ratio for LY/cis relative to cisplatin alone.

Lilly tested three models in the prognostic evaluation of survival. The models are described below.

Model 1:

- Therapy Group: alimta/cisplatin versus cisplatin alone
- Supplementation Group: *fully supplemented (FS) versus partially and never supplemented (PS + NS)*
- Age: continuous regression variable
- Gender: male versus female
- Geography: U.S./Canada versus Western Europe/Australia versus Others
- Race: Caucasian versus others
- KPS Group: 90 and 100 versus 70 and 80
- Disease Stage Group: Stages I and II versus Stages III and IV
- Histological Subtype: epithelial versus sarcomatoid versus mixed versus other
- Time from Diagnosis: continuous regression variable
- WBC: continuous regression variable
- Prior Radiotherapy: yes versus no
- Poststudy Chemo: yes versus no
- Poststudy Therapy (other than chemo): yes versus no
- Presupplementation homocysteine: continuous regression variable
- Presupplementation MMA: continuous regression variable
- Presupplementation cystathionine: continuous regression variable

Model 2:

- Supplementation Group: *fully and partially supplemented (FS + PS) versus never supplemented (NS)*
- All other factors parameterized the same as Model 1

Model 3:

- *Supplementation Group: fully and partially supplemented (FS + PS) versus never supplemented (NS)*
- Postsupplementation homocysteine: continuous regression variable
- Postsupplementation MMA: continuous regression variable
- Postsupplementation cystathionine: continuous regression variable
- All other factors parameterized the same as Model 1

The two tables below describe the data.

Table JMCH.11.73. Summary of Prognostic Factors Considered in the Model RT Population Excluding Patients with Missing Baseline Data (N=434) H3E-MC-JMCH

	LY/cis (N=216)	Cisplatin (N=218)
Supplementation Group		
FS	165 (76.4)	161 (73.9)
PS+NS	51 (23.6)	57 (26.2)
FS+PS	189 (87.5)	182 (83.5)
NS	27 (12.5)	36 (16.5)
Age*		
<65	138 (63.9)	132 (60.6)
≥65	78 (36.1)	86 (39.5)
Gender		
Male	175 (81.0)	177 (81.2)
Female	41 (19.0)	41 (18.8)
Geography		
U.S./Canada	44 (20.4)	47 (21.6)
W. Europe/Australia	122 (56.5)	125 (57.3)
Other	50 (23.2)	46 (21.1)
Race		
Caucasian	194 (89.8)	202 (92.7)
Other	22 (10.2)	16 (7.3)
KPS Group		
70, 80	101 (46.8)	96 (44.0)
90, 100	115 (53.2)	122 (56.0)
Disease Stage Group		
I, II	49 (22.7)	47 (21.6)
III, IV	167 (77.3)	171 (78.4)
Histological Subtype		
Epithelial	146 (67.6)	151 (69.3)
Sarcomatoid	18 (8.3)	24 (11.0)
Mixed	35 (16.2)	35 (16.1)
Other	17 (7.9)	8 (3.7)
Time from Diagnosis*		
<1.0 months	34 (15.7)	34 (15.6)
≥1.0 months	182 (84.3)	184 (84.4)
WBC*		
<8.2 GI/L	87 (40.3)	82 (37.6)
≥8.2 GI/L	129 (59.7)	136 (62.4)

Table JMCH.11.73. Summary of Prognostic Factors Considered in the Model RT Population Excluding Patients with Missing Baseline Data (N=434) H3E-MC-JMCH (concluded)

	LY/cis (N=216)	Cisplatin (N=218)
Prior Radiotherapy		
Yes	22 (10.2)	29 (13.3)
No	194 (89.8)	189 (86.7)
Poststudy Chemotherapy		
Yes	82 (38.0)	104 (47.7)
No	134 (62.0)	114 (52.3)
Other Poststudy Therapy		
Yes	38 (17.6)	26 (11.9)
No	178 (82.4)	192 (88.1)
Pre-FA Homocysteine*		
<15 µmol/L	183 (84.7)	187 (85.8)
≥15 µmol/L	33 (15.3)	31 (14.2)
Post-FA Homocysteine*		
<15 µmol/L	202 (93.5)	204 (93.6)
≥15 µmol/L	14 (6.5)	14 (6.4)
Pre-FA MMA*		
<272 µmol/L	180 (83.3)	180 (82.6)
≥272 µmol/L	36 (16.7)	38 (17.4)
Post-FA MMA*		
<272 µmol/L	194 (89.8)	193 (88.5)
≥272 µmol/L	22 (10.2)	25 (11.5)
Pre-FA Cystathionine*		
<301 µmol/L	145 (67.1)	150 (68.8)
≥301 µmol/L	71 (32.9)	68 (31.2)
Post-FA Cystathionine*		
<301 µmol/L	159 (73.6)	152 (69.7)
≥301 µmol/L	57 (26.4)	66 (30.3)

Abbreviation: W = Western

* Included in the regression models as continuous regression variable. Dichotomized in this table for summary purposes.

The table below included the Wald chi-square p-values for the three competing models. The p-value for the treatment group variable (alimta/cisplatin versus cisplatin alone) was significant in all three models (and the regression coefficients were all positive). This indicated that, regardless of which model was considered the best fitting model, survival time was significantly longer in the alimta/cisplatin arm compared to the cisplatin alone arm. The analysis indicated that the survival advantage of alimta/cisplatin over cisplatin alone was not an artifact of any potential confounding effect attributable to the 16 prognostic factors considered.

Among the three models considered, the optimal parameterization was found to be Model 2. A comparison of Models 1 and 2 suggests that the supplementation classification as defined in the statistical analysis plan (*FS versus PS+NS*) had less prognostic power than the alternative parameterization (*FS+PS versus NS*). This finding was based on the fact that Model 2 had a smaller p-value for the supplemenatation group factor and a larger log-likelihood value. These results suggested that, with respect to survival, PS patients were more like FS patients than NS patients.

A comparison of Wald chi-square p-values and the log-likelihood values between Models 2 and 3 suggests that the presupplementation metabolite determinations had slightly better prognostic value than the postsupplementation metabolite determinations.

Table JMCH.11.74. Model Selection for Survival Time Cox Regression Analysis RT Population Excluding Patients with Missing Baseline Data (N=434) H3E-MC-JMCH

	Wald Chi-Square p-values		
Parameter	Model 1	Model 2	Model 3
Therapy Group	<0.001	<0.001	<0.001
Supplementation Group	0.022	<0.001	<0.001
Age	0.359	0.269	0.408
Gender	0.611	0.970	0.972
Geography	0.857	0.825	0.536
Race	0.921	0.889	0.919
KPS Group	<0.001	<0.001	<0.001
Disease Stage Group	<0.001	<0.001	<0.001
Histological Subtype	<0.001	<0.001	<0.001
Time from Diagnosis	0.473	0.260	0.263
White Blood Cell	<0.001	<0.001	<0.001
Prior Radiotherapy	0.331	0.128	0.061
Poststudy Chemotherapy	<0.001	<0.001	<0.001
Other Poststudy Therapy	0.808	0.557	0.517
Homocysteine	0.091	0.080	0.250
Methylmalonic Acid	0.622	0.612	0.861
Cystathionine	0.024	0.019	0.058
Log-likelihood	-432.7	-427.4	-429.2

Model 1 Supplementation group split: FS versus PS and NS; presupplementation vitamin metabolites.
Model 2 Supplementation group split: FS and PS versus NS; presupplementation vitamin metabolites.
Model 3 Supplementation group split: FS and PS versus NS; postsupplementation vitamin metabolites.

Time to Progression

The time to progression (TTP) was defined as the time from study enrollment until the time that the patient was classified as having progressive disease or death because of any cause. For patients without documentation of progressive disease, TTP was considered to be right-censored at the date of last assessment for progressive disease for purposes of these analyses.

The medians for TTP in the randomized and treated groups were 5.7 months for alimta/cisplatin and 3.9 months for cisplatin alone (p = 0.001); the hazard ratio was 0.68. For the fully supplemented groups, the TTP medians were 6.1 and 3.9 months for alimta/cisplatin and cisplatin alone, respectively (p = 0.008); the hazard ratio was 0.64. For the partially supplemented/never supplemented groups, the medians for TTP were 4.6 and 2.8 months for alimta/cisplatin and cisplatin alone, respectively (p = 0.032); the hazard ratio was 0.61. The table and figures below are provided for illustration.

MEDICAL OFFICER NOTE: Interestingly, the addition of folic acid and B12 (supplementation) added 1.5 months to the median TTP survival of the alimta/cisplatin arm and 1.1 months to the median survival of the cisplatin alone arm.

Table JMCH.11.21. Summary of Time to Progressive Disease (Months)
RT Population
H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=168)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
Minimum						
25th percentile	3.3	1.4	3.9	1.4	2.8	1.4
Median	5.7	3.9	6.1	3.9	4.6	2.8
95% CI for median	4.9 -6.5	2.8 -4.4	5.3 -7.0	2.8 -4.5	3.7 -6.6	1.5 -4.6
75th percentile	9.3	6.7	9.5	7.0	8.0	6.0
Maximum						
Hazard ratio	0.68		0.64		0.61	
95% CI for hazard ratio	0.59 – 0.87		0.58 – 0.92		0.45 – 0.95	
Log-rank p-value	0.001		0.008		0.032	
Wilcoxon p-value	<0.001		<0.001		0.022	
Probability of TTPD lasting at least (n^1):						
3 months	0.76 (171)	0.52 (113)	0.78 (131)	0.53 (85)	0.70 (40)	0.47 (28)
6 months	0.49 (107)	0.29 (62)	0.50 (83)	0.31 (48)	0.44 (24)	0.24 (14)
9 months	0.27 (57)	0.16 (32)	0.29 (46)	0.18 (26)	0.20 (11)	0.10 (6)
12 months	0.15 (26)	0.10 (18)	0.14 (18)	0.12 (14)	0.15 (8)	0.07 (4)
Percent censored	7.5	9.0	8.9	12.3	3.5	0.0

[1]n = number of patients known to be progression-free at indicated time.

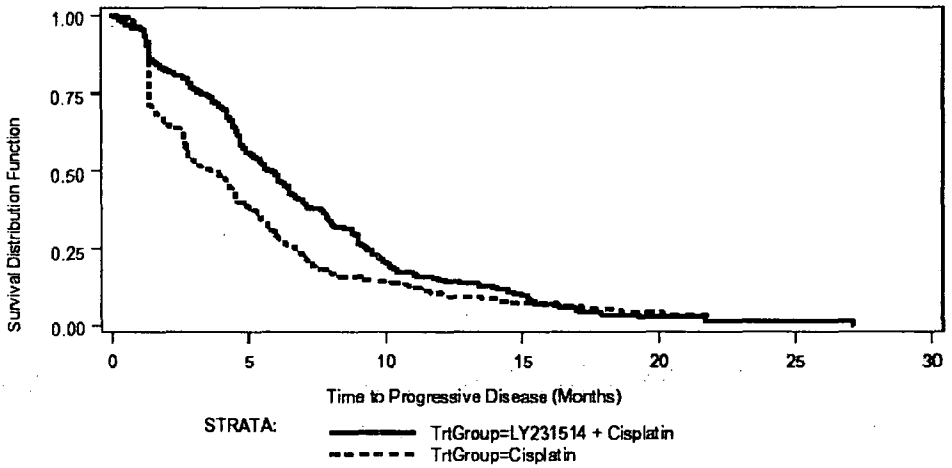


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Figure JMCH.11.4. K-M estimates of TTPD for LY/cis and cisplatin alone, RT population.

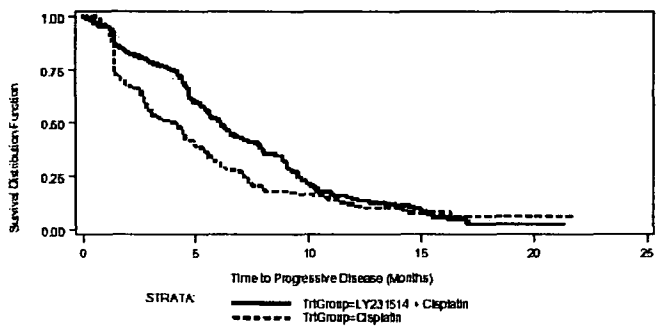

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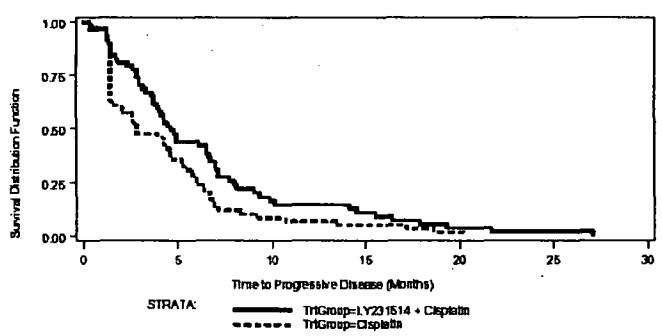
Figure JMCH.11.5. K-M estimates of TTPD for LY/cis and cisplatin alone, FS subpopulation.



Program name: ttevent4.SAS. Variable name: timepdps. Population: Nonsupplemented.

Figure JMCH.11.6. K-M estimates of TTPD for LY/cis and cisplatin alone, PS+NS subpopulation.

Below is a table illustrating the subgroup analyses of the randomized and treated patients for TTP. Note that for the supplementation analyses, Lilly grouped the patients as *FS + PS and NS* (above the groupings were FS and PS + NS except for the survival subgroup analyses). For all the subgroups (supplementation status, performance status, stage, histology, time from diagnosis, WBC, pre-folate homocysteine, and pre-folate cystathionine) analyzed, the addition of alimta to cisplatin resulted in an increased TTP.

Table JMCH.11.79. Summary of Results from TTPD Subgroup Analyses H3E-MC-JMCH

	All RT				LY/Cis			Cis			
	N	Median (mo)	% Censored	HR[1]	N	Median (mo)	% Censored	N	Median (mo)	% Censored	HR[2]
Supplementation Group											
FS+PS	378	5.1	9.8	0.48	194	6.1	8.8	184	4.3	10.9	0.70
NS	70	2.45	0	--	32	4.15	0	38	1.4	0	0.34
Race											
Caucasian	410	4.6	7.3	--	204	5.7	6.4	206	3.4	8.3	0.60
Other	38	6.2	18.4	0.74	22	6.2	18.2	16	5.85	18.8	0.94
KPS Group											
70, 80	206	4.5	5.3	--	109	5.6	5.5	97	2.6	5.2	0.46
90, 100	242	5.2	10.7	0.87	117	6.1	9.4	125	4.4	12.0	0.72
Disease Stage Group											
I, II	98	6.3	18.4	0.71	51	6.5	13.7	47	5.7	23.4	0.88
III, IV	347	4.5	5.5	--	174	5.4	5.8	173	3.0	5.2	0.56
Histological Subtype											
Epithelial	306	5.2	7.5	0.50	154	6.1	5.2	152	4.3	9.9	0.70
Sarcomatoid	43	2.6	16.3	--	18	4.45	27.8	25	1.4	8.0	0.31
Mixed	73	4.25	6.9	0.61	37	4.65	8.1	36	2.7	5.6	0.58
Other	26	6.5	7.7	0.40	17	6.8	5.9	9	6.1	11.1	0.90
Time from Diagnosis											
<1.0 mo	69	2.9	5.8	--	34	4.3	8.8	35	1.9	2.9	0.44
≥1.0 mo	379	5.2	8.7	0.56	192	6.1	7.3	187	4.3	10.2	0.70

Table JMCH.11.79. Summary of Results from TTPD Subgroup Analyses (concluded) H3E-MC-JMCH

WBC											
<8.2 GI/L	176	5.8	10.8	0.74	92	6.5	9.8	84	4.6	11.9	0.71
≥8.2 GI/L	272	4.3	6.6	--	134	4.9	6.0	138	2.8	7.3	0.57
Pre-FA Homocysteine											
<15 µmol/L	382	4.5	7.6	--	191	5.6	7.3	191	3.3	7.9	0.59
≥15 µmol/L	66	6.5	12.1	0.69	35	8.1	8.6	31	5.1	16.1	0.63
Pre-FA Cystathionine											
<301 µmol/L	298	5.0	9.1	0.86	146	6.1	8.9	152	4.2	9.2	0.69
≥301 µmol/L	139	4.3	7.2	--	71	5.1	5.6	68	2.75	8.8	0.54

1 Hazard ratio for subgroup relative to complementary subgroup. For Histological subtype, hazard ratio relative to sarcomatoid subgroup.
2 Hazard ratio for LY/cis relative to cisplatin alone.

The table below included the Wald chi-square from the prognostic factor analysis of TTP, tumor response, response duration, and TTF p-values for Model 2.

Table JMCH.11.76. Wald Chi-Square p-values from Prognostic Factor Analysis of Secondary Time-to-Event Parameters and Tumor Response Rate Using Model 2
RT Population Excluding Patients with Missing Baseline Data (N=434)
H3E-MC-JMCH

Parameter	Wald Chi-Square p-values			
	TTPD	Tumor Response	Duration of Response	TTTF
Therapy Group	<0.001	<0.001	0.424	<0.001
Supplementation Group	<0.001	<0.001	0.262	<0.001
Age	0.885	0.249	0.533	0.086
Gender	0.496	0.066	0.852	0.944
Geography	0.823	0.216	0.835	0.037
Race	0.041	0.256	0.945	0.131
KPS Group	0.007	0.813	0.841	0.085
Disease Stage Group	0.002	0.503	0.322	<0.001
Histological Subtype	0.028	0.184	0.348	0.013
Time from Diagnosis	0.009	0.583	0.785	<0.001
White Blood Cell	<0.001	0.011	0.661	<0.001
Prior Radiotherapy	0.995	0.113	0.847	0.287
Poststudy Chemotherapy	0.702	0.100	0.026	0.007
Other Poststudy Therapy	0.598	0.844	0.013	0.436
Homocysteine[1]	0.013	0.106	0.203	0.036
Methylmalonic Acid[1]	0.764	0.293	0.535	0.543
Cystathionine[1]	0.033	0.521	0.162	0.324

[1] Presupplementation.

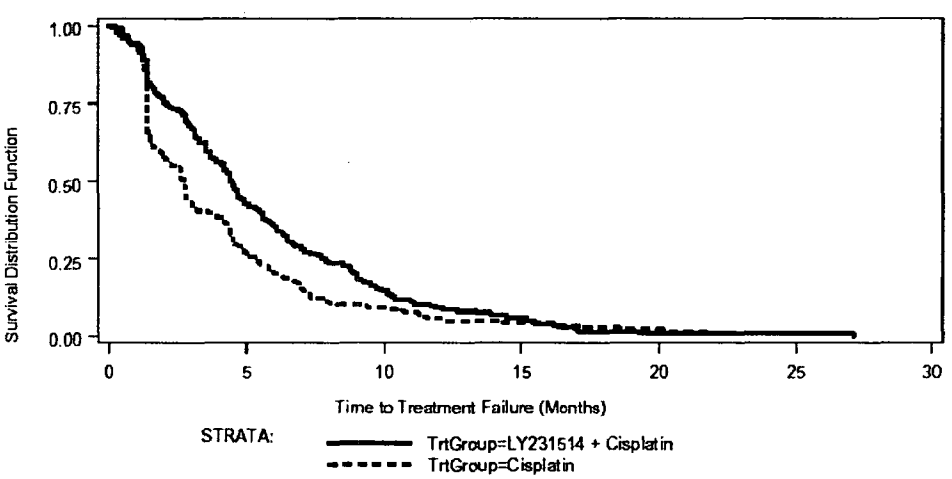
Time to Treatment Failure

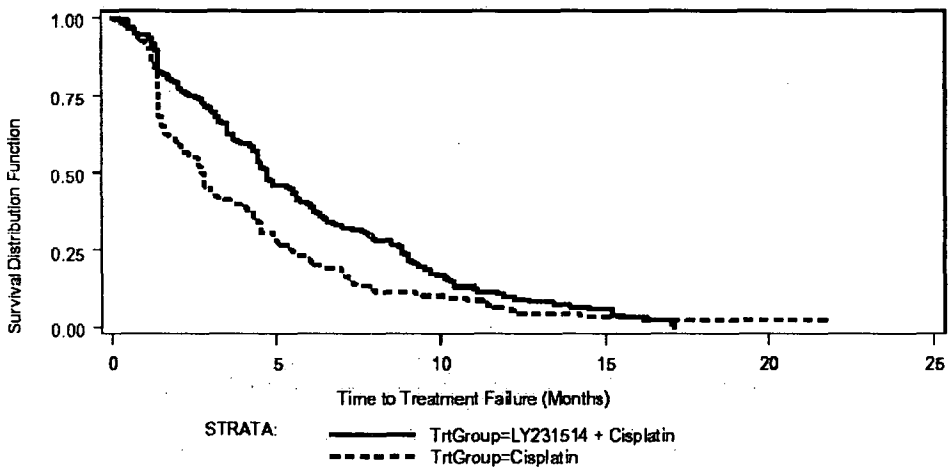
The TTF was defined as the time from study enrollment until the time of death or discontinuation for any reason. This is a composite endpoint containing events from study discontinuation (e.g., death, safety, TTP, and discontinuation for any investigator- or patient-generated reason). Below are the results in a table and the figures.

Table JMCH.11.26. Time to Treatment Failure Summary (Months)
RT Population
H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=168)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
Minimum						
25th percentile	2.1	1.4	2.4	1.4	1.6	1.4
Median	4.5	2.7	4.7	2.7	3.7	2.6
95% CI for median	3.9 -4.9	2.1 -2.9	4.3 -5.6	2.2 -3.1	2.8 -4.6	1.4 -3.0
75th percentile	7.8	5.4	8.8	5.5	6.1	4.7
Maximum						
Hazard ratio	0.61		0.57		0.71	
95% CI for hazard ratio	0.59 – 0.86		0.55 – 0.85		0.55 – 1.13	
Log-rank p-value	0.001		0.001		0.233	
Wilcoxon p-value	<0.001		<0.001		0.101	
Probability of TTTF lasting at least (n^1):						
3 months	0.67 (151)	0.41 (92)	0.70 (117)	0.43 (70)	0.59 (34)	0.37 (22)
6 months	0.35 (80)	0.20 (44)	0.39 (65)	0.21 (34)	0.26 (15)	0.17 (10)
9 months	0.18 (40)	0.10 (21)	0.22 (35)	0.11 (17)	0.09 (5)	0.07 (4)
12 months	0.09 (16)	0.06 (10)	0.10 (12)	0.06 (7)	0.07 (4)	0.05 (3)
Percent censored	4.0	3.6	5.4	4.9	0.0	0.0

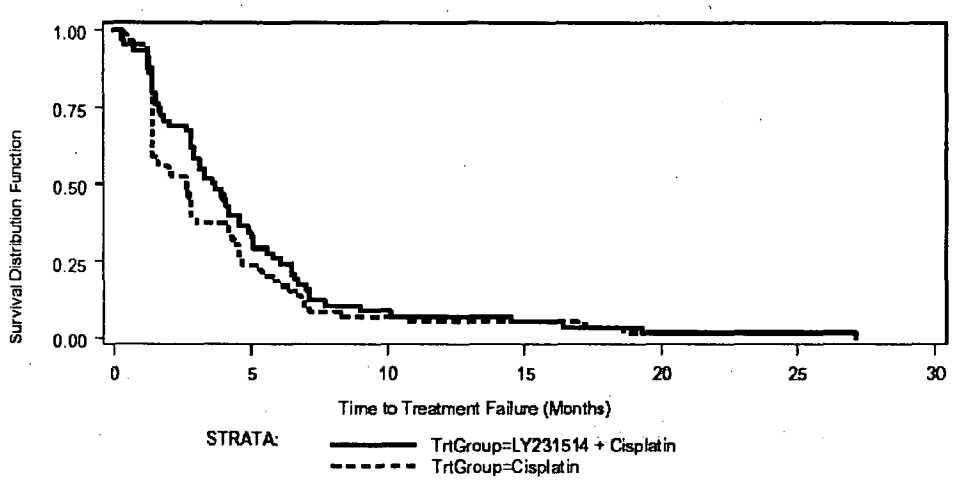
[1] n = number of patients who did not discontinue early and who are known alive and progression-free at indicated time.





Program name: ttevent4.SAS. Variable name: tttfswog. Population: Supplemented.

Figure JMCH.11.11. K-M curves for time to treatment failure for LY/cis and cisplatin alone, FS subpopulation.



Program name: ttevent4.SAS. Variable name: tttfswog. Population: Nonsupplemented.

Figure JMCH.11.12. K-M curves for time to treatment failure for LY/cis and cisplatin alone, PS+NS subpopulation.

Tumor Response

Tumor response was evaluated by applying modified standard SWOG criteria. A responder was defined as any patient who exhibited a best response of CR or PR. Two independent radiologists and/or a pulmonologist conducted a peer review of tumor response, and the patient treatment assignment was blinded. Patients who were qualified for tumor response were intended to be included in this peer review process. Lilly provided a list of patients' best response determined by the investigators and peer reviewers.

A total of 225 patients on the alimta/cisplatin arm and 222 on the cisplatin alone arm were included in the tumor response analysis. One patient (on the alimta/cisplatin arm) did not have measurable disease at baseline and therefore did not meet the criteria for inclusion in the analysis of tumor response.

> **MEDICAL OFFICER NOTE: According to the protocol, patients, who did not have measurable disease at baseline, were not eligible to be randomized and enrolled on study.**

Tumor response data from the independent peer review are presented as of 13 February 2002 and as of 10 June 2002.

According to Lilly, of the 447 patients qualified for tumor response evaluation, 194 patients on the alimta/cisplatin arm and 195 patients on the cisplatin alone arm were included in the independent review. As of the 10 June 2002 update, a total of 50 patients (11.2%) were excluded from the peer review for the following reasons: missing scans or scans that were uninterpretable because of poor quality.

> **MEDICAL OFFICER NOTE: 447 qualified for response - 50 patients with missing or uninterpretable scans = 397; the number of patients submitted for independent review: 194 alimta/cisplatin + 195 cisplatin alone = 387. It appears that 10 patients were missing. However, the table below indicated that 397 patients' images were sent for independent review as of June 10, 2002.**

According to the *investigators' assessment* of tumor response, 93 of 225 (41%) alimta/cisplatin RT patients and 37 of 222 (17%) RT cisplatin alone patients had an objective response (PR + CR) ($p < 0.001$). 76 of 167 (46%) alimta/cisplatin FS patients and 32 of 163 (20%) FS cisplatin alone patients had an objective response (PR + CR) ($p < 0.001$). 17 of 58 (29%) alimta/cisplatin PS + NS patients and 5 of 59 (9%) PS + NS cisplatin alone patients had an objective response (PR + CR) ($p = 0.005$).

It is noted that within the alimta/cisplatin arm, adding folic acid + B12 added 9% to the response rate or increased the response rate by 25%. It is noted that within the cisplatin alone arm, adding folic acid + B12 added 7% to the response rate or increased the response rate by 76%.

MEDICAL OFFICER NOTE: The list of responders sent by Lilly had 94 alimta/cisplatin responders and 37 cisplatin responders.[138]

Table JMCH.11.22 Summary of Best Tumor Response (Investigator-Determined) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=225)	Cisplatin (N=222)	LY/cis (N=167)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
Number of responding patients	93*	37	76*	32	17*	5
Response rate (%)	41.3	16.7	45.5	19.6	29.3	8.5
95% CI for response rate	34.8 - 48.1	12.0 - 22.2	37.8 - 53.4	13.8 - 26.6	18.1 - 42.7	2.8 - 18.7
Fisher exact p-value	<0.001		<0.001		0.005	

* Three CRs were on the LY/cis arm (2 FS patients and 1 PS+NS patient).

According to the *independent reviewers' assessment (June 10, 2002)* of tumor response, 86 of 197 (44%) alimta/cisplatin RT patients and 30 of 200 (15%) RT cisplatin alone patients had an objective response (PR + CR) ($p < 0.001$). 68 of 148 (46%) alimta/cisplatin FS patients and 25 of 148 (17%) FS cisplatin alone patients had an objective response (PR + CR) ($p < 0.001$). 18 of 49 (37%) alimta/cisplatin PS + NS patients and 5 of 52 (10%) PS + NS cisplatin alone patients had an objective response (PR + CR) ($p = 0.002$).

MEDICAL OFFICER NOTE: According to the protocol, the assessment by the independent reviewers' had priority over the assessment by the investigators.

It is noted that within the alimta/cisplatin arm, adding folic acid + B12 added 9% to the response rate or increased the response rate by 24%. It is noted that within the cisplatin alone arm, adding folic acid + B12 added 7% to the response rate or increased the response rate by 70%.

[138] Cover letter from Lilly dated 10/22/2002

Table JMCH.11.23. Summary of Best Tumor Response (Independent Reviewer-Determined) As of Database Lock (13 February 2002) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=194)	Cisplatin (N=195)	LY/cis (N=145)	Cisplatin (N=143)	LY/cis (N=49)	Cisplatin (N=52)
Number of responding patients	85*	28	67*	23	18*	5
Response rate (%)	43.8	14.4	46.2	16.1	36.7	9.6
95% CI for response rate	36.7 - 51.1	9.8 - 20.1	37.9 – 54.7	10.5 - 23.2	23.4 - 51.7	3.2 - 21.0
Fisher exact p-value	<0.001		<0.001		0.002	

* Two CRs were on the LY/cis arm (1 FS patient and 1 PS+NS patient).

Table JMCH.11.24. Summary of Best Tumor Response (Independent Reviewer-Determined) As of — Update (10 June 2002) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=197)	Cisplatin (N=200)	LY/cis (N=148)	Cisplatin (N=148)	LY/cis (N=49)	Cisplatin (N=52)
Number of responding patients	86*	30	68*	25	18*	5
Response rate (%)	43.7	15.0	45.9	16.9	36.7	9.6
95% CI for response rate	36.6 - 50.9	10.4 - 20.7	37.7 - 54.3	11.2 - 23.9	23.4 - 51.7	3.2 - 21.0
Fisher exact p-value	<0.001		<0.001		0.002	

* Two CRs were on the LY/cis arm (1 FS patient and 1 PS+NS patient).

Below is a table illustrating the subgroup analyses of the randomized and treated patients for tumor response. Again, Lilly grouped the patients as *FS + PS and NS* (in the above tumor response results, the groupings were FS and PS + NS).

MEDICAL OFFICER NOTE: The response evaluation was based on the evaluations of the *investigators*. There was no subgroup analysis for the *independent reviewers'* results. The trends of the results were the same as the analysis above. The addition of vitamins was more prominent with this analysis.

Table JMCH.11.80. Summary of Results from Tumor Response Rate Subgroup Analyses H3E-MC-JMCH

	All RT			LY/cis			Cisplatin Alone		
	N	Number of Responders	Rate (%)	N	Number of Responders	Rate (%)	N	Number of Responders	Rate (%)
Supplementation Group									
FS+PS	377	123	32.6	193	88	45.6	184	35	19.0
NS	70	7	10.0	32	5	15.6	38	2	5.3
WBC									
<8.2 Gl/L	175	66	37.7	91	48	52.8	84	18	21.4
≥8.2 Gl/L	272	64	23.5	134	45	33.6	138	19	13.8

Duration of Response for Responding Patients

The duration of tumor response was defined as the time from first objective status assessment of tumor response to the first time of disease progression, or death because of any cause. The duration of investigator-determined responses was used for this analysis. Duration of tumor response was analyzed for responders only (n=130) and the results are shown in the table below.

MEDICAL OFFICER NOTE: The response duration evaluations were based on the evaluations of the *investigators*. There was no response duration analysis for the *independent reviewers'* results.

The response durations ranged from 4.5 to 5.75 months. There was no significant difference between the alimta/cisplatin and cisplatin alone arms; there was a trend favoring the alimta/cisplatin arm in the RT (by approximately a month) and FS groupings compared to the cisplatin alone arm. There is minimal change in the duration of response with the addition of folic acid + B12.

Table JMCH.11.25. Duration of Tumor Response Summary (Months)
RT Population
H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=93)	Cisplatin (N=37)	LY/cis (N=76)	Cisplatin (N=32)	LY/cis (N=17)	Cisplatin (N=5)
Minimum						
25th percentile	3.55	3.6	3.6	3.6	3.0	4.7
Median	5.75	4.7	5.8	4.5	5.7	5.6
95% CI for median	4.9 -6.6	4.1 -6.6	4.9 -6.5	3.9 -6.6	3.0 -12.7	2.9 -15.8
75th percentile	9.1	8.8	8.8	7.9	12.7	9.4
Maximum						
Hazard ratio	0.82		0.80		0.98	
95% CI for hazard ratio	0.60 – 1.34		0.57 – 1.38		0.30 – 2.31	
Log-rank p-value	0.589		0.596		0.723	
Wilcoxon p-value	0.380		0.277		0.939	
Probability of duration of tumor response lasting at least (n[1]):						
3 months	0.86 (79)	0.78 (29)	0.89 (67)	0.78 (25)	0.71 (12)	0.80 (4)
6 months	0.48 (44)	0.35 (13)	0.48 (36)	0.34 (11)	0.47 (8)	0.40 (2)
9 months	0.25 (19)	0.21 (7)	0.21 (12)	0.18 (5)	0.41 (7)	0.40 (2)
12 months	0.12 (9)	0.09 (2)	0.07 (4)	0.07 (1)	0.29 (5)	0.20 (1)
Percent censored	7.5	10.8	9.2	12.5	0.0	0.0

[1]n = number of responding patients known to be progression-free at indicated time.

Clinical Benefit

The Clinical Benefit (CB) response rate was evaluated by using an algorithm of performance status, analgesic consumption, patient-reported pain intensity, and dyspnea. CB response was analyzed using three different methods. See table below.

	FDA Recommendations for Mesothelioma trial	Lilly Mesothelioma MTA Trial	Most Conservative Evaluation Method
Change in Pain Intensity	≥ 50% reduction	≥ 10 mm decrease on a 100 mm visual analog scale	≥ 50% reduction together with a > 10 mm decrease on a 100 mm visual analog scale
Change in Analgesic Consumption	≥ 50% reduction	≥ 50% reduction	≥ 50% reduction
Change in Performance Status (Karnofsky)	≥ 20 point improvement	≥ 20 point improvement	≥ 20 point improvement
Dyspnea	≥ 50% reduction	≥ 10 mm decrease on a 100 mm visual analog scale	≥ 50% reduction together with a > 10 mm decrease on a 100 mm visual analog scale

The results for duration of CB response and individual parameter changes using the hybrid method were also provided.

Patients were qualified for the CB analysis if they had baseline observations for all four parameters and if they were symptomatic in terms of dyspnea, pain intensity, or analgesic consumption. Additionally, patients must have had at least one postbaseline observation in any of the parameters. A total of 184 patients in each treatment arm qualified for analysis of CB response (table below).

Table JMCH.11.27. Baseline Clinical Benefit Response Qualification
RT Population
H3E-MC-JMCH

	LY/cis (N=226)	Cisplatin (N=222)
Number of patients qualified	184	184
Based on dyspnea	164	164
Based on pain intensity	147	134
Based on analgesic consumption	93	79
Number of patients not qualified	42	38
Missing baseline parameter	14	11
Not symptomatic	28	27

The table below summarizes the CB response rates for all three methods. For all methods, CB response rates were higher in the alimta/cisplatin arm than the cisplatin alone arm; these differences were not statistically significant. The data indicate that a number of patients on the alimta/cisplatin arm had palliation of symptoms or improved performance status. Response rates in both treatment arms were lowest with the hybrid method and highest with the Lilly method. Patients scoring high baseline values for pain and dyspnea were less likely to show improvement under the FDA method as compared to the Lilly method because greater magnitudes of change were required. Using the hybrid method, the median duration of response was three cycles for cisplatin alone (range, 2 to 6) and four cycles for LY/cis (range, 2 to 11).

As an example, using the FDA criteria for clinical benefit response 44 of 194 (24%) alimta/cisplatin RT patients and 17 of 184 (17%) RT cisplatin alone patients had a clinical benefit response (PR + CR) ($p = 0.12$). 36 of 135 (27%) alimta/cisplatin FS patients and 28 of 137 (20%) FS cisplatin alone patients had an objective response (PR + CR) ($p = 0.254$). 8 of 49 (16%) alimta/cisplatin PS + NS patients and 3 of 47 (6%) PS + NS cisplatin alone patients had an objective response (PR + CR) ($p = 0.2$).

It is noted that within the alimta/cisplatin arm, adding folic acid + B12 added 10.4% to the response rate or increased the response rate by 69%. It is noted that within the cisplatin alone arm, adding folic acid + B12 added 14% to the response rate or increased the response rate by 233%.

Table JMCH.11.28. Summary of Clinical Benefit Response
RT Population
H3E-MC-JMCH

	LY/cis (N=184)	Cisplatin (N=184)	Fischer Exact p-value
FDA	44 (23.9%)	31 (16.8%)	0.120
Lilly	50 (27.2)	43 (23.4)	0.472
Hybrid	39 (21.2)	25 (13.6)	0.073

Table JMCH.11.29. Summary of Clinical Benefit Response – FS
RT Population
H3E-MC-JMCH

	LY/cis (N=135)	Cisplatin (N=137)	Fischer Exact p-value
FDA	36 (26.7%)	28 (20.4%)	0.254
Lilly	42 (31.1)	36 (26.3)	0.422
Hybrid	31 (23.0)	23 (16.8)	0.226

Table JMCH.11.30. Summary of Clinical Benefit Response – PS+NS
RT Population
H3E-MC-JMCH

	LY/cis (N=49)	Cisplatin (N=47)	Fischer Exact p-value
FDA	8 (16.3%)	3 (6.4%)	0.200
Lilly	8 (16.3)	7 (14.9)	1.000
Hybrid	8 (16.3)	2 (4.3)	0.092

Table JMCH.11.31. Summary of Patients with Improved Clinical Benefit Parameters (Hybrid)
RT Population
H3E-MC-JMCH

	LY/cis		Cisplatin	
CB Parameter	All (N=184)	CB Responders (N=39)	All (N=184)	CB Responders (N=25)
Performance status	5	4	5	4
Dyspnea	25	18	11	8
Pain intensity	30	22	13	10
Analgesic consumption (AC)	37	20	19	10
Pain (pain intensity + AC)	46	32	21	17
1 parameter	48	21	33	19
2 parameters	15	12	6	5
3 parameters	5	5	1	1
4 parameters	1	1	0	0

The table below compares clinical benefit response (the hybrid method) with best tumor response. The table provides a summary of CB response based on the hybrid method versus best tumor response. Lilly notes that *patients with insufficient data were primarily those who had a best tumor response of progressive disease or whose lesions were considered nonevaluable; there is no indication whether responders were derived from the investigators pool or the independent reviewers pool.* Although most patients who were CB responders were also tumor responders or had stable disease, most patients who were tumor responders were not clinical benefit responders.

Table JMCH.11.32. Clinical Benefit Response by Tumor Response
RT Population
H3E-MC-JMCH

		HTA/Cisp					Sal/Cisp				
		Clinical Benefit					Clinical Benefit				
		Responder	Stable	Failure	Insufficient Data	Total	Responder	Stable	Failure	Insufficient Data	Total
Overall Study Tumor Response	CR + PR	26	16	34	2	78	8	10	11	0	29
	SD	10	17	29	5	61	14	26	34	3	77
	PD	3	10	7	14	34	3	19	25	21	68
	Other	0	1	0	10	11	0	1	0	9	10
	Total	39	44	70	31	194	25	56	70	33	194

Clinical Benefit Response Definition - HYBRID
RHP.ONCP.SASMACRO(SCRRTUMA) FINAL LOCK

APPEARS THIS WAY
ON ORIGINAL

Completion of six cycles of treatment was achieved in 53.1% of alimta/cisplatin treated patients compared to 40.1% of those treated with cisplatin alone. According to Lilly, the most common reasons for not completing six cycles included unsatisfactory response to treatment (alimta/cisplatin 27.0% versus cisplatin alone 45.5%), one or more adverse events (alimta/cisplatin 11.9% versus cisplatin alone 8.1%), patient decision or personal conflict (alimta/cisplatin 4.9% versus cisplatin alone 5.0%), and satisfactory response as perceived by patient and/or physician (alimta/cisplatin 5.3% versus cisplatin alone 1.9%).

Although the median number of cycles given was the same for both alimta/cisplatin and cisplatin arms with no folic acid + B12 supplementation, there was a larger increase in cycles given in the alimta/cisplatin arm compared to the cisplatin arm with the addition of folic acid + B12. *Interestingly, there was an increase in cycles given within a treatment arm with the addition of folic acid + B12 in both the Alimta/cispaltin treatment arm and the cisplatin alone treatment arm* (table below).

Table JMCH.12.13. Summary of Cycles Given
RT Population
FS and NS
H3E-MC-JMCH

	LY/cis		Cisplatin	
Completed Cycles	FS (N=168)	NS (N=32)	FS (N=163)	NS (N=38)
Mean	4.9	3.2	4.0	3.2
Median	6.0	2.0	4.0	2.0
Standard Deviation	2.2	1.8	2.1	1.8
Minimum				
Maximum				

Sponsor's Summary of Efficacy

1) Treatment with LY231514/cisplatin was superior to cisplatin monotherapy in the randomized and treated population in terms of the following endpoints:

- longer survival
- longer time to disease progression
- higher tumor response rates
- improvement in pulmonary function
- improvement in clinically relevant symptoms commonly associated with malignant pleural mesothelioma.

2) The superiority of LY231514/cisplatin over cisplatin monotherapy was maintained even when clinically relevant prognostic factors were taken into account.

3) The superiority of LY231514/cisplatin over cisplatin monotherapy was maintained in the fully supplemented subgroup.

4) Folic acid and vitamin B12 supplementation also improved the clinical outcome regardless of the treatment arm. The advantage was associated with more cycles delivered in the fully supplemented subgroups.

3.3 FDA's Assessment of JMCH Efficacy

Clinical Issues

The Number of Patients

574 patients were consented and entered; patients deemed eligible were randomized. Of the 456 randomized patients, 228 patients were randomized to the MTA/cisplatin arm, and 226 of these patients received the assigned study drugs. Similarly, 228 patients were randomized to the cisplatin alone arm and 222 of these patients received at least one dose of cisplatin.

Below is a table that illustrates the variation in the number of patients reported as entered and enrolled on the JMCH study and used in the analyses.

	TOTAL	ALIMTA/CISPLATIN	CISPLATIN
Original designed enrollment	280		
Population entered and screened for eligibility (2002 ASCO plenary session presentation)	472		
Entered (consented) in NDA	574		
Entered (consented) in 3/17/2003 Lilly submission	573		
Enrolled (randomized)	456[139]		
Randomized and treated	448		
Fully supplemented + (partially supplemented + not supplemented)		168[140] + 58[141] = 226	163 + 59 = 222
Supplemented with (folic acid + vitamin B12) + not supplemented 3/17/2003 submission	*331 + 117*		
Survival, TTP, TTF, subgroup analyses	448		
Model selection for survival time Cox regression analysis	434		
Eligible for response evaluation	447	225[142]	222
Independent review, 2/13/2002		194	195
Independent review 6/10/2002		197	200

[139] This should be the intent-to-treat population.
[140] This represents a 15% increase over the designed enrollment.
[141] Not supplemented: 32 alimta/cisplatin; 38 cisplatin alone

The Sponsor labeled the patients randomized and treated as the RT population (i.e., 226 MTA/cisplatin; 222 cisplatin). This was *in lieu* of intent to treat population (ITT) (i.e., 228 for both the MTA/cisplatin and cisplatin arms; it was noted that in the published report about the results of the JMCH trial, the population of patients defined as RT was called the ITT population[143]; "intent to treat", "intent-to-treat", and "ITT" were not found in the 25,000 page clinical study report. The table below illustrates the discrepancy between what the protocol states and how the reports were written.

PROTOCOL page number in JMCH study report	STUDY REPORT, ORIGINAL PACKAGE INSERT, JCO ARTICLE page number in JMCH study report
All randomized patients will be evaluated for survival and secondary time to event Efficacy measures. p. 962	All patients in the RT population were included in the analyses of survival and other time-to-event measures.[144] p. 5
All enrolled patients meeting the following criteria will be evaluated for tumor response: • Histologic diagnosis of malignant pleural mesothelioma. • No prior systemic chemotherapy. • No concurrent systemic chemotherapy or radiotherapy. • Presence of unidimensionally and/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	Enrolled patients who met the following criteria were included in the analyses of tumor response rate: • histologic diagnosis ofMPM • no prior systemic chemotherapy • no concurrent systemic chemotherapy or radiotherapy • presence of unidimensionally or bidimensionally measurable disease or both • treatment with at least one dose of LY231514 and cisplatin (Arm A) or one dose of cisplatin (Arm B). p. 5

[142] According to Lilly, "One patient (on the LY/cis arm) did not have measurable disease at baseline and therefore did not meet the criteria for inclusion in the analysis of tumor response."

[143] Vogelzang et al. J Clin Onc. 2003;21:2636-2649

[144] The JMCH study report acknowledges this discrepancy on p. 122.

PROTOCOL page number in JMCH study report	STUDY REPORT, ORIGINAL PACKAGE INSERT, JCO ARTICLE page number in JMCH study report
therapy will be included in the efficacy Analysis. p.962	
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. p. 962	Safety: All patients who received at least one dose of LY231514 or cisplatin (Arm A) or one dose of cisplatin (Arm B) were evaluated for safety by assessments of exposure to study drug, treatment-emergent adverse events, serious adverse events, CTC (Version 2) toxicities for both laboratory and nonlaboratory values, central laboratory analytes, vital sign measurements, and blood transfusions. p. 6
Potential discontinuation from study for both alimta + cisplatin for severe toxicity, except for tinnitus or significant clinical hearing loss (only cisplatin discontinued) p. 940 -942	CRF Alimta: no adjustment of dose Cisplatin: no adjustment, reduction, or omission of dose
While tumor response data as reported by study investigators will be Presented in the final report, the final tumor response rate results will be based on the independently reviewed response data. p. 966-967 For a discrepancy between the assessment of the independent panel and that Of the investigator, the independent panel's assessment	

PROTOCOL page number in JMCH study report	STUDY REPORT, ORIGINAL PACKAGE INSERT, JCO ARTICLE page number in JMCH study report
was to take precedence. p. 107	

The table below lists the reasons why 8 patients did not receive study drug, and thus were not included in the safety analyses. Non-inclusion of these 8 patients is appropriate in the safety analyses because the patients did not receive drug. However, they should be included in an ITT analyses of efficacy.

Table JMCH.12.1. Patients Randomly Assigned Treatment But Not Treated H3E-MC-JMCH

Investigator Site / Patient Number	Treatment Arm	Reason
111-1342	Cisplatin	Inclusion criteria not met
136-1634	Cisplatin	Patient decision
142-1472	Cisplatin	Patient decision
201-2200	Cisplatin	Patient decision
213-2133	Cisplatin	Inclusion criteria not met
301-3161	LY/cis	Discontinued because of hypertension[1]
510-5109	LY/cis	Death (from study disease)
601-6014	Cisplatin	Patient decision

[1] This patient received hydration, experienced an SAE, and discontinued. Study drug was not administered.

These patients were included in a FDA intent-to-treat survival analyses but not in the safety analyses because they did not receive treatment. This will be provided in FDA's section regarding the survival analysis.

APPEARS THIS WAY
ON ORIGINAL

Below is a table illustrating by country the pleural "mesothelioma" patients who were entered and enrolled. Nineteen percent of the patients enrolled were from the United States; 81% were from outside the United States. Out of the 574 patients consented and entered, 118 were not enrolled on study JMCH. Twenty-nine percent of the entered patients from the United States were not enrolled in the JMCH study; overall 21% of patients entered were not enrolled on the study.

	ENTERED	ENROLLED	% ENROLLED	**% NOT ENROLLED IN STUDY**	% OF PATIENTS ENROLLED IN STUDY AS A WHOLE
United States	122	87	71.31148	**28.68852**	19.10
Germany	90	80	88.88889	11.11111	17.5
France	55	48	87.27273	12.72727	10.5
Argentina	15	11	73.33333	26.66667	2.4
Australia	34	33	97.05882	2.941176	7.2
Belgium	26	18	69.23077	30.76923	3.9
Italy	39	30	76.92308	23.07692	6.6
United Kingdom	31	20	64.51613	35.48387	4.4
Canada	7	6	85.71429	14.28571	1.3
Czech Republic	6	6	100	0	1.3
Finland	22	19	86.36364	13.63636	4.2
India	16	12	75	25	2.6
Poland	38	31	81.57895	18.42105	6.8
Spain	16	14	87.5	12.5	3.1
Taiwan	2	2	100	0	0.4
Chile	7	5	71.42857	28.57143	1.1
Mexico	25	16	64	36	3.5
Slovakia	3	2	66.66667	33.33333	0.4
Singapore	1	0	0	100	0
Turkey	19	16	84.21053	15.78947	3.5
Total	574	456	79.44251%	**20.55749**	
		Difference (not entered): **118**	Mean: 76.5%		
			Median: 79.3%		

Although specific reasons for not enrolling and randomizing patients were indicated on The ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT form (p. 1179-1181 of the JMCH study report), this source documentation information was not provided in the NDA. In response to a FDA query about the reason the 118 patients entered were not enrolled,[145] Lilly provided the information illustrated in the table below.[146] Again, no source documents were submitted and reviewed.

[145] FDA query sent 8/14/2003; Lilly response received 9/2/2003.

[146] No source documents, i.e., The ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT forms for the patients, were submitted.

MOST IMPORTANT REASON THAT PATIENT WAS NOT ENROLLED ON JMCH	TOTAL NUMBER OF PATIENTS
No histologically proven diagnosis of mesothelioma[147]	7
Non-measurable disease[148]	8
KPS < 70	14
Estimated life expectancy of a least 12 weeks	1
Patient compliance and geographic proximity	3
Adequate organ function: creatinine clearance < 45 ml/min	19
Adequate organ function: elevated liver enzymes	7
Adequate organ function: albumin < 3 g/dL or 2.5 g/dl (after amendment c)	25
Homocysteine level (amendment B)	4
Signed informed consent	1
Prior systemic chemotherapy	2
Serious concomitant systemic disorders	1
Second primary malignancy	1
Inability to interrupt aspirin or other nonsteroidal anti-inflammatory agents	1
Disease which cannot be radiologically imaged	2
Weight loss	1
Patient refusal	13
Early death (before randomization)	8

The reasons for non-inclusion in an ITT analysis given for the 8 randomized but not treated patients were not different than the reasons outlined for the 118 non-enrollees. Also, patients were enrolled, who did not have a histologically proven diagnosis of mesothelioma by independent pathologist review and for whom independent reviewers of the images did not record any measurements of the disease; these were reasons listed for not enrolling patients on study JMCH.

[147] 30 patients were enrolled (randomized and treated), in whom the pathology of malignant mesothelioma was not confirmed by the independent pathologist reviewers.

[148] 20 patients were enrolled (randomized and treated), who both independent reviewers did not record any measurable disease in the images for the patients. 37 patients were enrolled (randomized and treated), who one of the independent reviewers did not record any measurable disease in the images for the patients; in nine of the cases, two out of three independent reviewers did not record any measurable disease.

Cisplatin Exposure in JMCH

In the pre-NDA meeting Briefing Document (scheduled for the January 30, 2002), the proposed Indication for malignant pleural mesothelioma stipulated: '. Also, the proposed Dosage and Administration section of the package insert outlined three regimens: The draft Protocol for treatment, JMFE (submitted April 3, 2002, serial #399), initially contained these regimens. The rationale for the inclusion of the was based on patients who could not tolerate cisplatin. FDA disagreed with the inclusion of two of the three regimens in the label and in the expanded access program. This was because the combination of alimta + cisplatin was reported to increase survival in JMCH and there was no data that showed an increase in survival with alimta alone or the combination of Thus, the FDA did not believe it was appropriate to offer expanded access to alimta alone or the combination of

Later, in an amendment to JMFE (submitted 12/16/2002;), it was stipulated that patients would receive alimta + cisplatin who have been previously treated with cisplatin-based regimen and responded for six months, and who did not have medical contra-indications to receiving more cisplatin, i.e., renal insufficiency, significant neuropathy, ototoxicity and very low left ventricular ejection fraction. Again, all of these reasons did not appear appropriate to exclude cisplatin. First, patients, who have renal insufficiency and cannot have more cisplatin, cannot receive alimta--a drug excreted renally. Second, patients who have a very low left ventricular ejection fraction, which contra-indicated cisplatin, may not tolerate three days of potent corticosteroids--a part of the alimta regimen. Third, patients who have a non-response to prior cisplatin can have cisplatin + alimta in view of the claimed synergy between cisplatin and alimta in an in *vitro model.*

However, the promotion of may have been derived from safety concerns or investigator preferences in JMCH. Review of the dose-intensity tables provided by Lilly in the JMCH study report suggested that overall planned cisplatin dose-intensity was the same as planned alimta dose-intensity (table below). Based on this analysis, it did not appear that alimta was given without cisplatin to a significant extent.

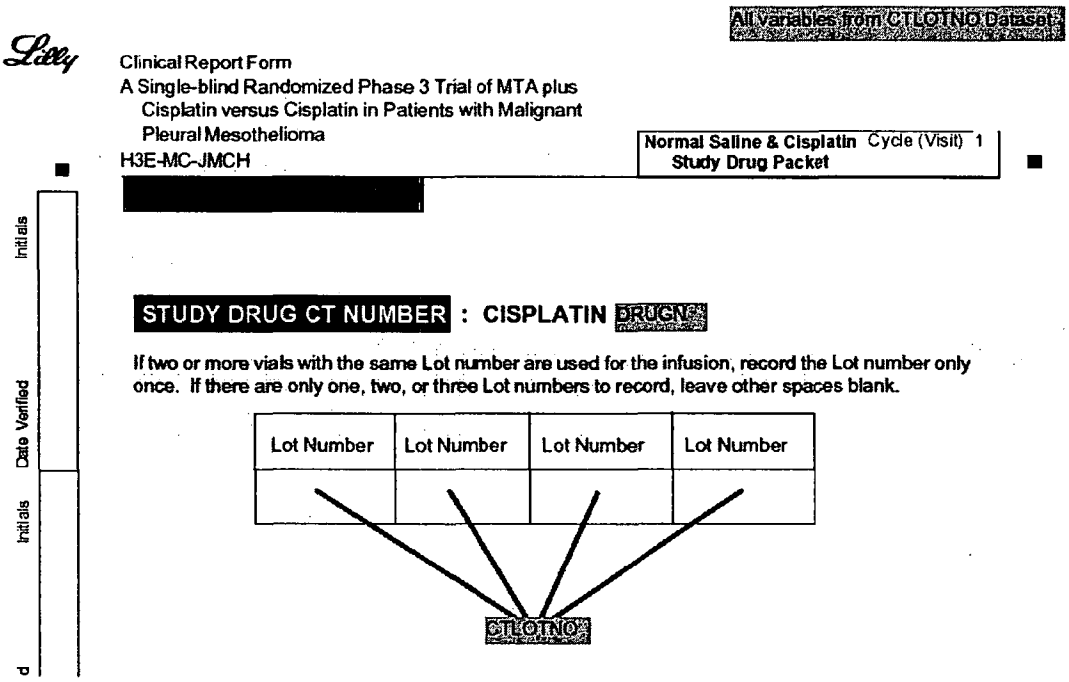
**Table JMCH.12.4. Dose Intensity (DI)
RT Population
H3E-MC-JMCH**

	LY/cis		Cisplatin
Statistics	LY231514	Cisplatin	Cisplatin
Number of Patients	226	226	222
Planned Mean / Patient (mg/m²/week)	166.7	25	25
Delivered Mean / Patient	153.4	23.2	24.1
Percent of planned DI (delivered/planned)	92.0%	92.8%	96.4%

**Table JMCH.12.5. Dose Intensity (DI)
RT Population by Supplementation Status
H3E-MC-JMCH**

	LY/cis				Cisplatin	
	LY231514		Cisplatin		Cisplatin	
Statistics	FS	PS+NS	FS	PS+NS	FS	PS+NS
Number of Patients	168	58	168	58	163	59
Planned Mean / Patient (mg/m²/week)	166.7	166.7	25	25	25	25
Delivered Mean / Patient	154.6	149.7	23.4	22.6	24.1	24.2
Percent of planned DI (delivered/planned)	92.7%	89.8%	93.6%	90.4%	96.4%	96.8%

In Appendix 16.1.10, **Listing of Patients Receiving Test Drug(s) or Investigational Product(s) by Lot or Batch Number (p. 1763-1874),** of the JMCH study report, it appeared that there were several patients who did not have cisplatin lot or batch numbers recorded at baseline and/or at some time during the study. Non-recording of the cisplatin lot number may have been because the site did not record it or the cisplatin lot number was not recorded because cisplatin was not given to the patient. Below is the portion of the CRF where the information was to be recorded.

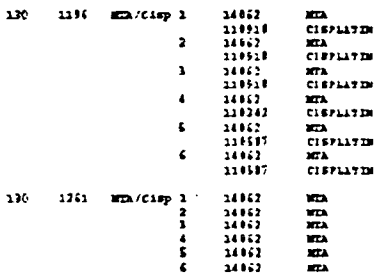


Below is a table of patients on the alimta + cisplatin arm, who the cisplatin lot number was not reported at baseline and throughout the treatment.

INVESTIGATOR SITE	PATIENT #	# OF CYCLES	dose delayed or reduced cycle#-reason for dose delay or reduced
107	1072	4	No
107	1073	6	No
107	1074	1	No
109	1092	1	No
124	1201	2	No
130	1261	6	2,3,6-cisplatin & alimta delayed, creatinine clearance; 5-cisplatin & alimta delayed, neutrophil; 5-alimta reduced, stomatitis
131	1272	4	4-cisplatin & alimta delayed, creatinine clearance
131	1277	6	No
142	1475	2	No

INVESTIGATOR SITE	PATIENT #	# OF CYCLES	dose delayed or reduced cycle#-reason for dose delay or reduced
510	5100	2	2-cisplatin & alimta delayed, anemia
802	8020	2	No
804	8040	1	No

A sample from Appendix 16.1.10 is patient #130-1261 (also, included is patient #130-1196 who had the cisplatin lot numbers recorded).

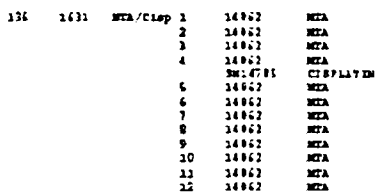


Below is a table of patients on the alimta + cisplatin arm, who the cisplatin lot number was not reported at baseline and the cisplatin lot number was reported in later cycle(s).

INVESTIGATOR SITE	PATIENT #	# OF CYCLES CISPLATIN LOT NUMBER NOT REPORTED	TOTAL # CYCLES	dose delayed or reduced cycle#-reason for dose delay or reduced
130	1266	1st 2 cycles, 6th cycle	6	no
131	1044	1st 2 cycles, 6th cycle	10	no
136	1631	1st 3 cycles, 5th-12th cycle; only 4th cycle with cisplatin	12	4-cisplatin reduced, deafness; 5-12-cisplatin omitted, deafness; 9-alimta delayed, URI
140	1450	1st cycle	2	2-cisplatin & alimta reduced, nausea
251	2550	1st 2 cycles	3	2-cisplatin & alimta reduced, platelet count reduced
510	5103	1st cycle	6	5-cisplatin & alimta reduced, dehydration
554	5516	1st cycle	3	3-cisplatin & alimta

INVESTIGATOR SITE	PATIENT #	# OF CYCLES CISPLATIN LOT NUMBER NOT REPORTED	TOTAL # CYCLES	dose delayed or reduced cycle#-reason for dose delay or reduced
				delayed, creatinine clearance
805	8070	1st cycle	6	no

A sample from Appendix 16.1.10 is patient #136-1631.

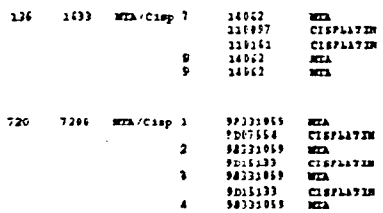


Below is a table of patients on the alimta + cisplatin arm, who the cisplatin lot number was reported at baseline and the cisplatin lot number was not reported in later cycle(s).

INVESTIGATOR SITE	PATIENT #	# OF CYCLES CISPLATIN LOT NUMBER NOT REPORTED	TOTAL # CYCLES	TOTAL # OF MTA+CISPLAT PTS. @ SITE	dose delayed or reduced cycle#-reason for dose delay or reduced
104	1046	2,3,8-11	11	2	no
119	1146	3,4	6	2	no
130	1191	2,3,4	6	4	no
131	1278	2	6	10	2-cisplatin & alimta delayed, creatinine clearance; 3-cisplatin & alimta delayed, white blood count
136	1633	8,9; CYCLES 1-6 were not reported for both cisplatin +alimta.	9	2	no
142	1476	2,3,4,5	5	3	2, 4, 5-cisplatin & alimta delayed, creatinine clearance; 2-cisplatin & alimta reduced, serum creatinine increased
510	5101	2,3	6	8	4-cisplatin & alimta

INVESTIGATOR SITE	PATIENT #	# OF CYCLES CISPLATIN LOT NUMBER NOT REPORTED	TOTAL # CYCLES	TOTAL # OF MTA+CISPLAT PTS. @ SITE	dose delayed or reduced cycle#-reason for dose delay or reduced
					reduced,neutrophil count reduced
720	7200	4	4	7	3-cisplatin & alimta delayed and reduced, vomiting; 4-cisplatin omitted, vomitting
804	8046	3,5	6	6	no

Samples from Appendix 16.1.10 are patients #136-1633 and #720-7200.



The tables suggested that several patients might not have received cisplatin at baseline and/or at some time during the JMCH study. In response to FDA concern about this, Lilly stated that only two patients--#136-1631 and #720-7200 had cisplatin omitted (response dated 9/19/2003). For patient #136-163, Lilly acknowledged that cisplatin was omitted cycles 5 -12. Appendix 16.1.10 indicated that the cisplatin lot number was also not reported for cycles 1-3. By using this appendix, there was no way to tell the difference between cycles that cisplatin was omitted and cycles that the cisplatin lot number was not recorded. Also, Lilly stated that no patients on the alimta/cisplatin arm of study JMCH received ——— at baseline or at any time during the study and that there were no patients on the alimta/cisplatin arm of study JMCH who had alimta omitted and received only cisplatin at baseline or at any time during the study.

In their response submitted 11/6/2003, Lilly stated, "on inspection of Appendix 16.1.10 in the JMCH study report, it might appear that some patients received Alimta but not cisplatin." Additionally, Lilly stated that the cisplatin lot numbers were not collected for these patients and that only two patients had cisplatin omitted in the alimta/cisplatin arm of study JMCH.

In conclusion, the requests for inclusion of regimens of a ——— in the first proposed package insert and Protocol for Treatment were not based on information generated in the pivotal trial, JMCH. Except for the two patients acknowledged by Lilly, Lilly stated that all patients on the alimta + cisplatin arm received both alimta + cisplatin while they were on the JMCH study.

No source documents were provided or reviewed. The FDA statistician used datasets submitted by Lilly on December 6, 2002. The datasets were located in the Electronic Document Room (EDR) of CDER of FDA under the Letter Date "24-OCT-2002" and "6-DEC-2002", respectively. The major data set for the efficacy analysis was "SURVLOCK" which defines the survival time and events.

Survival Analysis of Randomized and Treated Patients

Below are the results of the FDA statistician's survival analysis of study JMCH.

Table 1. Primary Endpoint: Survival for RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Patients dead[a]	145 (64)	159 (72)	95 (57)	103 (63)	50 (86)	56 (95)
Survival time (months)						
Median	12.1	9.3	13.3	10.0	9.5	7.2
(95% CI)	(10.0,14.4)	(7.8, 10.7)	(11.4,14.9)	(8.4, 11.9)	(8.1, 10.8)	(6.5, 9.9)
p-value[b]						
Long-rank	0.021		0.051		0.253	
Wilcoxon	0.028		0.039		0.440	
Hazard Ratio[c]	0.766		0.758		0.798	
95% CI for Hazard Ratio[c]	(0.61, 0.96)		(0.57, 1.0)		(0.54, 1.17)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients were died for different reasons: study disease related, study toxicity, and other causes.

[b] P-value is based on the test results for the two treatment groups.

[c] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

In the randomized and treated (RT) (n=448), the median survivals for alimta/cisplatin and cisplatin alone were 12.1 and 9.3 months, respectively (log-rank, p=0.021); this was a statistically significant increase in median survival of 2.8 months. In the subgroup[149] of the fully folic acid and vitamin B12 supplemented patients (n=331), the median survivals for alimta/cisplatin and cisplatin alone were 13.3 and 10 months, respectively (log-rank, p=0.051); this was a marginally statistically significant increase in median survival of 3.3 months. In the underpowered subgroup of partially folic acid and vitamin B12 supplemented plus never

[149] Lilly tested three models in the prognostic evaluation of survival the optimal parameterization was found to be Model *FS+PS versus NS*. A comparison of Model *FS versus PS+NS* (defined in the statistical analysis plan) had less prognostic power than the alternative parameterization (*FS+PS versus NS*). This finding was based on the fact that Model *FS+PS versus NS* had a smaller p-value for the supplemenatation group factor and a larger log-likelihood value. These results suggested that, with respect to survival, PS patients were more like FS patients than NS patients.

supplemented patients, the median survivals for alimta/cisplatin and cisplatin alone were 9.5 and 7.2 months, respectively (log-rank, p=0.253); although this was a 2.3 month increase in survival, it was not statistically significant. The hazard ratios of 0.766, 0.758, and 0.798, for the respective survival analyses were consistent with regard to a survival benefit in the alimta/cisplatin arm compared to the cisplatin alone arm.

"Intent-to-Treat" Analysis of Survival

There were 8 patients (2 alimta/cisplatin, 6 cisplatin alone) who were randomized and not included in the survival analysis. With 456 randomized patients (304 events, 152 censored), i.e., 448 + 8 patients, the results of the FDA survival analysis were:

INTENT-TO-TREAT	ALIMTA/CISPLATIN (N=153)	CISPLATIN ALONE (N=150)	p-value log-rank
Survival, median (95% CI)	12 months (10, 14.4)	9.3 months (7.8, 10.7)	0.0205

In the intent-to-treat population (n=456), the median survivals for alimta/cisplatin and cisplatin alone were 12 and 9.3 months, respectively (log-rank, p=0.0205); this was a statistically significant increase in median survival of 2.7 months.

The intent-to-treat analysis (with the inclusion of the 8 patients, i.e., n=456) was comparable to the randomized and treated analysis (n=448) of survival.

Confirmed Pathological Diagnosis of Mesothelioma

In the past, expert panels have been set up to review suspected malignant pleural mesothelioma cases. One editorialist wrote about the need for a panel of experts to review pathological material to guarantee the accuracy of diagnosis.[150] The reason for this is three-fold. First, epithelial cell type has been associated with a more favorable prognosis in most large series; the fibrosarcomatous type carries the worst prognosis, and the mixed type is intermediate. Second, it is important to differentiate mesothelioma from adenocarcinoma--tumors with histologic similarities--since it may influence the treatment and the natural history. Adenocarcinomas from primary lung, breast, ovary, stomach, kidney, or prostate cancer frequently metastasize to the pleura and can be extremely difficult to distinguish from epithelial mesothelioma cytologically or histologically. Metastatic adenocarcinoma with extensive pleural involvement may grossly resemble mesothelioma and has been called pseudomesothelioma. Third, sarcomatous mesotheliomas must be distinguished from fibrosarcoma, malignant fibrous histiocytoma, malignant schwannoma, and hemangiopericytoma. Synovial sarcoma and carcinosarcomas,

[150] Jett JR. Malignant pleural mesothelioma. A proposed new staging system. Chest. 1995;108:895-897)

which may also have mixed sarcomatous and epithelial components, usually present as a localized mass in the lung.

In general, mesothelioma is difficult to diagnose, even by expert pathologists. Initial misdiagnosis is common.

In a FDA comment faxed to Lilly on 8/31/2000,[151] the importance of independent pathology review was stated:

> Although all patients may not have sufficient tissue for an independent review of histopathology, the slides should be available for review by an independent pathologist. The rigor of the study, regarding confidence in the histopathological diagnosis, will be decreased without independent review of all cases. In view that only one randomized trial in mesothelioma will be accepted for this indication, the one study in mesothelioma must be strictly performed.

The following were amendments made to the JMCH protocol, regarding pathology and its independent review:

19 June 2000 (~323 out of 574 patients entered on study JMCH at this time)[152]:

> **3.4.2.1. Inclusion Criteria** – Not all patients have sufficient tissue for an independent review, but will still be allowed in our analysis. (p. 1141 of study report JMCH)
>
> Patients may be entered and randomized based on local pathology; however, independent centralized pathology review will be carried out on all patients <u>if feasible</u>. In case of a discrepancy between the assessment of the independent reviewer and the investigator, the assessment of the independent reviewer will take precedence. (p. 1145)

24 January 2001 (~518 out of 574 patients entered on study JMCH at this time):

> Patients may be entered and randomized based on local pathology; however, independent centralized pathology review will be carried out on all patients if feasible. ~~In case of a discrepancy between the assessment of the independent reviewer and the investigator, the assessment of the independent reviewer will take precedence.~~ [153](p. 1166)

[151] This was in response to submission serial #242, dated 7/12/2000).

[152] Lilly met with the FDA on 6/21/2000, This was a follow-up to EOP2 re: mesothelioma indication. One of issues for discussion was whether FDA would accept an interim analysis of secondary endpoints from the mesothelioma trial.

[153] The strikeouts were part of the citation.

The protocol submitted in the JMCH study report stated:

> Histologically proven diagnosis of mesothelioma of the pleura in patients not candidates for curative 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 pathology review will be carried out on all patients if feasible.[154]

On page 959 of the JMCH study report, it was stated that: "\ —— will assay the blood chemistries, homocysteine, and calculated creatinine clearance (CrCl) and will manage the centralized independent pathology review and pharmacokinetic samples."

However, the ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT form[155] indicated that independent centralized pathology review was to be carried out on all patients.

Lilly

WORKSHEET
H3E-MC-JMCH

Fax Entry Criteria Checklist to: Janine Kropf (317-277-3236)

Visit 0
Page 1 of 5

ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT

CONTRACEPTION is ensured through (check one):

- ☐ Sterilization (surgical or radiation-induced)
- ☐ Post-menopausal
- ☐ Oral contraceptives*
- ☐ Diaphragm
- ☐ Sponge* or spermicide*
- ☐ Condom and spermicide*
- ☐ Intra-uterine device (IUD)
- ☐ Contraceptive implant* or Depo-Provera®*
- ☐ Strict abstinence
- ☐ Solitary partner who is vasectomized
- ☐ Not sexually active
- ☐ Not applicable (applies to male patients or prepubertal females)

*Enter description/brand name on the Concomitant Medication page (located behind a separate tab).

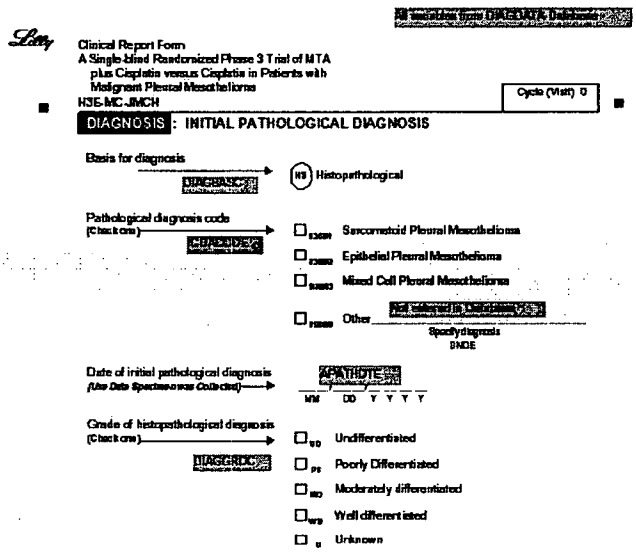
Inclusion Criteria: The answers for items 1-10 must be YES to qualify for study.

Yes No

☐ ☐ 1. Histologically proven diagnosis of mesothelioma of the pleura in patients not candidates for curative 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 pathology review will be carried out on all patients. In case of a discrepancy between the assessment of the independent reviewer and the investigator, the assessment of the independent reviewer will take precedence.

For pathological diagnosis, the case report form (CRF) provided for checking-off of the box. There was no indication on whether the pathological and subtype diagnoses were from the local site or from independent centralized pathology review.

[154] Page 932 of the JMCH study report
[155] Page 1179 of the JMCH study report


Clinical Report Form
A Single-blind Randomized Phase 3 Trial of MTA plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma
H3E-MC-JMCH
Cycle (Visit) 0
DIAGNOSIS : INITIAL PATHOLOGICAL DIAGNOSIS
Basis for diagnosis
Histopathological
Pathological diagnosis code (Check one)
Sarcomatoid Pleural Mesothelioma
Epithelial Pleural Mesothelioma
Mixed Cell Pleural Mesothelioma
Other
Specify diagnosis
Date of initial pathological diagnosis (Use Date Specimen was Collected)
Grade of histopathological diagnosis (Check one)
Undifferentiated
Poorly Differentiated
Moderately differentiated
Well differentiated
Unknown

In response to FDA query, Lilly responded with (dated 1/10/2003): "One of the entry requirements for study JMCH was to have local pathologic confirmation of malignant pleural mesothelioma. This requirement was validated by independent (independent from the site) monitors who were fluent in the local language. In addition, local pathology could be validated by the FDA during site audits."

In response to FDA query, Lilly responded with (dated 2/13/2003): "Regarding DODP's request for pathological confirmation documentation for the patients entered on JMCH, the monitors (independent from the site) verified that the diagnosis of mesothelioma on the Case Report Form (CRF's) matches the diagnosis shown on the local pathology report."

Although the published report of the JMCH study did not mention central review of pathology specimens,[156] the accompanying editorial stated that "Central review of all CT scans and all pathology specimens was performed. This rigorous approach to analysis lends credibility to the study results, especially in a disease for which correct pathologic diagnosis can still be difficult, and for which there has been little uniformity in measuring response to treatment."[157]

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[156] Vogelzang NJ, Rusthoven JJ, Symanowski J, et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636-2644, 2003

[157] Rusch VW. Pemetrexed and Cisplatin for Malignant Pleural Mesothelioma: A New Standard of Care? *Jou*rnal of Clinical Oncology, 21:2629-2630, 2003

The information below, regarding independent central pathology review, was requested from Lilly on 9/2/2003 and the response received by FDA on 9/22/2003.

INDEPENDENT CENTRAL PATHOLOGY REVIEW CATEGORIES	RANDOMIZED AND TREATED, N=448 (%)
Independent review confirmed pathology of malignant mesothelioma	302 (67%)
Independent review suggestive/consistent of malignant mesothelioma	16 (3.6%)
Independent review did not confirm pathology of malignant mesothelioma	30 (6.7%)
Documented as tissue unsatisfactory to confirm pathology	13 (2.9%)
Not feasible to send in samples for independent pathology review	87 (19.4%)

67% of the randomized and treated patients had the diagnosis of mesothelioma confirmed by independent review; 3.6% of the randomized and treated patients' pathology was suggestive of/consistent with malignant mesothelioma. 6.7% of the patients did not have the diagnosis of mesothelioma confirmed. 22.3% of the patients' either had tissue that was unsatisfactory to confirm pathology or it was not feasible to send samples for independent pathology review. In view that only one randomized trial in mesothelioma will be accepted for this indication, the JMCH study in mesothelioma was not strictly performed.

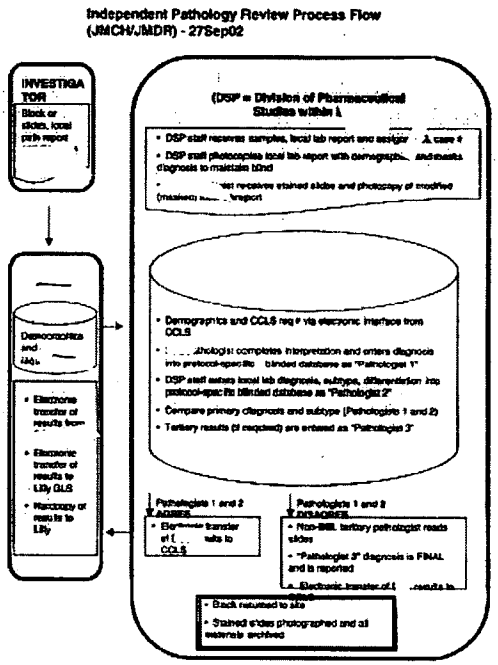
Lilly stated that "no adjudication took place in cases where there was discrepancy between local and centralized pathology reviews."[158]

The information provided on independent pathology review did not take into account the histological subtypes of mesothelioma , i.e., epithelial, sarcomatoid, and mixed. As stated in FDA's BACKGROUND ON MESOTHELIOMA section in this review, *the histological subtype of mesothelioma--a baseline stratification factor in study JMCH--can have impact on prognosis and an imbalance would affect the results of a survival analysis.* FDA requested this

[155] Response received from Lilly dated 9/22/2003.

information, as well as, the charter of the independent pathology review and what responsibilities were charged to the review.[159]

Lilly sent FDA a flow sheet, illustrating the Independent Pathology Review on 12/16/2003. Note the date on the sheet is "27Sep02"--about a month prior to when Rolling submission of NDA began and conflicts with prior amendments and correspondences from Lilly.



Summary of the Independent Pathology Review process:

- Local investigator site: slides or blocks, and local pathology report were sent to ——
- At ——
  — pathologist interprets slide and enters diagnosis into a blinded database--Pathologist 1

  DSP staff enters *local* diagnosis, subtype, differentiation into a blinded database--Pathologist 2

  IF $\text{Diagnosis}_{\text{Pathologist1}} = \text{Diagnosis}_{\text{Pathologist2}} \rightarrow$ results entered

[159] From the JMCH study report (p. 77): — :Analysis of tumor-tissue samples for pathological determination (transported and reported via —

IF $\text{Diagnosis}_{\text{Pathologist1}} \neq \text{Diagnosis}_{\text{Pathologist2}} \rightarrow$ Pathologist 3 reads slides$\rightarrow$ $\text{Diagnosis}_{\text{Pathologist3}} \rightarrow$ FINAL

In Lilly's response (dated 9/22/2003) to FDA query, a statement was made that "no adjudication took place in cases where there was discrepancy between local and centralized pathology reviews". According to the Independent Pathology Review Process Flow outlined above, it appears that the determination by Pathologist 3 was the final diagnosis if there was a discrepancy between local and Pathologist 1 (review pathologist).

Below is the analysis of mesothelioma subtype derived from independent pathology review submitted by Lilly on 12/16/2003. This analysis is on patients whose diagnosis of mesothelioma was confirmed and the mesothelioma subtype was confirmed or determined after independent review. *21% of the 302 confirmed mesothelioma patients (alimta/cisplatin: 24%, 37 out of 153 confirmed; cisplatin alone: 18%, 27 out 149 confirmed) had their subtype changed from the designation determined at the investigators' site.*

153 patients on the alimta/cisplatin arm had the diagnosis of mesothelioma confirmed by independent pathology review; 149 patients on the cisplatin alone arm had the diagnosis confirmed.

Folic acid and vitamin B12 supplement statuses were balanced on both arms in confirmed mesothelioma pathology patients (table below).

FOLIC ACID/VITAMIN B12 SUPPLEMENT STATUS	ALIMTA/CISPLATIN	CISPLATIN ALONE
FS	111	108
NS	20	27
PS	22	14
total	153	149

Stage was balanced on both arms in confirmed mesothelioma pathology patients (table below).

STAGE	ALIMTA/CISPLATIN	CISPLATIN ALONE
Ia	6	4
1b	1	4
II	26	23
III	47	45
IV	73	72
?		1
total	153	149

Gender was balanced on both arms in confirmed mesothelioma pathology patients (table below).

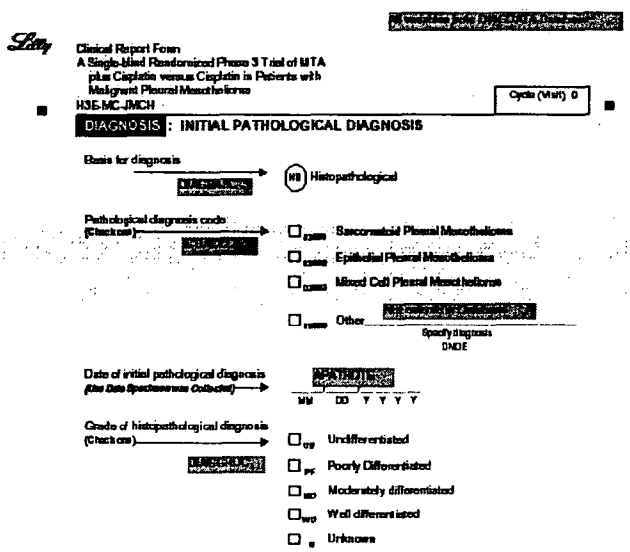
GENDER	ALIMTA/CISPLATIN	CISPLATIN ALONE
female	26 (17%)	25 (17%)
male	127 (83%)	124 (83%)
total	153	149

Confirmed Pathological Diagnosis of Mesothelioma Subtypes

The table below illustrates the list of pathological diagnoses entered from the investigators' site from patients with confirmed mesothelioma. The independent review consolidated the varied mesothelioma diagnoses to subtypes of epithelial, mixed, and sarcomatoid.

PATHOLOGIC DIAGNOSIS	INVESTIGATOR'S		INDEPENDENT REVIEW	
	Alimta/cisplatin	cisplatin alone	alimta/cisplatin	Cisplatin alone
Epithelial Pleur. Meso	107	107	130	127
Mixed Cell Pleur. Meso	27	22	15	13
Sarcomatoid Pleur. Meso	10	10	8	9
Biphasical Pleur. Meso	1	2		
Meso Fibrosum Cellular		1		
Neop M, Meso	5	3		
Papillar Pleur. Meso		1		
Pleur. Meso		1		
Poorly Differentiated Carcinoma		1		
Tubulo-Papillar, Spindle Cell		1		
Meso Malignum	1			
Other	1			
Spindle and Epitheloid	1			
total	153	149	153	149

None of the results of the independent pathology subtype review and diagnoses were recorded in the DIAGDATA database (the CRF page is below) and there was no "blank" to record the information on the CRF.


Lilly

Clinical Report Form
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H3E-MC-JMCH

Cycle (Visit) 0

DIAGNOSIS : INITIAL PATHOLOGICAL DIAGNOSIS

Basis for diagnosis → (HI) Histopathological

Pathological diagnosis code (Check one) →
- Sarcomatoid Pleural Mesothelioma
- Epithelial Pleural Mesothelioma
- Mixed Cell Pleural Mesothelioma
- Other
  Specify diagnosis
  DNOE

Date of initial pathological diagnosis (the Date Specimen was Collected) → PATHDT
MM DD Y Y Y Y

Grade of histopathological diagnosis (Check one) →
- Undifferentiated
- Poorly Differentiated
- Moderately differentiated
- Well differentiated
- Unknown

37 alimta/cisplatin patients had their mesothelioma subtype changed or determined after independent pathology review; 27 cisplatin alone had the subtype changed or determined.

The table below illustrates the pattern of change in or determination of subtype diagnoses from the investigator to the independent review for the alimta/cisplatin arm.

CHANGE IN PATHOLOGY FROM INVESTIGATOR TO INDEPENDENT REVIEW

investigator's pathology	independent review pathology	alimta/cisplatin
Mixed Cell Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	17
Neop M, Meso	Malign. Meso, Epithelial Type, Pleur.	5
Sarcomatoid Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	3
Spindle and Epitheloid	Malign. Meso, Epithelial Type, Pleur.	1
Other	Malign. Meso, Epithelial Type, Pleur.	1
Biphasical Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	1

investigator's pathology	independent review pathology	alimta/cisplatin
Epithelial Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	3
Meso Malignum	Malign. Meso, Mixed Type, Pleur.	1
Sarcomatoid Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	2
Epithelial Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	1
Mixed Cell Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	2

The table below illustrates the pattern of change in or determination of subtype diagnoses from the investigator to the independent review for the cisplatin alone arm.

CHANGE IN PATHOLOGY FROM INVESTIGATOR TO INDEPENDENT REVIEW

investigator's pathology	independent review pathology	cisplatin alone
Biphasical Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1
Mixed Cell Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	12
Neop M, Meso	Malign. Meso, Epithelial Type, Pleur.	2
Neop M, NOS	Malign. Meso, Epithelial Type, Pleur.	1
Papillar Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1
Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1
Poorly Differentiated Carcinoma	Malign. Meso, Epithelial Type, Pleur.	1
Sarcomatoid Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	2
Tubulo-Papillar, Spindle Cell	Malign. Meso, Epithelial Type, Pleur.	1
Biphasical Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	1
Epithelial Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	2
Meso Fibrosum Cellular	Malign. Meso, Mixed	1

	Type, Pleur.	
Mixed Cell Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	1

In both treatment arms, independent pathology review shifted more patients to the epithelial mesothelioma subtypes or good prognosis subtype. There was a moderate decrease in the mixed subtype or intermediate prognosis subtype. There was minimal change in the sarcomatoid subtype or poor prognosis subtype.

The two tables below illustrate the effect on prognosis due to the change in mesothelioma subtype from the investigators's site diagnosis to the independent pathology review diagnosis. Although there is an overall improvement in subtype prognosis, the changes appear balanced with respect to both treatment arms.

investigator's pathology	Independent review pathology	Alimta/cisplatin	change in prognosis or prognosis determination
Mixed Cell Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	17	intermediate • good
Neop M, Meso	Malign. Meso, Epithelial Type, Pleur.	5	good
Sarcomatoid Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	3	poor• good
Spindle and Epitheloid	Malign. Meso, Epithelial Type, Pleur.	1	intermediate• good
Other	Malign. Meso, Epithelial Type, Pleur.	1	good
Biphasical Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	1	unchanged
Epithelial Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	3	good • intermediate
Meso Malignum	Malign. Meso, Mixed Type, Pleur.	1	intermediate
Sarcomatoid Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	2	poor • intermediate
Epithelial Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	1	good• poor
Mixed Cell Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	2	intermediate • poor

Investigator's pathology	Independent review pathology	cisplatin	change in prognosis or prognosis determination
Biphasical Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1	intermediate • good
Mixed Cell Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	12	intermediate• good
Neop M, Meso	Malign. Meso, Epithelial Type, Pleur.	2	good
Neop M, NOS	Malign. Meso, Epithelial Type, Pleur.	1	good
Papillar Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1	unchanged
Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1	good
Poorly Differentiated Carcinoma	Malign. Meso, Epithelial Type, Pleur.	1	good
Sarcomatoid Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	2	poor• good
Tubulo-Papillar, Spindle Cell	Malign. Meso, Epithelial Type, Pleur.	1	intermediate • good
Biphasical Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	1	unchanged
Epithelial Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	2	good• intermediate
Meso Fibrosum Cellular	Malign. Meso, Mixed Type, Pleur.	1	intermediate
Mixed Cell Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	1	intermediate • poor

Survival Analyses of Confirmed Mesosthelioma Pathology

On page 962 of the JMCH study report was the following statement:

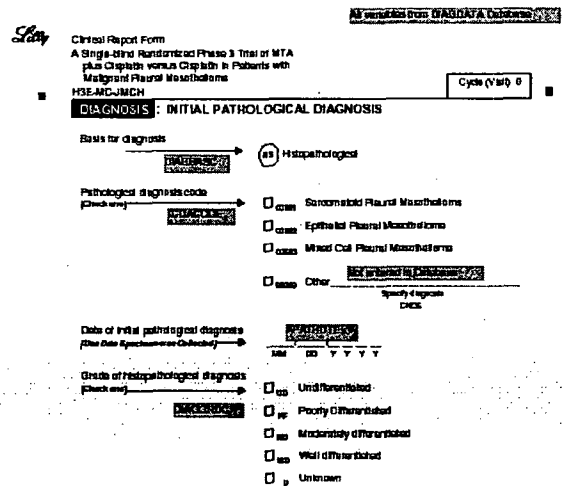
> "Because there may be a discrepancy between the pathological diagnosis assessment of the independent reviewer and the investigator, data analysis will also be performed on all patients whose diagnoses were confirmed by the independent reviewer."

This analysis was not in the JMCH study report. Below is that analysis:

In the 9/22/2003 Lilly response, the following directions were provided in order that a survival analysis of the mesothelioma confirmed patients who were the randomized and treated and the fully folic acid/vitamin B12 supplemented on study JMCH.

> **In Stage A of the Alimta mesothelioma NDA, there is a SAS data file titled, "LABRESLT.XPT". This file is located in the Stage A of the NDA as follows:**
>
> **N21462**
> **CRT**
> **datasets**
> **JMCH**
> **LABRESLT.XPT**
>
> **Column 13 of this data file is titled TESTCODE. The test code for the diagnosis is "P14". In the rows where the TESTCODE equals "P14", the code for the diagnosis can be found in Column 20 titled "CHLBRSLT". The table below provides descriptions for the diagnosis.**

As stated above, it is noted that the CRF page for INITIAL PATHOLOGICAL DIAGNOSIS did not indicate whether or not the diagnosis was the investigator's, independent reviewer's, or confirmed. Also, the CRF page LABORATORY VALUES (this page has the same SAS data file name and data file titles as the directions, i.e., LABRESLT, TESTCODE, CHLBRSLT) did not have a "blank" for pathological diagnosis nor did it indicate whether or not the diagnosis is the investigator's, independent reviewer's, or confirmed. The pages are below.



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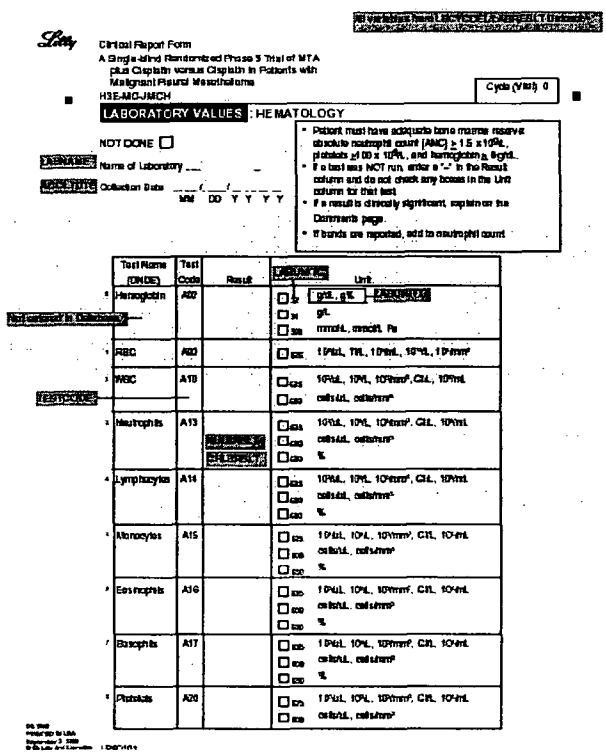
DIAGNOSIS : INITIAL PATHOLOGICAL DIAGNOSIS

Basis for diagnosis
DIAGBASIS
Histopathological

Pathological diagnosis code
(Check one)
DIAGCODE
Sarcomatoid Pleural Mesothelioma
Epithelial Pleural Mesothelioma
Mixed Cell Pleural Mesothelioma
Other
Specify diagnosis
DIAGS

Date of initial pathological diagnosis
(The Date Specimen was Collected)
DIAGDAT
MM DD Y Y Y Y

Grade of histopathological diagnosis
(Check one)
DIAGGRADE
Undifferentiated
Poorly Differentiated
Moderately differentiated
Well differentiated
Unknown



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Cycle (Visit) 0

LABORATORY VALUES : HEMATOLOGY

- Patient must have adequate bone marrow reserve: absolute neutrophil count (ANC) ≥ 1.5 x 10⁹/L, platelets ≥ 100 x 10⁹/L, and hemoglobin ≥ 9g/dL.
- If a test was NOT run, enter a "-" in the Result column and do not check any boxes in the Unit column for that test.
- If a result is clinically significant, explain on the Comments page.
- If bands are reported, add to neutrophil count.

NOT DONE
LABNAME Name of Laboratory
LABDATE Collection Date MM DD Y Y Y Y

	Test Name (LBLBE)	Test Code	Result	Unit
*	Hemoglobin	A02		g/L, g/dL
				g/L
				mmol/L, mmol/L Fe
*	RBC	A03		10⁶/uL, TPL, 10⁶/mL, 10¹²/L, 10⁶/mm³
*	WBC	A10		10⁹/uL, 10³/L, 10³/mm³, Cl/L, 10³/mL
				cells/uL, cells/mm³
*	Neutrophils	A13		10⁹/uL, 10³/L, 10³/mm³, Cl/L, 10³/mL
				cells/uL, cells/mm³
				%
*	Lymphocytes	A14		10⁹/uL, 10³/L, 10³/mm³, Cl/L, 10³/mL
				cells/uL, cells/mm³
				%
*	Monocytes	A15		10⁹/uL, 10³/L, 10³/mm³, Cl/L, 10³/mL
				cells/uL, cells/mm³
				%
*	Eosinophils	A16		10⁹/uL, 10³/L, 10³/mm³, Cl/L, 10³/mL
				cells/uL, cells/mm³
				%
*	Basophils	A17		10⁹/uL, 10³/L, 10³/mm³, Cl/L, 10³/mL
				cells/uL, cells/mm³
				%
*	Platelets	A20		10⁹/uL, 10³/L, 10³/mm³, Cl/L, 10³/mL
				cells/uL, cells/mm³

For the randomized and treated-mesothelioma confirmed patients, the results of the FDA survival analysis were:

RT-MESOTHELIOMA CONFIRMED	ALIMTA/CISPLATIN (N=153)	CISPLATIN ALONE (N=150)	p-value log-rank Wilcoxon
Survival, median (95% CI)	13 months (10.8, 14.8)	10.2 months (8, 12)	0.066 0.101

In the randomized and treated (RT) (n=303), the median survivals for alimta/cisplatin and cisplatin alone were 13 and 10.2 months, respectively (log-rank, p=0.066); this was a marginally statistically significant increase in median survival of 2.2 months.

For the fully folic acid/vitamin B12 supplemented-mesothelioma confirmed patients, the results of the FDA survival analysis were:

FOLIC ACID/VITAMIN B12 SUPPLEMENTED-MESOTHELIOMA CONFIRMED	ALIMTA/CISPLATIN (N=111)	CISPLATIN ALONE (N=109)	p-value log-rank Wilcoxon
Survival, median (95% CI)	14.4 months (12.1, 15.7)	10.3 months (8, 12.2)	0.058 0.045

In the subgroup of the fully folic acid and vitamin B12 supplemented patients (n=220), the median survivals for alimta/cisplatin and cisplatin alone were 14.4 and 10.3 months, respectively (log-rank, p=0.058); this was a marginally statistically significant increase in median survival of 4.1 months.

Below are the results of the FDA statistician's gender survival analysis of study JMCH.

Table 10. Primary Endpoint: Survival Time for Subgroup Analyses in RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Multivariate Analysis						
p-value[a]						
Treatment	0.011		0.008		0.995	
Gender	0.489		0.483		0.998	
Treatment * Gender	0.072		0.035		0.604	
Hazard Ratio (95% CI)[a]						
Treatment	0.480 (0.27, 0.84)		0.381 (0.19, 0.78)		1.003 (0.40, 2.51)	
Gender	0.867 (0.58 1.30)		0.833 (0.50, 1.39)		0.999 (0.52, 1.94)	
Treatment * Gender	1.759 (0.95, 3.25)		2.305 (1.06, 5.01)		0.766 (0.28, 2.10)	
Male						
Total number of patients	184	181	136	134	48	47
Patients with event[b]	124 (67)	130 (72)	82 (60)	85 (63)	42 (87)	45 (96)
Survival time (months)						
Median	11.0	9.4	12.8	10.4	9.85	7.1
(95% CI)	(9.4, 13.3)	(7.9, 10.8)	(9.9, 14.6)	(8.7, 13.2)	(8.1, 11.0)	(6.5, 9.9)
p-value[c]						
Long-rank	0.176		0.388		0.219	
Wilcoxon	0.233		0.390		0.343	
Hazard Ratio (95% CI)[d]	0.843 (0.66, 1.08)		0.875 (0.65, 1.18)		0.767 (0.50, 1.17)	
Female						
Total number of patients	42	41	32	29	10	12
Patients with event[b]	21 (50)	29 (71)	13 (41)	18 (62)	8 (80)	11 (92)
Survival time (months)						
Median	15.7	7.5	18.9	7.4	8.2	9.3
(95% CI)	(10.6,25.8)	(5.8, 11.9)	(15.3, -)	(5.5, 12.2)	(5.4, 20.6)	(5.7, 12.0)
p-value[c]						
Long-rank	0.012		0.010		0.878	
Wilcoxon	0.008		0.003		0.913	
Hazard Ratio (95% CI)[d]	0.479 (0.27, 0.85)		0.381 (0.18, 0.79)		0.927 (0.36, 2.42)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Multivariate analysis is based on a multivariate Cox regression model with treatment, covariate, interaction.

[b] Patients were died by different reasons: study disease related, study toxicity, and other causes.

[c] P-value is based on the test results for the two treatment groups.

[d] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

In the multivariate analysis, there was an interaction of treatment and gender that was marginally significant in the randomized and treated population (p=0.072); in the fully folic acid/vitamin B12 supplemented population, this interaction was statistically significant (p=0.035); the interaction was not statistically significant for the partially supplemented/never supplemented population (p=0.604).

In the female subgroup, the analysis showed that alimta/cisplatin was favored over cisplatin alone in the randomized and treated population and the fully folic acid/vitamin B12 supplemented population (log-rank: p-=0.012 and p=0.010, respectively); although there was a trend in favor of the alimta/cisplatin arm, it was not significant in the partially supplemented÷never supplemented population. Although the male population was four-fold greater than the female population (i.e., more power), there were trends in favor of alimta/cisplatin in all the treatment populations but none was statistically significant.

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Below are the results of the FDA statistician's race survival analysis of study JMCH.

Table 11. Primary Endpoint: Survival Time for Subgroup Analyses in RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Multivariate Analysis						
p-value[a]						
Treatment	0.581		0.566		0.114	
Race	0.674		0.821		0.478	
Treatment * Race	0.901		0.238		0.173	
Hazard Ratio (95% CI)[a]						
Treatment	0.802 (0.37, 1.76)		1.339 (0.49, 3.63)		0.274 (0.06, 1.37)	
Race	0.881 (0.49, 1.59)		1.100 (0.48, 2.51)		0.734 (0.31, 1.72)	
Treatment * Race	0.949 (0.42, 2.16)		0.535 (0.19, 1.51)		3.158 (0.60, 16.52)	
Caucasian						
Total number of patients	204	206	150	153	54	53
Patients with event[b]	132 (65)	147 (71)	84 (56)	56 (63)	48 (89)	50 (94)
Survival time (months)						
Median	12.2	9.3	13.3	10.2	9.3	7.2
(95% CI)	(10.1,14.4)	(7.8, 10.8)	(12.1,15.3)	(8.5, 12.2)	(7.1, 10.8)	(6.4, 10.7)
p-value[c]						
Long-rank	0.024		0.026		0.487	
Wilcoxon	0.030		0.021		0.693	
Hazard Ratio (95% CI)[d]	0.762 (0.60, 0.97)		0.717 (0.54, 0.96)		0.868 (0.58, 1.29)	
Others						
Total number of patients	22	16	18	10	4	6
Patients with event[b]	13 (59)	12 (75)	11 (61)	6 (60)	2 (50)	6 (100)
Survival time (months)						
Median	9.0	8.4	8.8	9.55	17.2	8.0
(95% CI)	(6.7, 17.2)	(6.6, 12.9)	(6.2, 16.0)	(6.6, -)	(9.8, -)	(6.4, 10.7)
p-value[c]						
Long-rank	0.715		0.619		0.093	
Wilcoxon	0.894		0.596		0.077	
Hazard Ratio (95% CI)[d]	0.863 (0.39, 1.90)		1.291 (0.47, 3.53)		0.159 (0.02, 1.36)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Multivariate analysis is based on a multivariate Cox regression model with treatment, covariate, interaction.

[b] Patients were died by different reasons: study disease related, study toxicity, and other causes.

[c] P-value is based on the test results for the two treatment groups.

[d] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

In multivariate analysis, there was no interaction of treatment and race that was statistically significant for the randomized and treated population, fully folic acid/vitamin B12 supplemented population, and partially supplemented+never supplemented population (p-values: 0.901, 0.238, 0.173, respectively).

In the white subgroup, the analysis showed that alimta/cisplatin was favored over cisplatin alone in the randomized and treated population and the fully folic acid/vitamin B12 supplemented population (log-rank: p-=0.024 and p=0.026, respectively); although there was a trend in favor of the alimta/cisplatin arm, it was not significant in the partially supplemented+never supplemented population (p=0.487). There was a trend in favor of alimta/cisplatin in the randomized and treated populations for the non-white subgroup; in the fully supplemented group, the trend was in favor of the cisplatin alone arm; the never supplemented group was marginally statistically significant (p=0.093).

Age Survival Analysis

Below are the results of the FDA statistician's age survival analysis of study JMCH.

Table 12. Primary Endpoint: Survival Time for Subgroup Analyses in RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Multivariate Analysis						
p-value[a]						
Treatment	0.410		0.546		0.448	
Age (< 65 years)	0.584		0.621		0.556	
Treatment * Age	0.447		0.453		0.950	
Hazard Ratio (95% CI)[a]						
Treatment	0.860 (0.60, 1.23)		0.875 (0.57, 1.35)		0.781 (0.41, 1.48)	
Age (< 65 years)	0.915 (0.67, 1.26)		0.906 (0.61, 1.34)		0.845 (0.48, 1.48)	
Treatment * Age	0.836 (0.52, 1.33)		0.804 (0.46, 1.42)		1.026 (0.46, 2.30)	
Age (< 65 years)						
Total number of patients	143	136	107	97	36	39
Patients with event[b]	88 (61)	95 (70)	57 (53)	58 (60)	31 (86)	37 (95)
Survival time (months)						
Median	13.3	10.2	14.7	10.8	9.4	9.3
(95% CI)	(10.7, 15.7)	(8.4, 11.9)	(11.7, 17.6)	(8.7, 12.7)	(7.9, 14.0)	(6.6, 12.0)
p-value[c]						
Long-rank	0.020		0.052		0.277	
Wilcoxon	0.076		0.079		0.643	
Hazard Ratio (95% CI)[d]	0.704 (0.53, 0.95)		0.693 (0.48, 1.00)		0.760 (0.46, 1.25)	
Age (≥ 65 years)						
Total number of patients	83	86	61	66	22	20
Patients with event[b]	57 (69)	64 (74)	38 (62)	45 (78)	19 (86)	19 (95)
Survival time (months)						
Median	10.0	7.5	12.2	8.7	9.7	6.45
(95% CI)	(8.3, 12.9)	(6.5, 10.4)	(7.9, 14.4)	(6.8, 14.2)	(5.1, 12.8)	(4.2, 9.3)
p-value[c]						
Long-rank	0.376		0.503		0.457	
Wilcoxon	0.186		0.311		0.418	
Hazard Ratio (95% CI)[d]	0.850 (0.59, 1.22)		0.862 (0.56, 1.33)		0.783 (0.41, 1.49)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.
[a] Multivariate analysis is based on a multivariate Cox regression model with treatment, covariate, interaction.
[b] Patients were died by different reasons: study disease related, study toxicity, and other causes.
[c] P-value is based on the test results for the two treatment groups.
[d] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

The comparison were for age < 65 years and age ≥ 65 years. In the multivariate analysis, there was no interaction of treatment and age that was statistically significant for the randomized and treated population, fully folic acid/vitamin B12 supplemented population, and partially supplemented+never supplemented population (p-values: 0.447, 0.453, 0.95, respectively).

In the subgroup age (< 65 years), the analysis showed that alimta/cisplatin was favored over cisplatin alone in the randomized and treated population and the fully folic acid/vitamin B12 supplemented population (log-rank: p-=0.02 and p=0.052, respectively); there was no trend in favor of the alimta/cisplatin arm in the partially supplemented+never supplemented population (p=0.277). There were trends in favor of alimta/cisplatin in all the treatment populations for the subgroup of age (≥ 65 years), but none were statistically significant (p-values: 0.376, 0.503, and 0.457, respectively);

Summary of the FDA's Survival Analyses of Study JMCH

FDA SURVIVAL ANALYSES OF STUDY JMCH

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Randomized and treated (n=448)	12.1 months	9.3 months	0.021
Fully folic acid/vitamin B12 supplemented (n=331))	13.3 months	10 months	0.051
Partial supplemented + never supplemented (n=117)	9.5 months	7.2 months	0.253
Intent-to-treat (n=456)	12 months	9.3 months	0.0205
Confirmed mesothelioma pathology Randomized and treated (n=303)	13 months	10.2 months	0.066
Confirmed mesothelioma pathology Fully folic acid/vitamin B12 supplemented (n=220)	14.4 months	10.3 months	0.058
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388
Race White	12.2 months	9.3 monts	0.024

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Randomized and treated (n=410)			
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white Fully folic acid/vitamin B12 supplemented (n=28)	8.8 months	9.55 months	0.619
Age < 65 years Randomized and treated (n=279)	13.3 months	10.2 months	0.02
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The overall survival analyses of the randomized and treated and the intent-to-treat populations demonstrated a statistically significant improvement in survival in favor of the alimta/cisplatin arm. In the fully folic acid/vitamin B12 supplemented group, the alimta/cisplatin arm was favored and was marginally statistically significant. Sixty-seven percent of the patients enrolled on study had pathologically confirmed mesothelioma; in the confirmed mesothelioma subset, survival analyses of the randomized and treated and the fully folic acid/vitamin B12 supplemented groups demonstrated a marginally significant survival advantage in favor of the alimta/cisplatin arm. The under-powered female subgroup demonstrated in randomized and treated and the fully folic acid/vitamin B12 supplemented groups a statistically significant

survival advantage in favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm. The white subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the randomized and treated group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age ≥ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

IN CONCLUSION, alimta/cisplatin has satisfactorily demonstrated a consistent survival advantage compared to cisplatin alone in patients with pleural malignant mesothelioma in one randomized, single-blinded study.

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3.4 FDA's Assessment of Tumor Response in Study JMCH

Introduction

The Role of Lilly and —

At Lilly's request, — provided medical imaging core laboratory services in support of Protocol JMCH. — was contracted to collect, quality control and translate Computerized Tomography (CT) scans obtained on patients enrolled in this trial. Additionally, — was to perform preliminary lesion quantitation, program a Computer Assisted Masked Read (CAMR) system and conduct a blinded read of trial-related images. Two readers reviewed the data and a third reader functioned as an adjudicator to review any discrepancies in the Best Overall Response. The CAMR for this study consisted of two separate sessions, each of which was designed to derive an interpretation in an unbiased fashion.

— was sent directly to Lilly in Indianapolis. Lilly forwarded all of the imaging data to — A total of 428 patients were received which included 3588 timepoints, 1659 timepoints were quantitated. All CT scans obtained on patients enrolled in Protocol JMCH were read by two readers who had no knowledge of patient identity, medical history or treatment group. If either reader disagreed a third reader (adjudicator) was used to read the patients. His decision was final. The readers were oriented to the CAMR process by — and Lilly personnel. The reader was responsible for reading all two CAMR sessions.

Two independent readers and an Adjudicator were selected for Protocol JMCH. The two readers — MD, who was a radiologist employed by — and — MD, who was a pulmonologist employed by the — were recommended by Lilly. — MD, a radiologist at the — was the adjudicator for this study. All reads took place in the — headquarters in — on the dates indicated below:

JMCH Read Dates

— READ DATES	NO. PTS READ	/ READ DATES	NO. PTS READ	/ READ DATES	NO. PTS READ
30-Mar-2001	32	30-Mar-2001	13	11-Aug-2001	22
20-Apr-2001	6	16-May-2001	66	15-Dec-2001	54
07-Jun-2001	61	26-Jul-2001	84	12-May-2002	7
31-Jul-2001	Blank in report	03-Oct-2001	84		
25-Sep-2001	62	29-Nov-2001	144		
12-Nov-2001 13-Nov-2001	98	25-Feb-2002	6		
05-Dec-2001	68				
12-Apr-2001	6				

Exports were sent to Lilly in SAS format on the following dates:

08-Aug-2001 sample
14-Aug-2001
20-Dec-2001
18-Jan-2002
14-May-2002[160]

The Role of the FDA

In consultation with of Dr. George Mills (OND/ODEVI/DTBOP), radiologist, images were reviewed from study JMCH.

[redacted] loaded the independent review database on the imaging review system in Dr. Mill's office. The system was fully functional and presented the available CT scans and the independent review findings.

Dr. Mills and the Medical Officer (FDA Imaging Reviewers) reviewed subject image files during multiple review sessions. The Medical Officer chose the cases for review from a list of subjects (Desk copy Lilly list of all responders by study site [10/22/2003]) for each CDER imaging review session. In the course of the review, the Medical Officer identified the subject case numbers and Dr. Mills selected the case by the stated number from the imaging dataset and independently interpreted the images for tumor burden and response for the various time points. These assessments were correlated with the independent reviewer assessments documented in the imaging database.

The focus of the FDA Imaging Review was on the Lilly list of alimta + cisplatin responders. The FDA believed that these were the protocol-specified responders. For quality assurance reasons, review of the cisplatin alone arm would have required review of all the images from that arm; time limitations for the review restricted the review for response to the alimta + cisplatin arm. For purposes of comparison, the cisplatin alone responders will be referred to as Listed responders and not FDA confirmed responders.

With regard to the independent reviewers' evaluation in the database, the FDA imaging review included review of the measurements of lesions recorded by the independent reviewers, cursory calculations of baseline and follow-up evaluations for response, sites of disease evaluation, cycle by cycle evaluation of response by each independent reviewer, and overall response determination. The review of the images for response included: a) focusing on evaluation timepoints that the independent reviewers scored a response, and b) confirmation of response, or progressive disease.

[160] The ASCO Plenary Session, where the results of JMCH were presented, was on May 20, 2002.

The Medical Officer received from Lilly a laptop that contained the —— —— of the independent reviewers' evaluations. This was not a searchable database. The information in the database was used: a) to do response calculations from the measurements recorded by the independent reviewers, b) to identify patients whose images were not contained in the database, c) to compare the Lilly list of alimta + cisplatin responders with the overall response determination by the independent reviewers of alimta + cisplatin responders, d) to identify, in all cases, the type of measureable disease evaluated by the independent reviewers, i.e., unidimensional and/or bidimensional disease, e) to identify cases who the independent reviewer(s) did not record measurements of disease, and f) to identify cases that the independent reviewer(s) evaluated metastatic disease, i.e., liver metastases. There was no verification of the time of response confirmation, i.e., the difference in the dates of response and confirmation of response were not checked.

Also, the Medical Officer supplemented the review with the following items:

Case report forms
Investigator lesion measurements in SITINVOL dataset
Overall response from OVRRESP dataset

Prospectively, the review of the JMCH images was intended to validate alimta + cisplatin arm responders. Retrospectively, due to deficiencies detected, the review involved: a) review of the listed alimta + cisplatin responders, b) review of the independent review-determined alimta + cisplatin responders, c) independent reviewers' assessments of distant metastases, measurability of disease, determinations of unidimensional and bidimensional disease, d) missing patients in the independent review of images, and e) the independent review process.

Missing Images

456 patients were enrolled in JMCH. 448 patients were randomized and treated. According to the final report of the Computer Assisted Masked Read Methodology Report of Protocol JMCH, dated October 28, 2002, [161] imaging data was sent directly to Lilly. Lilly forwarded all of the imaging data to —. Imaging data on a total of 428 patients were received[162]. However, based on the number of patients read by Dr. —, only 397 patients had their images read (the number recorded for Dr. — was 333).

During the review of the 94 alimta + cisplatin responders on the list provided by Lilly, FDA Imaging Reviewers noted that patients #503-5052, #601-6007, and #851-8512 were absent from the imaging database. The entire database of both alimta + cisplatin and cisplatin alone patients was examined. There were 55 additional patients with whole sets of images missing from the imaging database and thus, not reviewed by the independent reviewers. The table below contains the 58 patients with whole sets of images missing from the imaging database.

PATIENT #	ARM [163]	US CITY OR COUNTRY	LISTED AS RESPONDER
101-1017	c	NJ	no
102-1022	c	Pittsburgh	no
104-1043	a	NY	no
107-1074	a	Baltimore	no
109-1092	a	Houston	no
111-1342	c	Turkey	no
111-1354	a	Turkey	no
111-1357	c	Turkey	no
112-1290	c	Czech Republic	no
114-1402	a	Slovakia	no
118-1133	c	Miami	no
124-1201	a	Wisconsin	no
126-1222	c	Colorado	no
136-1634	c	Los Angeles	no
141-1463	c	Louisiana	no
142-1472	c	Cleveland	no
150-1580	a	Czech Republic	no
150-1582	c	Czech Republic	no
201-2187	c	Mexico City	no

[161] —

[162] There has been no audit of the completeness of the images: 1) performed at site, 2) submitted to Lilly, 3) submitted to —, and 4) reviewed by the independent reviewers.

[163] Key a=alimta + cisplatin arm; c=cisplatin alone arm

PATIENT #	ARM [163]	US CITY OR COUNTRY	LISTED AS RESPONDER
201-2191	a	Mexico City	no
201-2200	c	Mexico City	no
213-2133	c	Belgium	no
214-2148	a	Belgium	no
214-2401	c	Belgium	no
301-3159	a	France	no
301-3161	a	France	no
402-4025	a	Germany	no
402-4036	a	Germany	no
409-4164	c	Germany	no
409-4333	c	Germany	no
413-4241	a	Germany	no
413-4243	c	Germany	no
413-4244	a	Germany	no
453-4519	a	India	no
501-5007	a	Italy	no
501-5062	c	Italy	no
502-5017	c	Italy	no
502-5052	a	Italy	yes
502-5054	a	Italy	no
510-5109	a	Australia	no
510-5144	c	Australia	no
513-5121	a	Australia	no
552-5508	a	Argentina	no
558-5537	c	Chile	no
558-5538	a	Chile	no
558-5541	c	Chile	no
601-6005	a	Spain	no
601-6007	a	Spain	yes
601-6008	c	Spain	no
601-6010	c	Spain	no
601-6011	a	Spain	no
601-6014	c	Spain	no
804-8040	a	UK	no
804-8044	a	UK	no
851-8512	a	Poland	yes
412-4221	c	Germany	no
513-5125	c	Australia	no
556-5526	a	Argentina	no

Only three of these cases were listed as responders; the FDA requested these images from Lilly. The independent reviewers did not review these alimta + cisplatin patients who were listed as responders. Patient #851-8512 was a responder by FDA review of images. Patient #502-5052, was not a responder by FDA review of images. The FDA did not review patient #601-6007 because according to a Lilly correspondence about this patient, there was either no baseline scan or baseline scans were incomplete[164].

After FDA request, the scans for the following formerly missing scans (n=26) were provided by Lilly. The independent reviewers did not review these patients' images. The FDA reviewed these images for the presence of measurable disease and liver metastases. The FDA did not evaluate the images for response.

PATIENT#	ARM[165]	IMAGES RECEIVED AFTER REQUEST	MEASURABLE DISEASE/LIVER METS
107-1074	a	received 8/28/2003	yes/no
111-1354	a	Received 8/28/2003	yes/no
111-1357	c	Received 8/28/2003	yes/no
114-1402	a	Received 8/28/2003	yes/no
124-1201	a	received 8/28/2003	yes/no
150-1582	c	received 8/28/2003	NO/no
201-2187	c	received 8/28/2003	yes/no
201-2191	a	received 8/28/2003	yes/no
214-2148	a	received 8/28/2003	yes/no
214-2401	c	received 8/28/2003	yes/no
402-4025	a	received 8/28/2003	yes/space-occupying lesion
402-4036	a	received 8/28/2003	yes/no
409-4164	c	received 8/28/2003	yes/no
413-4241	a	received 8/28/2003	yes/no
413-4243	c	received 8/28/2003	yes/no scans of abdomen
413-4244	a	received 8/28/2003	yes/no
453-4519	a	received 8/28/2003	yes/no
501-5007	a	received 8/28/2003	yes/no
501-5062	c	received 8/28/2003	yes/no
502-5017	c	received 8/28/2003	yes/no
510-5144	c	received 8/28/2003	yes/no
513-5121	a	received 8/28/2003	yes/no
552-5508	a	received 8/28/2003	yes/no
601-6005	a	received 8/28/2003	yes/no scans of liver except for 1 cut of liver
804-8040	a	received 8/28/2003	yes/no
804-8044	a	received 8/28/2003	yes/no

Except for one patient (#150-1582), all of these patients had measurable disease at baseline. One patient did not have the protocol-specified abdominal CT scan and another patient had only one cut of the liver[166]. Only one patient, #402-4025, had a space-occupying lesion in the liver.

[164] Eligibility could not be confirmed on this patient.

[165] Key a=alimta + cisplatin arm; c=cisplatin alone arm

After FDA request, the following missing scans of 30 patients were not provided to the FDA. The presence of measurable disease--an eligibility criterion--could not be verified in these patients. The presence or absence of liver metastases could not be verified in these patients. The independent reviewers did not review these patients' images. No secondary review for disease measurability (and study eligibility) was performed.

PATIENT#	ARM[167]	SPONSOR RESPONSE TO FDA REQUEST FOR SCANS
101-1017	c	scans not available
102-1022	c	scans not available
104-1043	a	scans not available
109-1092	a	scans not available
111-1342	c	patient did not receive drug
112-1290	c	either no baseline scan or baseline scans incomplete
118-1133	c	scans not available
126-1222	c	either no baseline scan or baseline scans incomplete
136-1634	c	patient did not receive drug
141-1463	c	either no baseline scan or baseline scans incomplete
142-1472	c	patient did not receive drug
150-1580	a	either no baseline scan or baseline scans incomplete
201-2200	c	patient did not receive drug
213-2133	c	patient did not receive drug
301-3159	a	scans not available
301-3161	a	patient did not receive drug
409-4333	c	scans not available
502-5054	a	either no baseline scan or baseline scans incomplete
510-5109	a	patient did not receive drug
558-5537	c	either no baseline scan or baseline scans incomplete
558-5538	a	either no baseline scan or baseline scans incomplete
558-5541	c	either no baseline scan or baseline scans incomplete
601-6007	a	either no baseline scan or baseline scans incomplete
601-6008	c	either no baseline scan or baseline scans incomplete
601-6010	c	scans not available
601-6011	a	either no baseline scan or baseline scans incomplete
601-6014	c	patient did not receive drug
412-4221	c	Lilly received scans
513-5125	c	none of the imaging data was digitized--patient was screen failure[168]
556-5526	a	none of the imaging data was digitized--patient was screen failure[169]

[166] These should be protocol violations.

[167] Key a=alimta + cisplatin arm; c=cisplatin alone arm

[168] Patient's lot number for cisplatin was listed on p. 1865 of the JMCH study report.

[169] Patient's lot numbers for alimta and cisplatin were listed on p. 1822 of the JMCH study report.

Below are the numerical values for the reasons the scans were not provided to the FDA. Over 60% of these scans (19 of 30) were not done at baseline, incomplete at baseline, or not available.

REASONS FOR NOT PROVIDING THE FDA (AND INDEPENDENT REVIEWERS WITH THE SCANS)	NUMBER OF PATIENTS WITH MISSING SCANS
either no baseline scan or baseline scans incomplete	11
scans not available	8
patient did not receive drug	8
none of the imaging data was digitized--patient was screen failure	2
Lilly received scans	1

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Subjects with No Disease Measured by Both Independent Reviewers

The following is taken from the final report of the Computer Assisted Masked Read Methodology Report of Protocol JMCH, dated October 28, 2002.[170] The FDA Medical Reviewer inserted the *italics*.

> "Another core laboratory service provided by —— for Protocol H3E-MC-JMCH was the *pre-quantification of lesions on the CT scans*. This function was performed in order to expedite review of lesions during the blinded reads of the CT data. All measurements performed by —— were overread by a physician as part of the blinded read sessions." (page 6)
>
> "Uni-dimensional (rind thickness, drawn manually) and Bi-dimensional (cross product) measurement techniques were employed to measure pleural based disease. —— *was to identify up to nine index lesions for measurement.* An index lesion was defined as one that met certain minimum size criteria for the rind thickness (uni) or lesion diameter (bi)." (page 7)
>
> "The purpose of Session #1 of the JMCH Computer Assisted Masked Read (CAMR) was to provide an overall assessment of each available CT scan for a given patient. This session required an assessment of the overall technical adequacy of the images and definition and characterization of the index lesions to be followed through all other CAMR sessions." (page 9)
>
> "Upon selection of a patient for review, the Screening CT scan was displayed. Once technical adequacy was rated, *the reader was prompted to identify the presence or absence of lesions. If the presence of lesions was indicated, the reader was then to determine the number of index lesions that were present.* The CAMR accepted the designation of up to six (6) index lesions per patient. Index lesions were to be measurable which, by definition, meant that they were to have bidimensional measurements of ≥ 0.8 x 0.8 cm." (page 9)
>
> "Session 1 also requested the identification of the number of "evaluable" lesions present, representing those that were to be visually evaluated during future sessions but did not meeting (sic) *the measurability criterion.* In determining the index lesions and the evaluable non-index lesions, the reader was required to review all ——-generated Regions of Interest (ROIs). *Any ROIs that did not meet the measurability criterion for index lesions were to be deleted by the reader.* After the identification of index and evaluable lesions, Session 1 required the reader to characterize each index lesion. This required the entry of a label, by which each lesion would be identified during subsequent CAMR sessions, and information on the location of each lesion." (page 10)

170 ——

There were 20 cases that both the independent reviewers did not record any measurable disease. *This was important because: 1) eligible patients were required to have measurable lesions with clearly defined margins by computerized tomography (CT) or MRI; 2) pleural effusions were not considered measurable; 3) patients were excluded who had disease which could not be radiologically imaged; and 4) degree of measurability of disease was a stratification factor.* For patient #302-3023, the adjudicator wrote, "Pt failed eligibility." For patient #804-8055, the baseline CT scan report from the investigator's site stated, "in the absence of any definite solid tumour I am uncertain whether the patient qualifies for the trial." The table below has the 20 cases that both the independent reviewers did not record any measurable disease.

PATIENT#	ARM [171]	US CITY OR COUNTRY	LISTED AS RESPONDER	ADJUDICATOR: NO MEASURABLE DISEASE	TECHNICAL COMMENT (S) FROM DATABASE
119-1141	a	NY	No	Yes	Optimal x 3 readers
130-1266	a	Chicago	Yes		Optimal x 2 readers
131-1286	c	Dallas	Yes		Not readable x 2
140-1450	a	NY	No		Not readable x 2
302-3023	a	France	No	yes: adjudicator stated "Pt failed eligibility."	Not readable by #1; optimal by other 2
409-4332	a	Germany	Yes	pleural effusion by #2	Optimal x 2 readers
453-4512	a	India	No		Not optimal @ baseline but readable by #1 then optimal; readable not optimal for all by #2
453-4513	a	India	No	#2 @ visit 2 no measurement possible	readable not optimal by both
453-4514	a	India	No	yes: adjudicator stated "no scale bar-can't measur"	not readable by #1; readable not optimal by other 2
453-4515	c	India	No		readable not optimal by both @ baseline; optimal by both @ visit 2 then readable not optimal by both at last evaluation
453-4516	a	India	No		readable not optimal by both; #2 multi-image, can't measure
502-5055	c	Italy	No	pleural effusion by #2	optimal by both
503-5024	c	Italy	No		optimal by both
510-5110	a	Australia	Yes		no measurements (0.0 by #1); optimal by #1; readable not optimal by #2; no scale bar at BL by both
512-5111	a	Australia	Yes		optimal by both
720-7203	a	Finland	No		optimal by #1; readable not optimal by #2

[171] Key a=alimta + cisplatin arm; c=cisplatin alone arm

PATIENT#	ARM [171]	US CITY OR COUNTRY	LISTED AS RESPONDER	ADJUDICATOR: NO MEASURABLE DISEASE	TECHNICAL COMMENT (S) FROM [redacted] DATABASE
804-8055	a	UK	Yes	pleural effusion by both	optimal by both
851-8519	c	Poland	Yes		optimal by both
852-8521	a	Poland	No		readable not optimal by both; no measureble disease
852-8523	c	Poland	Yes		not readable #1; readable not optimal by other 2 (optimal for other 2 evaluations)

In response to FDA request for clarification, for patients #852-8521, #852-8523, and #302-3023, Lilly stated they had no scans to review.

Also, for patients #512-5111 and #804-8055, who were listed as alimta/cisplatin responders, Lilly claimed that the patients had stable and progressive disease, respectively.[172]

Five of these cases were listed as alimta responders. As indicated below, only one of them was a responder after FDA review of the images.

PATIENT #	ARM [173]	LISTED AS RESPONDER	RESPONSE BY FDA REVIEW OF IMAGES OF LISTED ALIMTA RESPONDERS
130-1266	a	yes	no
409-4332	a	yes	no; pleural effusion
510-5110	a	yes	YES
512-5111	a	yes	no; fluid
804-8055	a	yes	no; fluid

The assessment by [redacted] and the independent reviewers was also to serve as check for the presence or absence of measurable disease--an eligibility criterion. The eligibility of many of these patients was questionable.

[172] Lilly response to FDA query dated 12/4/2003
[173] Key a=alimta + cisplatin arm; c=cisplatin alone arm

Subjects with No Disease Measured by One or More Independent Reviewers and the Independent Adjudicator

There were 37 cases that one or more independent reviewers and the independent adjudicator measured no disease although per protocol measurable disease was an eligibility criterion. *This was important because: 1) eligible patients were required to have measurable lesions with clearly defined margins by computerized tomography (CT) or MRI; 2) pleural effusions were not considered measurable; 3) patients were excluded who had disease which could not be radiologically imaged; and 4) degree of measurability of disease was a stratification factor.*

PATIENT#	ARM [174]	US CITY OR COUNTRY	LISTED AS RESPONDER	COMMENT[175]
103-1031	c	Chicago	no	no measurements #1; u for #2
113-1301	c	Czech Republic	yes	no measurements for #1; u for #2 and adjudicator
114-1403	c	Slovakia	yes	u by #2; no measurements for #1
119-1144	c	NY	no	u by #2; no measurements by #1
119-1147	c	NY	no	u by #2; no measurements by #1
125-1216	a	San Francisco	no	no measurements by #1 and adjudicator; u by #2
141-1461	a	Louisiana	yes	no measurements #1; b by #2
142-1475	a	Cleveland	no	no measurements #1; u by #2
301-3155	c	France	no	no measurements by #1; u by #2
301-3162	c	France	no	no measurements by #1 & adjudicator; u by #2
302-3022	C	France	no	no measurable disease #1; u by #2
302-3024	A	France	no	no measurable disease by #1; b by #2 and adjudicator
302-3025	a	France	no	no measurable disease by #1; b by#2: liver mets.
308-3180	c	France	no	no measurements by #1; b by #2: liver mets
401-4004	a	Germany	yes	no measurements by #1 & adjudicator; u by #2
401-4014	c	Germany	yes	no measurements by #1; u by #2
402-4301	c	Germany	no	u described for #2; no lesion described for #1
451-4509	a	India	yes	u by #2; no measurable disease by #1
452-4502	c	India	no	no measurements by #1 and adjudicator; u by #2; #2 called PR
501-5008	c	Italy	yes	u by #2; no measurements by #1
501-5061	a	Italy	yes	u by #2; no measurements by #1
502-5014	a	Italy	no	u by #2; no measurable disese by #1
502-5020	c	Italy	no	u by #2; no measurable disease by #1
505-5046	a	Italy	yes	no measurements by #1; u by #2
510-5143	a	Australia	yes	no measurements #1 & adjudicator; u by #2
510-5147	a	Australia	yes	no measurements #1 & adjudicator; b by #2
512-5116	c	Australia	yes	no measurements by #1 & #2; u by adjudicator
557-5531	c	Argentina	no	u by #1; no measurements by #2

[174] Key a=alimta + cisplatin arm; c=cisplatin alone arm

[175] #1 refers to independent reviewer #1; #2 refers to independent reviewer #2. Key u=unidimensional disease; b=bidimensional disease

PATIENT#	ARM [174]	US CITY OR COUNTRY	LISTED AS RESPONDER	COMMENT[175]
601-6009	a	Spain	no	no measurements #1; b by #2
601-6013	a	Spain	no	no measurements #1; u by #2
720-7200	a	Finland	no	no measurements for #1 & adjudicator; u only for #2;
720-7206	a	Finland	no	no measurements #1; b by #2
720-7212	a	Finland	yes	no measurements #1; b #2 and adjudicator
721-7225	a	Finland	yes	no measurements by #1 (not readable); u by #2
804-8047	c	UK	yes	no measurable disease by #1 & adjudicator; u by #2
850-8503	a	Poland	no	no measurements by #1; b by #2
851-8511	c	Poland	no	b #2; no measurements #1

Independent reviewer #1 recorded no measurable disease for 36 cases. Independent reviewer #2 recorded no measurable disease for 2 cases. The adjudicator recorded no measurable disease for 8 cases. There were 9 cases that 2 out of 3 independent reviewers did not recorded measurable disease. There were 3 cases that 2 out of 3 independent reviewers *did* record measurable disease.

In response to FDA response for clarification, for patients #119-1144, #142-1475, #301-3155, #301-3162, #302-3022, #302-3024, and #308-3180, Lilly stated they had no scans available to review.[176]

For patients, #141-1461, #401-4004, and #510-5143, who were listed as alimta/cisplatin responders, Lilly claimed that the patients had stable disease. Also, regarding patient # 510-5147, who was listed as an alimta/cisplatin responder, Lilly claimed that the patient had progressive disease.[177]

Nine of these cases were listed as alimta responders. As indicated below, only two of them were responders after FDA review of the images.

PATIENT#	ARM [178]	LISTED AS RESPONDER	RESPONSE BY FDA REVIEW OF IMAGES OF LISTED ALIMTA RESPONDERS
141-1461	a	yes	no
401-4004	a	yes	No; more fluid
451-4509	a	yes	YES
501-5061	a	yes	no; not impressive disease
505-5046	a	yes	no; fluid reduction, not a decrease in tumor
510-5143	a	yes	no; reduction in fluid
510-5147	a	yes	no; minimal disease
720-7212	a	yes	YES

[176] Lilly response to FDA query dated 12/4/2003
[177] Lilly response to FDA query dated 12/4/2003
[178] Key a=alimta + cisplatin arm; c=cisplatin alone arm

PATIENT#	ARM 178	LISTED AS RESPONDER	RESPONSE BY FDA REVIEW OF IMAGES OF LISTED ALIMTA RESPONDERS
721-7225	a	yes	no; artifact• cannot review films

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Subjects with Liver Metastases at Baseline by at Least One Independent Reviewer or FDA

Malignant pleural mesothelioma is a malignancy characterized by local progression with rare hematogenous spread compared to adenocarcinoma of the lung--a malignancy with common hematogenous spread. However, for malignant pleural mesothelioma, distant metastatic disease in at least 50% of all patients is an event at autopsy and at relapse in patients who have achieved local control of their disease via extrapleural pneumonectomy.[179]

Patients #306-3103 and #407-4125 were noted to have baseline space-occupying lesions in the liver by FDA review of the images, as well as, by independent reviewer #2. Search of the — — Base laptop data files and Appendix 16.2.7 (Individual Efficacy Response Data) revealed 21 patients with space-occupying lesions in their liver (8 alimta + cisplatin arm; 13 cisplatin alone arm). Most were called liver metastases by an independent reviewer and/or by the investigator. Importantly, nine of the 21 patients were reported on the case report form as Stage II or III (6 alimta + cisplatin arm; 3 cisplatin alone arm), suggesting an inaccuracy in staging.

PATIENT#	ARM[180]	US CITY OR COUNTRY	SITE OF OTHER LESIONS OR METASTASES ON IMAGES	STAGE
101-1017	c	NJ	Liver	IV
102-1024	c	Pittsburgh	Liver	III
104-1045	c	NY	Liver	IV
130-1192	c	Chicago	Liver	II
130-1270	c	Chicago	Liver	III
140-1451	c	NY	Liver	IV
215-2151	c	Belgium	liver???? May be anatomic structure in left-lobe of liver	IV
302-3022	c	France	Liver	IV
302-3025	a	France	Liver	III
306-3103	a	France	Liver	III
308-3180	c	France	Liver	IV
403-4048	c	Germany	Liver	IV
407-4125	a	Germany	Liver	III
410--4182	a	Germany	Liver	III
451-4507	a	India	Liver	II
512-5113	c	Australia	Liver	IV
512-5117	c	Australia	Liver	IV
554-5517	c	Argentina	Liver	IV
601-6012	a	Spain	Liver	IV
720-7205	a	Finland	Liver	III
850-8503	a	Poland	Liver	IV

[179] Rusch VW. Oncology 1999;13:931-932

[180] Key a=alimta + cisplatin arm; c=cisplatin alone arm

For 8 patients, independent reviewer #2 called the space-occupying lesions, liver metastases; all the cases were Stage II or III; independent reviewer #1 did not indicate the presence of the space-occupying lesions in the liver for these cases. Both independent reviewers called the lesions liver metastases for two patients (#104-1045 and #403-4048); both cases were Stage IV. For five patients (#101-1017, #140-1451, #215-2151, #302-3022, and #308-3180) liver metastases were not called by the independent reviewers but were recorded by the investigator; all these cases were Stage IV.

According to the response criteria in the Protocol,

> patients with bidimensionally and unidimensionally measurable disease: greater than or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of bidimensionally measurable disease (and no progression in the sum of the unidimensionally measurable lesions) ***or*** a 30% decrease under baseline in the sum of the greatest diameters of unidimensionally measurable lesions (and no progression in the sum of bidimensionally measurable lesions).

When both unidimensional and bidimensional measurable disease are evaluated, the declaration of a response by either unidimensional or bidimensional response may be appropriate for the same lesion but it may not be appropriate in the case of different lesions in the same organ (e.g., a unidimensional RUL lesion and a bidimensional RML lesion) or lesions in different organs (e.g., a unidimensional lung lesion and a bidimensional liver lesion). In the article that described the RECIST criteria, the interchangability of unidimensional and bidimensional response appeared to be with the same lesion and not lesions in a different part of an organ or lesions in different organs. In the case of the same lesion evaluated by either unidimensional or bidimensional measurements, there was no difference in response by both assessments of response. Also, in view that no pleural malignant mesothelioma patients were included in the RECIST criteria study,[181] there was no validation of these methods, i.e., RECIST, for malignant pleural mesothelioma.

[181] Therasse et al. J Natl Cancer Inst 2000; 92:205–16

The table below provides additional information, such as, 1) which independent reader saw liver metastases, 2) the independent reviewer's baseline measurements of disease: lung/liver, and 3) the independent reviewer's response evaluation: lung/liver.

PATIENT #	ARM [182]	STAGE	WHICH INDEPENDENT READER SAW LIVER METS?	FUTHER COMMENTS	RESPONDER'S LIST	INDEPENDENT REVIEWER 'S BASELINE MEASUREMENTS OF DISEASE::LUNG/LIVER	INDEPENDENT REVIEWER'S RESPONSE EVALUATION: LUNG/LIVER
101-1017	c	IV		not seen by independent reviewers; metastases seen by investigator	no: MISSING IMAGES; scans requested; Lilly response: scans not available	no measurement of lesion in liver by independent reviewers	
102-1024	c	III	2		No	14.088/2.34	
104-1045	c	IV	both	not noted by investigator	No	14.473/16.476	
130-1192	c	II	2		No	24.689/7.863	
130-1270	c	III	2; not seen by adjudicator		No	9.663/8.257	
140-1451	c	IV		not seen by independent reviewers; metastases seen by investigator; a few lesion seen by FDA imaging reviewers	No	no liver measurements	
215-2151	c	IV		not seen by independent reviewers; metastases seen by investigator; FDA imaging reviewers:questionable lesion???no clean, round lesion, anatomic structure of	No	no liver measurements	

[182] Key a=alimta + cisplatin arm; c=cisplatin alone arm

PATIENT #	ARM 182	STAGE	WHICH INDEPENDENT READER SAW LIVER METS?	FUTHER COMMENTS	RESPONDER'S LIST	INDEPENDENT REVIEWER 'S BASELINE MEASUREMENTS OF DISEASE::LUNG/LIVER	INDEPENDENT REVIEWER'S RESPONSE EVALUATION: LUNG/LIVER
				L-lobe of liver • doubt liver mets.			
302-3022	c	IV	none seen	baseline: cuts did not go far enough at baseline to see liver but on p. 14696 liver mets at baseline; in lung no L-lung • L-pneumo-ectomy???; mediastinal shifts; viisit 2:bad liver disease (gross disease); also brain scan at visit 2	no	no liver measurements	no liver measurements by independent reviewers
302-3025	a	III	2		no	no meas/11	
306-3103	a	III	2		yes	15.744/11.346	Yes/no
308-3180	c	IV	2	noted at site in response data	no	no meas/77.825	
403-4048	c	IV	both	not noted at site; abdomen disease followed for response, not reported by investigator as liver	no	no meas/194.165	
407-4125	a	III	2		yes	4.739/163.424	Yes/no
410--4182	a	III	2		yes	24.232/4.468	Yes/no
451-4507	a	II	none	lesions in liver only seen by FDA imaging reviewers	yes	not seen by readers	yes/no???
512-5113	c	IV	2	not noted by investigator	yes	15.997/8.461	no/no; overall was SD by

PATIENT #	ARM [182]	STAGE	WHICH INDEPENDENT READER SAW LIVER METS?	FUTHER COMMENTS	RESPONDER'S LIST	INDEPENDENT REVIEWER'S BASELINE MEASUREMENTS OF DISEASE::LUNG/LIVER	INDEPENDENT REVIEWER'S RESPONSE EVALUATION: LUNG/LIVER
							readers
512-5117	c	IV	2	not noted by investigator	no	13.239/49.292	
554-5517	c	IV	2		no	16.368/3.807	
601-6012	a	IV	2	not noted by investigator	no	21.427/3.109	
720-7205	a	III	2		no	5.953/1.87	
850-8503	a	IV	2	noted by investigator	no	no meas/33.615	

There were four alimta + cisplatin patients listed as responders (for one of these cases, the lesions in the liver were reported only by the FDA Imaging Reviewers [#451-4507]); there was one cisplatin alone patient listed as a responder. Independent reviewer #2 recorded and evaluated a) disease in the lung and the liver for 12 patients and b) only liver disease for three patients. Both independent reviewers recorded and evaluated only liver disease for one patient (#403-4048). The four alimta + cisplatin patients, who were listed as responders, *only* had a response in the unidimensional lung disease; there was no response recorded in the bidimensional liver disease (this includes the one case the FDA imaging reviewers evaluated).

The FDA requested source documents, i.e., CT scan reports, in order to determine if liver metastases were called by the radiologist at the investigator site. In general, the local radiologist, called the lesions hypodense lesions consistent with liver cysts or hemangiomas. Only for patient # 302-3022, did the local radiologist call the lesions liver metastases. Only three of the CT scan reports recommended additional studies to evaluate the lesions in the liver.

PATIENT#	ARM[183]	REVIEW OF CT SCAN REPORT FROM INVESTIGATOR SITE	BASED ON CT SCAN FROM INVESTIGATOR SITE, WERE LIVER METASTASES CALLED?
101-1017	c	CT scan report @ baseline: small left lobe hepatic hypodensity unchanged • in IMPRESSION: called small probable left hepatic lobe cyst or hemangioma	no
102-1024	c	CT scan at baseline: multiple hypodense lesions in the liver consistent with simple cysts• • suggested correlation with	no

[183] Key a=alimta + cisplatin arm; c=cisplatin alone arm

PATIENT#	ARM[183]	REVIEW OF CT SCAN REPORT FROM INVESTIGATOR SITE	BASED ON CT SCAN FROM INVESTIGATOR SITE, WERE LIVER METASTASES CALLED?
		MRI of liver; liver cysts again noted @ visit 2	
104-1045	c	CT scan @ baseline: liver is enlarged, low density mass in dome of liver, 4.3 cm, nodular peripheral enhancement on early post contrast images• hemangioma, correlate with MR; visit 2: mass in liver • suggestive of hemangioma	no
130-1192	c	CT scan @ baseline: numerous probable liver cysts (HU 8 of 8); visit 2: hypodense lesions in liver, probable cysts	no
130-1270	c	CT scan @ baseline: multiple hypodensities in liver likely representing hemangioma or cysts; visit 2: hypodense lesions in liver unchanged	no
140-1451	c	CT scan report baseline: no mention of liver but a mass seen in retrocrural region and a mass in posterior abdomen• called intraabdominal disease	no
215-2151	c	CT scan report @ baseline: mass 30 x 20 mm near left point of liver	no
302-3022	c	CT scan report @ baseline: liver mets.; multiple hypodense nodular lesions, deforming contours of liver, lesion in left liver appears to invade liver capsule	yes
302-3025	a	CT scan report at baseline: hypodense lesions in liver, unchanged with IV contrast; visit 3:nodular hypodense cystic formation; visit 4:	no

PATIENT#	ARM[185]	REVIEW OF CT SCAN REPORT FROM INVESTIGATOR SITE	BASED ON CT SCAN FROM INVESTIGATOR SITE, WERE LIVER METASTASES CALLED?
		secondary lesions or hepatic cysts? • suggested echo; noted again in subsequent studies	
306-3103	a	CT scan report at baseline & follow-up studies: liver biliary cysts; liver cysts unchanged with time	no
308-3180	c	CT scan report at baseline & follow-up: liver cysts in right liver	no
403-4048	c	CT scan report at baseline: massive destruction of liver, particularly lower lobe, unusual for pleural mesothelioma, look to peritoneum; also noted in follow-up & growing	no but reported as unusual for pleural mesothelioma and disease called destructive of liver
407-4125	a	CT scan report at baseline & follow-up studies: extended cystic hepatic lesions, 11 cm	no
410--4182	a	CT scan report at baseline: hepatic cyst? Vs. hepatic mets.?; follow-up studies: liver cysts, unchanged	no
451-4507	a	CT scan @ baseline: focal lesion in posterior of right lobe of liver, a known case of hemangioma, written on report Stage II, T2N0M0; visits 2 & 4: focal lesion in liver, known case of hemangioma	no
512-5113	c	CT scan report at baseline: multiple low attenuation lesions in liver compatible with cysts; visit 3: multiple low density lesions in liver consistent with cysts; visit 7:low attenuation areas in liver	no
512-5117	c	CT scan report @ baseline: multiple cysts visible in the	no

PATIENT#	ARM[183]	REVIEW OF CT SCAN REPORT FROM INVESTIGATOR SITE	BASED ON CT SCAN FROM INVESTIGATOR SITE, WERE LIVER METASTASES CALLED?
		liver; on follow-up report: no mention of liver cysts and no mention of any measurements or status of disease	
554-5517	c	CT scan report at baseline: hepatic single cysts: not noted at visit 2	no
601-6012	a	CT scan report visit 4: hepatic cyst	no
720-7205	a	CT scan report visit 2: liver cyst size of finger tip noted	no
850-8503	a	CT scan report at baseline: focuses in liver, right diaphragmatic lobe (5x4) and left lobe (02 cm), meta? Hemangioma? Visit 2: right lobe 5x4, left lobe 2.5x2	no

Eleven of the patients with space-occupying lesions in the liver had a confirmed pathological diagnosis of mesothelioma. For patient #302-3022, who the investigator-site radiologist called the lesions in the liver, metastases, the diagnosis of mesothelioma was not confirmed. It is unknown how this information may have influenced the investigator-site radiologist's interpretation of the space-occupying lesions in the liver.

Regarding patients with space-occupying lesions in the liver, the table below provides the results of independent pathology review or indicates patients who did not have independent pathology review.

PATIENT#	ARM[184]	WAS PATHOLOGY CONFIRMED?
101-1017	c	not feasible
102-1024	c	yes
104-1045	c	not feasible
130-1192	c	not feasible
130-1270	c	yes
140-1451	c	yes
215-2151	c	yes
302-3022	c	not feasible
302-3025	a	not feasible

[184] Key a=alimta + cisplatin arm; c=cisplatin alone arm

306-3103	a	yes
308-3180	c	yes
403-4048	c	yes
407-4125	a	yes
410--4182	a	no
451-4507	a	tissue unsatisfactory
512-5113	c	not feasible
512-5117	c	yes
554-5517	c	yes
601-6012	a	consistent with
720-7205	a	yes
850-8503	a	Consistent with

There were divergent interpretations of the space-occupying lesions in the liver between: a) the independent reviewers, b) investigators, and c) investigator-site radiologists. No responses in the liver were recorded in the JMCH study.

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ON ORIGINAL

Subjects Listed as Alimta Responders but Independent Reviewers' Tumor Measurements do not Calculate as Responders

There were 19 patients listed as alimta responders whose disease measurements that were derived from the independent reviewers did not calculate to a response. In 7 of these patients, the unidimensional disease calculated to PR but the bidimensional disease--and at times larger--did not calculate to PR. In 7 patients, the calculations from the independent reviewers diverged with regard to response, i.e., in 7 patients, reviewer #1's measurements calculated to response but reviewer #2's measurements did not calculate to response and in 2 cases the reverse was the case. In one patient, both independent reviewers' measurements did not calculate to response but the adjudicator's measurements did calculate to response.

PATIENT#	US CITY OR COUNTRY	COMMENT	LILLY RESPONSE TO FDA QUERIES ABOUT CALCULATIONS	RESPONSE BY FDA REVIEW OF IMAGES
107-1072	Baltimore	unidimensional calculates OK; larger bidimensional disease does not calculate to PR.	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
111-1344	Taiwan	No; OK by reader #1; SD by numbers by reader #2; response also not confirmed on CRF (PD)	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
111-1351	Taiwan	No; PR by reader #1;no PR by reader #2's numbers; adjudicator not confirmed by numbers	CT scan reports suggest response; Lilly response dated 11/26/2003 not adequate • no mention of adjudicator and dredging for response with data	YES
136-1631	Los Angeles	unidimensional calculates OK; larger bidimensional disease does not calculate to PR.	8/21/2003: referred back to response dated 8/15/2003	no
201-2192	Mexico	no; reviewer #1: PD; reviewer #2: PR; no adjudication	Lilly response dated 11/26/2003 does not take into account reviewer #1 PD and no adjudicator	YES???
216-2164	Belgium	No; called PR but numbers do not support	Lilly response dated 11/26/2003 agrees that numbers do not calculate to PR	no
301-3170	France	No; problematic; do not meet criteria for PR #1; #2 OK not confirmed ;(no #s for 103)	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate	no

PATIENT#	US CITY OR COUNTRY	COMMENT	LILLY RESPONSE TO FDA QUERIES ABOUT CALCULATIONS	RESPONSE BY FDA REVIEW OF IMAGES
			to PR	
306-3103	France	No; reader #2: unidimensional disease & bidimensional disease; bidimensional disease does not calculate to PR	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
308-3178	France	no; calculates to SD	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	YES
402-4029	Germany	no: no for reader #1; reader #2:yes for unidimensional, no for bidimensional SD	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	YES
407-4125	Germany	no; response in unidimensional disease in lung but no effect in massive disease in liver	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
410-4182	Germany	No; response only by unidimensional disease; only #2 saw liver mets. • •SD	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
501-5001	Italy	No; #1 & #2 do not calculate to PR; only adjudicator calculates but not @ 4 & 6 only @ 101 & 192	Lilly response dated 11/26/2003 agrees that numbers do not calculate to PR	YES???
501-5061	Italy	No measurements for #1; #2 unidimensional yes, bidimensional no	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
505-5041	Italy	No; #1 & #2: PR @ visit1 but PD by #s visit 4;	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
510-5103	Australia	no; #1 does not calculate at confirmation; #2 calculates to PR	response dated 8/15/2003 did not challenge that numbers did not calculate to PR	no
510-5141	Australia	no;#s by readers do not calculate to PR	8/15/2003 Lilly response: Lilly did not challenge that	no

PATIENT#	US CITY OR COUNTRY	COMMENT	LILLY RESPONSE TO FDA QUERIES ABOUT CALCULATIONS	RESPONSE BY FDA REVIEW OF IMAGES
			numbers do not calculate to PR	
851-8518	Poland	no; visit 6 calculates to PR but at confirmation (visit 102) #s double and calculate to PD	Lilly response dated 9/2/2003: confirms FDA's findings about the numbers but believes and implies that independent reviewers evaluated overall tumor burden • by Lilly's assessment PR	no
852-8532	Poland	no; calculates to PD at 1st evaluation	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no

In response to FDA queries, Lilly either agreed or did not challenge that the measurements of an independent reviewer or both independent reviewers did not calculate to an objective response. Five of these 19 patients had a response based on FDA review of the images.

APPEARS THIS WAY
ON ORIGINAL

Subjects Listed as Alimta Responders in the NDA But Reported as SD, PD, or UK in the Independent Imaging Review

There were 22 patients listed as alimta responders whose overall response by the independent review was stable disease (SD), progressive disease (PD), or unknown (UK). It has not been clarified why these patients were on the responders' list; according to the protocol, the assessment by the independent review would have priority.

PATIENT#	US CITY OR COUNTRY	OVERALL BEST RESPONSE SCORE BY INDEPENDEPENT READERS	INFORMATION CONFIRMED BY LILLY	RESPONSE BY FDA REVIEW OF IMAGES
3-3001	Taiwan	SD	yes	no
107-1073	Baltimore	SD	yes	no
125-1217	San Francisco	SD	yes	no
130-1191	Chicago	SD	yes	no
131-1272	Dallas	SD even though calculates to PR	yes	YES
141-1461	Louisiana	SD	yes	no
401-4011	Germany	PD	yes	no
409-4170	Germany	SD	yes	no
501-5006	Italy	SD	yes	no
503-5022	Italy	SD	yes	no
505-5042	Italy	calculates to PD but scored as SD	yes	no
509-5133	Australia	SD; reviewer #2 confirmed PR with PD x 3	yes	no
510-5143	Australia	UK; reviewer #2: 1st response does not calculate to PR but scored as SD	yes	no
510-5147	Australia	SD; reviewer #2 scored as PD	yes	no
511-5151	Australia	SD; #s do not calculate to PR although scored as PR by reviewer #2	yes	no
512-5112	Australia	SD	yes	no
554-5516	Argentina	SD	yes	no
721-7225	Finland	SD	yes	no
722-7251	Finland	SD	yes	no
804-8055	UK	PD	yes	no
805-8070	UK	SD	yes	no
851-8517	Poland	SD; numbers calculate to PR	yes	no

In response to FDA queries, Lilly either agreed that the overall response by the independent review panel was as cited above or did not challenge the assertion that the independent review

panel scored the patient as a nonresponder.. One of these 22 patients had a response based on FDA review of the images.

APPEARS THIS WAY
ON ORIGINAL

Listed Subjects as Alimta Responders in Study JMCH and FDA Agreed as Responders

Below were 47 alimta patients who were listed as responders, declared a responder by independent review, and scored a responder by FDA Imaging Review. The shaded rows were FDA responder patients who had the diagnosis of mesothelioma confirmed on independent review.

PATIENT#	ASSESSMENT BY THE NUMBERS	REVIEW OF IMAGES: ASSESSMENT	CONFIRMED RESPONSE	BIDIMENSIONAL (B) OR UNIDIMENSIONAL (U) BY INDEPENDENT REVIEWERS
111-1351	no; PR by reader #1;no PR by reader #2's numbers; adjudicator not confirmed by numbers	Yes; "knuckles of tumor to a rind"	yes; PR confirmed by imaging @ 5	u by all 3
118-1134	Yes	Yes; response confirmed by images	Yes	u
119-1146	yes	Yes	yes?	u
131-1272	yes but best overall response was SD even though calculates to PR	yes	Yes (response confirmed before 28 days)	u
131-1278	yes	yes	Yes	u
136-1633	yes	yes; remarkable response	Yes	u
141-1465	yes; little-minimal disease	yes; minimal disease	Yes	u
142-1476	yes	yes	Yes	u
201-2192	no; reviewer #1: PD; reviewer #2: PR; no adjudication	yes; remarkable response	yes but need adjudication	u
201-2202	yes	yes; remarkable response	yes; remarkable response	u
250-2500	yes	yes	yes	u
250-2502	yes	yes	yes	u
252-2565	yes	yes	yes	u
301-3150	yes	yes	yes	u
301-3151	yes; ask why images required an adjudicator because #1 PR, PR, PD, #2 PR, SD, SD, adjudicator PR, PR, PR	yes	yes	u by #1 & #2; u & b by adjudicator

PATIENT#	ASSESSMENT BY THE NUMBERS	REVIEW OF IMAGES: ASSESSMENT	CONFIRMED RESPONSE	BIDIMENSIONAL (B) OR UNIDIMENSIONAL (U) BY INDEPENDENT REVIEWERS
301-3156	yes	yes	yes	u
302-3021	yes	yes	yes	u
308-3176	yes	yes	yes	u
308-3177	yes	yes	yes	u
308-3178	no; calculates to SD	yes	yes	u
308-3181	yes	yes	yes	u & b by both
308-3182	Yes	yes	yes	u
309-3192	Yes	yes	yes	u
401-4001	yes with PR by adjudicator	yes but not a lot of disease and not impressive	yes; weak	u by all 3
401-4009	Yes	yes	yes	u
402-4029	no: no for reader #1; reader #2:yes for unidimensional, no for bidimensional SD	yes; anterior mediastinum clean with response and opening up; images #25-28	yes	u & b by reader #2 only
403-4042	Yes	yes	yes	u
406-4102	yes but readers using same #s diverged in assessment	yes	yes	u by #1 & #2; u & b by adjudicator
406-4104	Yes	yes; good response by 101		u
409-4179	Yes	yes	yes	u
413-4242	Yes	yes; maybe CR		u
451-4508	yes but at later points calling PR when PD by #s	yes; transient response	yes	u
451-4509	yes but only had #s for #2	yes	yes	u by #2; no measurable disease by #1
501-5001	no; #1 & #2 do not calculate to PR; only adjudicator calculates but not @ 4 & 6 only @ 101 & 192	yes	yes???	u by all 3
501-5004	yes; #1 calculated to PR sooner than declared	yes	yes	u
510-5101	Yes	yes	yes	u
510-5110	no; no disease measurements but reader #1 counted 9	yes	yes	no measurements (0 by #1)

PATIENT#	ASSESSMENT BY THE NUMBERS	REVIEW OF IMAGES: ASSESSMENT	CONFIRMED RESPONSE	BIDIMENSIONAL (B) OR UNIDIMENSIONAL (U) BY INDEPENDENT REVIEWERS
	index rind lesions			
512-5114	Yes	yes	yes	u
552-5509	Yes	yes	yes	u
552-5510	Yes	yes	yes	u
720-7212	Yes	yes but PR	Yes PR	no measurements #1; b #2 and adjudicator
721-7229	yes	yes	Yes	u
804-8048	yes: #1 calculates to PD in b; #2 & adjudicator calculates to PR	Yes	Yes	u & b by all 3 but may have been measuring different bidimensional disease
851-8512	Not read by independent readers because images not provided to readers or to FDA until requested	Yes: V2: PR, V3: confirmed PR; time points: baseline, V2, V3	Yes	missing images: images received & reviewed **no independent review of measurability of disease**
851-8515	yes	yes	yes	u
852-8525	yes	yes	yes	u
852-8534	yes	yes	yes	u

Except for six patients, all the patients had a response by calculation of the measurements reported by the independent reviewer(s); one patient (#851-8512) had no measurements from the independent reviewers because the independent reviewers did not review the images. Except for six patients, who also had assessment of bidimensional disease and the one patient that the independent reviewers did not review, the independent reviewers based all the patients' responses on assessment of unidimensional disease.

Alimta Responders by Independent Review in Study JMCH and FDA Agreed as Responders

Although the published report of the JMCH study did not mention independent review of the images,[185] the accompanying editorial stated that "Central review of all CT scans and all pathology specimens was performed. This rigorous approach to analysis lends credibility to the study results, especially in a disease for which correct pathologic diagnosis can still be difficult, and for which there has been little uniformity in measuring response to treatment."[186] In an earlier article about the results from a Phase II trial of alimta in malignant pleural mesothelioma, there was "an external expert panel" who "independently assessed the best response status of each patient at a later date". The article also compared Investigator-Determined Best Tumor Responses and Independent Reviewer–Determined Best Tumor Responses. The co-authors wrote that "independent review of patient responses increases confidence that the response rate is a true result for this patient population".[187]

The list of responders sent by Lilly had 94 alimta/cisplatin responders and 37 cisplatin responders.[188] There was a minor difference with the number of alimta/cisplatin responders reported in the JMCH study report, i.e., 93.

Table JMCH.11.22 Summary of Best Tumor Response (Investigator-Determined) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=225)	Cisplatin (N=222)	LY/cis (N=167)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
Number of responding patients	93*	37	76*	32	17*	5
Response rate (%)	41.3	16.7	45.5	19.6	29.3	8.5
95% CI for response rate	34.8 - 48.1	12.0 - 22.2	37.8 - 53.4	13.8 - 26.6	18.1 - 42.7	2.8 - 18.7
Fisher exact p-value	<0.001		<0.001		0.005	

* Three CRs were on the LY/cis arm (2 FS patients and 1 PS+NS patient).

[185] Vogelzang NJ, Rusthoven JJ, Symanowski J, et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636-2644, 2003

[186] Rusch VW. Pemetrexed and Cisplatin for Malignant Pleural Mesothelioma: A New Standard of Care? Journal of Clinical Oncology, 21:2629-2630, 2003

[187] Scagliotti et al. Phase II Study of Pemetrexed With and Without Folic Acid and Vitamin B12 as Front-Line Therapy in Malignant Pleural Mesothelioma. J Clin Oncol. 2003; 21:1556-1561

[188] Cover letter from Lilly dated 10/22/2002

The tables below are from the JMCH study report. In the two tables below, the alimta + cisplatin arm number of responders after independent review was not as different (i.e., alimta/cisplatin responders: 93 by the investigator vs. 86 by independent review) as one would expect in view of the FDA's review of the — database revealed 22 patients listed as alimta responders whose overall response by the independent review was stable disease (SD), progressive disease (PD), or unknown (UK), meaning the number of alimta + cisplatin responders should be 94 - 22 = 72. Since the assessment by the independent reviewers of response was to take precedence in determination of response, the FDA believed that the list of 94 alimta + cisplatin provided by Lilly to the FDA were the valid responders. Based on the information provided in the NDA, it was not apparent how the numbers for independent reviewer-determined best tumor response were derived. After further review, it appeared that the list provided to the FDA was the list of investigator-determined responders.

Table JMCH.11.23. Summary of Best Tumor Response (Independent Reviewer-Determined) As of Database Lock (13 February 2002) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=194)	Cisplatin (N=195)	LY/cis (N=145)	Cisplatin (N=143)	LY/cis (N=49)	Cisplatin (N=52)
Number of responding patients	85*	28	67*	23	18*	5
Response rate (%)	43.8	14.4	46.2	16.1	36.7	9.6
95% CI for response rate	36.7 - 51.1	9.8 - 20.1	37.9 - 54.7	10.5 - 23.2	23.4 - 51.7	3.2 - 21.0
Fisher exact p-value	<0.001		<0.001		0.002	

* Two CRs were on the LY/cis arm (1 FS patient and 1 PS+NS patient).

Table JMCH.11.24. Summary of Best Tumor Response (Independent Reviewer-Determined) As of — Update (10 June 2002) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=197)	Cisplatin (N=200)	LY/cis (N=148)	Cisplatin (N=148)	LY/cis (N=49)	Cisplatin (N=52)
Number of responding patients	86*	30	68*	25	18*	5
Response rate (%)	43.7	15.0	45.9	16.9	36.7	9.6
95% CI for response rate	36.6 - 50.9	10.4 - 20.7	37.7 - 54.3	11.2 - 23.9	23.4 - 51.7	3.2 - 21.0
Fisher exact p-value	<0.001		<0.001		0.002	

* Two CRs were on the LY/cis arm (1 FS patient and 1 PS+NS patient).

The inconsistency of response assessments between the NDA dataset (the Lilly list of responders) and the independent review dataset (see section, **Subjects Listed as Alimta Responders in the NDA But Reported as SD, PD, or UK in the Independent Imaging Review**) suggested that the response assessments reported in the NDA were not based on the independent review.

The FDA requested the best tumor response data from the investigator, independent reviewer #1, independent reviewer #2, and the adjudicator.

The investigator's assessments of the alimta + cisplatin arm are in the table below. The number of objective responders--CR + PR--was 3 + 91 or 94.

ALIMTA + CISPLATIN BEST OVERALL RESPONSE	NUMBER
CR	3
ND	5
PD	39
PR	91
SD	80
U	8

The investigator's assessments of the cisplatin alone arm are in the table below. The number of objective responders- PR--was 37.

CISPLATIN ALONE BEST OVERALL RESPONSE	NUMBER
ND	7
PD	78
PR	37
SD	94
U	6

There were 28 patients on the alimta + cisplatin arm that did not have their images reviewed by the independent panel. The images of patients with progressive disease were most frequently not reviewed by the independent panel.

ALIMTA + CISPLATIN BEST OVERALL RESPONSE BY THE INVESTIGATOR	NUMBER
ND	4
PD	13
PR	3
SD	4
U	4
TOTAL	28

There were 22 patients on the cisplatin alone arm who did not have their images reviewed by the independent panel. The images of patients with stable disease were most frequently not reviewed by the independent panel.

CISPLATIN ALONE BEST OVERALL RESPONSE BY THE INVESTIGATOR	NUMBER
BEST OVERALL RESPONSE	NUMBER
ND	6
PD	4
SD	7
U	5
TOTAL	22

There were 66 patients on the alimta + cisplatin arm that had the investigator's response changed with independent review. As described in the section **Subjects Listed as Alimta Responders in the NDA But Reported as SD, PD, or UK in the Independent Imaging Review** of this review, there were 22 patients who had the investigator's assessment of partial response downgraded to non-response by independent review of the images. There were 17 patients who had their response upgraded from SD to PR. The data from the 16 patients who had their assessment changed from PD to SD may have an effect on the analysis of time to progression, i.e., increase the time to progression. Although less frequent, patients who had their assessment changed from PR to PD and SD to PD may also have an effect on the analysis of time to progression.

ALIMTA + CISPLATIN CHANGE IN BEST OVERALL RESPONSE AFTER INDEPENDENT REVIEW INVESTIGATOR RESULT • INDEPENDENT RESULT	NUMBER
ND • SD	1
PD • SD	16
PD • U	2
PR • PD	2
PR • SD	19
PR • U	1
SD • PD	2
SD • PR	17
SD • U	2
U • SD	4
Total	66

The results of independent review of alimta + cisplatin arm patients are below. The final number--89--does not match the independent-reviewer determined response number in the JMCH study report, i.e., 86.

Alimta + cisplatin arm	NUMBER
Investigator responders	94
Investigator responders downgraded to non-responders	-22
Investigator non-responders upgraded to responders	+17
Total	89

There were 38 alimta + cisplatin patients who the assessment of their imaging studies required adjudication of the independent review; nine cases of investigator-determined SD were upgraded to PR by independent review plus adjudication.

The FDA reviewed the images of the 17 alimta + cisplatin patients who the investigator scored the best overall response as SD and the independent reviewers scored the best overall response as PR; 9 cases had the non-response upgraded to response by adjudication (marked as PR*). These 17 patients were not on the list of responders provided to the FDA by Lilly and thus, were not reviewed when the FDA reviewed the alimta + cisplatin responders on the list. Only 6 of the 17 patients' disease measurements calculated to a response. Six patients had a response by FDA review of the images; 5 cases had lesion measurements that calculated to a response; 1 case had lesion measurements that calculated to a non-response. Only 2 of the 9 adjudicated responders were responders on FDA review of the images. The shaded rows were FDA responder patients who had the diagnosis of mesothelioma confirmed on independent review.

PATIENT#	INVESTIGATOR RESPONSE	INDEPENDENT REVIEWERS' RESPONSE	COMMENTS BY FDA	FDA ASSESSMENT OF RESPONSE BY NUMBERS	FDA REVIEW OF IMAGES FOR RESPONSE
102-1026	SD	PR*	All reviewers evaluated different disease; adjudicator's numbers confirm response as PD	No	Visit 2 PD in ant. Mediastinum; use as example
111-1347	SD	PR	#2: numbers confirm response as PD	No	visit 2 to viisit 4: PD
111-1352	SD	PR*	#2: measured both uni- and bidimensional disease, SD on uni, bidimensional confirms to PD by numbers; adjudicator: measured both uni-	No	SD

PATIENT#	INVESTIGATOR RESPONSE	INDEPENDENT REVIEWERS' RESPONSE	COMMENTS BY FDA	FDA ASSESSMENT OF RESPONSE BY NUMBERS	FDA REVIEW OF IMAGES FOR RESPONSE
			and bidimensional disease, SD on uni, bidimensional confirms to PD by numbers		
131-1274	SD	PR	Both reviewers had numbers as PR	Yes	PR
131-1283	SD	PR	#1: numbers calculate to SD; #2 same as #1	No	SD
131-1044	SD	PR*	both uni & bidimensional disease: same numbers for all three reviewers; numbers do not calculate to PR or no numbers and next value would be PD	No	SD
214-2145	SD	PR*	#1,#2, and adjudicator: measured both uni- and bidimensional disease (unidimensional larger• anidimension al PR, bidimensional SD; only #2 called it SD	No	SD
216-2165	SD	PR	Both reviewers had numbers as PR for visit 2; 2nd visit calculates to PD with new baseline but still in range for PR with old baseline	no???	SD/PD
302-3025	SD	PR	#1: no numbers; #2 bidimensional in liver only: NR	No	SD
402-4039	SD	PR*	#1:calculates to PR visit 2 but calculates to PD visit 4 although still in range of PR of old baseline; #2:same as	No	PR

PATIENT=	INVESTIGATOR RESPONSE	INDEPENDENT REVIEWERS' RESPONSE	COMMENTS BY FDA	FDA ASSESSMENT OF RESPONSE BY NUMBERS	FDA REVIEW OF IMAGES FOR RESPONSE
			#1; adjudicator: visit 2 & visit 4 measurements about the same -->PR but response less than visit 2 for #1 and #2		
406-4101	SD	PR*	#1, #2, and adjudicator: visit 2 calculates to PR but visit #4 calculates to PD although within range of PR with old baseline;	No	PD; inadequate scan• • missing 1/2 lung at baseline
407-4121	SD	PR*	#1 does not calculate; both #2 and adjudicator calculate to PR and then 0.00	Yes	SD; low tumor burden • • minimal disease; right fluid and left fluid; check pathology (OK, confirmed mesothelioma), Stage IV
409-4162	SD	PR	Both calculate to PR	Yes	PR; more fluid response; disease on both sides
501-5010	SD	PR	Both calculate to PR	Yes	PR
502-5018	SD	PR	Both calculate to PR	Yes	PR
553-5511	SD	PR*	#2 & adjudicator calculate to PR	Yes	PR
804-8041	SD	PR*	#1 calculates to PR, #2 measured uni- & bidimensional disease: unidimensional calculates to PR, bidimensional disease calculates to SD; adjudicator only measured unidimensional disease• •PR	no???	SD; bidimensional disease not a response; unidimensional disease a response

*adjudicated

Recall from the introduction to this section that the FDA did not review images of the listed cisplatin alone responders. There were 60 patients on the cisplatin arm alone who had the investigator's response changed with independent review. There were 14 patients who had the investigator's assessment of partial response downgraded to non-response by independent review of the images. There were 6 patients who had their response upgraded from ND, PD, or SD to PR. The data from the 34 patients who had their assessment changed from PD to SD may have

an effect on the analysis of time to progression, i.e., increase the time to progression. Although less frequent, the data from patients who had their assessment changed from PD to PR and SD to PD may also have an effect on the analysis of time to progression.

CISPLATIN ALONE CHANGE IN BEST OVERALL RESPONSE AFTER INDEPENDENT REVIEW INVESTIGATOR RESULTS-->INDEPENDENT PANEL RESULTS	NUMBER
ND• •PR	1
PD• •PR	1
PD• •SD	34
PD• •U	2
PR• •SD	13
PR• •U	1
SD• •PD	3
SD• •PR	4
U• •SD	1
Total	60

The results of independent review of cisplatin alone arm patients are below. The final number--29--does not match the independent-reviewer determined response number in the JMCH study report, i.e., 30.

Cisplatin alone arm	NUMBER
Investigator responders	37
Investigator responders down-graded to non-responders	-14
Investigator non-responders up-graded to responders	+6
Total	29

There were 45 cisplatin alone patients who the assessment of their imaging studies required adjudication of the independent review; one case of investigator-determined SD was upgraded to PR by independent review plus adjudication.

Nine cases of SD were upgraded to PR.

An analysis of the results of the independent review for both treatment arms is below. A higher proportion of cisplatin alone patients had their investigator's PR downgraded than the alimta + cisplatin alone patients. Response upgrading to PR by independent review was balanced in both arms.

RESULT OF INDEPENDENT REVIEW	ALIMTA/CISPLATIN	CISPLATIN ALONE
Response downgraded	22/94 (23%)	14/37 (38%)
Response upgraded	17/94 (18%)	6/37 (16%)
Total changed	39/94 (41%)	20/37 (54%)

APPEARS THIS WAY
ON ORIGINAL

Agreed upon Alimta Responders with a Confirmed Pathology Diagnosis of Mesothelioma

The 38 FDA confirmed alimta + cisplatin with a confirmed pathology diagnosis are derived from tables in sections "**Listed Subjects as Alimta Responders in Study JMCH and FDA Agreed as Responders**" (32 patients) and "**Alimta Responders by Independent Review in Study JMCH and FDA Agreed as Responders**" (6 patients). Identification of patients with a confirmed pathological diagnosis of mesothelioma and the patients' folic acid/vitamin B12 supplementation status was derived from Lilly correspondences dated 12/16/2003 and 8/21/2003, respectively.

RESPONSE RATE IN PATIENTS WITH CONFIRMED PATHOLOGY

	ALIMTA + CISPLATIN, FDA CONFIRMED RESPONDERS			CISPLATIN ALONE, LILLY LISTED RESPONDERS		
	Proportion	Response rate	95% CI	Proportion	Response rate	95% CI
overall response rate	38/153	25%	18,32	25/149	17%	11,23
epithelial	35/130	27%	29,35	22/127	17%	11,24
Mixed	3/15	20%	-0.2,37	1/13	8%	-7,22
Sarcomatoid	0/8	0%		2/9	22%	-5, 49
folic acid/vitamin B12 supplementation	29/111	26%	18,34	21/108	19%	12,27
Partial supplementation	3/20	15%	-0.7,31	3/14	21%	-0.1, 43
never supplemented	6/22	27%	9,46	1/27	4%	-3,11

Regulatory Decision Concerning the Inclusion of Response Rate and Time to Progression in the Label

Response rate was originally the proposed primary endpoint for study JMCH. Unidimensional measurements were believed to be sufficient to provide information for response. The FDA required survival as the primary endpoint and was uncertain about the application of unidimensional disease for response assessments.

Based on FDA review of the images alimta + cisplatin responders and the — database, response rate and time to progression should not be included in the label.

A summary of the problems found during the FDA with review of images follows.

- Patients who were screening failures were entered on study.
- CT scans were not performed in some patients as required by protocol, i.e., upper abdomen scans.
- There were missing images (NRs > RRs) from the imaging database; for some of these patients the reasons included: no baseline scans, baseline scans incomplete, or scans not available
- Not all patients had independent review of their images.
- The independent reviewers did not record disease measurements in all patients. Specifically, there was non-agreement of measurability of disease (inclusion criteria for entry in the study; stratification factor) between the investigators and independent readers and between independent readers.
- Patients were listed as responders by Lilly who were scored as a non-responder by the independent reviewers. Specifically, there was non-agreement of response between the investigators and independent readers, i.e., SD, PD, and UK for cases listed by Lilly as PR.
- Patients were listed as responders who were later called non-responders by Lilly.
- Patients who were scored a responder by the independent reviewers but a non-responder by the investigator were not on the Lilly responder list.
- There was non-agreement in some patients of sites of disease between investigators and independent readers at baseline and at time of progressive disease.
- There was dissociation of response in the chest and non-response in the "liver" in some patients, i.e., response in the chest (unidimensional disease) and non-response in the "liver" (bidimensional disease).

- There was dissociation of overall response scoring and calculation of response by independent readers, i.e., patients were scored as PR but calculations of measurements indicated NR or PD.
- FDA review of imaging studies confirmed only 47 of 94 responses listed by Lilly in the alimta/cisplatin group.

Also, according to Lilly:

- In patients with "extensive lobulated disease", it was difficult to select the appropriate lesions to follow and the tumor burden may not be accurately represented by the lesions chosen at baseline.[189]
- When the disease is "extensive and lobulated" or has "irregular contours", it makes it difficult to measure.[190]

[189] Lilly correspondence dated 11/26/2003
[190] Lilly correspondence dated 12/4/2003

4. **Efficacy Conclusions**

In the pivotal trial, A Single-blind Randomized Phase 3 Trial of MTA[191] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma, survival was the primary endpoint. The following table illustrates the survival benefit achieved in this randomized, controlled trial.

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Randomized and treated (n=448)	12.1 months	9.3 months	0.021
Fully folic acid/vitamin B12 supplemented (n=331))	13.3 months	10 months	0.051
Partial supplemented + never supplemented (n=117)	9.5 months	7.2 months	0.253
Intent-to-treat (n=456)	12 months	9.3 months	0.0205
Confirmed mesothelioma pathology Randomized and treated (n=303)	13 months	10.2 months	0.066
Confirmed mesothelioma pathology Fully folic acid/vitamin B12 supplemented (n=220)	14.4 months	10.3 months	0.058
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176

[191] alimta

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388
Race White Randomized and treated (n=410)	12.2 months	9.3 monts	0.024
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white Fully folic acid/vitamin B12 supplemented (n=28)	8.8 months	9.55 months	0.619
Age < 65 years Randomized and treated (n=279)	13.3 months	10.2 months	0.02
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The data supports the following indication:

> ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are not candidates for curative surgery.

The combination of Alimta plus cisplatin is the first chemotheraupetic regimen to demonstrate a survival benefit in malignant pleural mesothelioma in comparison to a control regimen.

Response rate was a secondary endpoint for study JMCH. The following table illustrates the response rate demonstrated in patients with a confirmed pathological diagnosis of mesothelioma.

	ALIMTA + CISPLATIN, FDA CONFIRMED RESPONDERS			CISPLATIN ALONE, LILLY LISTED RESPONDERS		
	Proportion	Response rate	95% CI	Proportion	Response rate	95% CI
overall response rate	38/153	25%	18,32	25/149	17%	11,23
epithelial	35/130	27%	29,35	22/127	17%	11,24
Mixed	3/15	20%	-0.2,37	1/13	8%	-7,22
Sarcomatoid	0/8	0%		2/9	22%	-5, 49
folic acid/vitamin B12 supplementation	29/111	26%	18,34	21/108	19%	12,27
Partial supplementation	3/20	15%	-0.7,31	3/14	21%	-0.1, 43
never supplemented	6/22	27%	9,46	1/27	4%	-3,11

In contrast to the survival endpoint and although the response rate of the alimta + cisplatin arm was higher than the cisplatin alone arm, response rate was not a rigorous endpoint in study JMCH for a number of reasons.

At the End of Phase II meetings, the FDA indicated to Lilly that tumor response rate in mesothelioma could not be reliably assessed and that the FDA would not make any important decisions regarding efficacy based on tumor response rate or time to tumor progression.

VII. Integrated Review of Safety

1. Brief Statement of Conclusions

The pivotal trial was a multicenter, randomized, single-blind Phase III trial in chemo-naïve patients with malignant pleural mesothelioma (MPM) treated with Alimta in combination with cisplatin compared to patients who received cisplatin alone. Alimta was administered at a dose of 500 mg/ m^2 intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/ m^2 intravenously over approximately 2 hours on Day 1 of each 21- day cycle. In the cisplatin only arm, normal saline which did not contain Alimta was administered intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/ m^2 intravenously over approximately 2 hours on Day 1 of each 21- day cycle. Patients in both arms were pre- and post- hydrated according to local practice. Dexamethasone 4 mg, or equivalent corticosteroid was taken orally twice per day on the day before, the day of, and the day after each dose of Alimta plus cisplatin. Folic acid supplementation, 350–1000 µg or equivalent was taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of Alimta plus cisplatin and continued daily until the patient discontinued from study therapy. A vitamin B_{12} injection, 1000 µg was given intramuscularly approximately 1 to 3 weeks prior to the first dose of Alimta plus cisplatin and was repeated approximately every 9 weeks until the patient discontinued from study therapy.

The median age of patients at the time of randomization was 60 years. Although 456 patients were randomized, 8 patients did not receive the study drug; a total of 448 patients were treated and received at least one dose of study drug(s). The primary analysis of this study was performed on the population of all patients who received study drug in the treatment arm. A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy. Randomized and treated patients completed a median of 6 cycles of the Alimta/cisplatin arm and 4 cycles of the cisplatin only arm. Supplemented patients completed a median of six cycles and nonsupplemented patients completed a median of 2 cycles of Alimta/cisplatin. The planned mean dose for Alimta and cisplatin were 166.7 and 25 mg/m^2/wk respectively. The mean dose delivered was 153.4 mg/m^2/wk of Alimta and 23.2 mg/m^2/wk of cisplatin in the RT group and 154.6 mg/m^2/wk and 23.4 mg/m^2/wk in the FS group. When used alone, cisplatin was given at 24.1 mg/m^2/wk. The percent of planned dose intensity was 92/92.8% for Alimta/cisplatin in the RT group and 92.7/93.6% Alimta/cisplatin in the FS group. 96.4% of cisplatin alone could be given in both the RT and FS groups. In the RT group, 308 (28.9%) dose delays were reported in the Alimta/cisplatin arm and 171 (19.5%) in the cisplatin alone arm. Scheduling conflicts constituted the majority of dose delays. The most common clinical cause of dose delay on both arms was neutropenia. On both arms, cycle 4 was the cycle with the most delays. The common grade 3 or grade 4 laboratory toxicities in the RT group treated with Alimta/cisplatin were neutropenia (28.8%), leucopenia (18.1%), thrombocytopenia (5.8%) and anemia (6.2%). In the cisplatin only arm, neutropenia (2.3%), leucopenia (1.4%) and decreased creatinine (1%). In the FS group, the Alimta/cisplatin treated arm had neutropenia (24.4%), leucopenia (15.5%), anemia

(6%), thrombocytopenia (5.4%) while the cisplatin only arm had neutropenia (3.1%), leucopenia (0.6%) and decreased creatinine (1%). The common nonlaboratory grade 3 and grade 4 adverse events in the RT group treated with Alimta/cisplatin were fatigue (18.1%), nausea (14.6%), vomiting (13.7%), diarrhea (4.9%), dehydration (4.4%), stomatitis (4%), anorexia (3.5%) and rash (1.3%). In the cisplatin alone arm the common adverse events were fatigue (15.3%), nausea (6.3%), and vomiting (3.6%). In the FS group, the patients treated with Alimta/cisplatin had fatigue (17.3%), nausea (11.9%), vomiting (10.7%), dehydration (4.2%), diarrhea (3.6%), stomatitis (3%) and anorexia (2.4%). Those in the cisplatin alone arm had fatigue (12.9%), nausea (5.5%) and vomiting (4.3%). A comparison between the two treatment arms in the FS group showed a statistically significant difference for neutrophils and leukocytes with more neutropenia and leucopenia in the Alimta/cisplatin group. Effect of supplementation reduced many of the laboratory and non-laboratory toxicities.

Use of vitamin supplementation by patients must be emphasized. Patients treated with Alimta must be instructed to take low-dose folic acid daily so that at least 5 doses are taken during the 7-day period preceding the first dose of Alimta and continuing until 21 days after the last dose. Patients must also receive 1 injection of vitamin B_{12} during the week prior to receiving the first dose of Alimta and every 3 cycles thereafter during therapy. Subsequent vitamin B_{12} injections may be given the same day as Alimta.

Alimta with dexamethasone or equivalent reduces the incidence and severity of cutaneous reactions.

As a class, folic acid antimetabolites have been demonstrated to produce manifestations of developmental toxicity such as growth retardation, embryo lethality, and malformations. Alimta was found to be embryo toxic at doses of 10 mg/ kg (30 mg/ m^2) and fetotoxic causing fetal malformations (cleft palate) at doses of 5 mg/ kg (15 mg/ m^2). There are no studies of Alimta in pregnant women. If Alimta is used during pregnancy, or if the patient becomes pregnant while taking Alimta, the patient should be apprised of the potential hazard to the fetus.

As with other anti-folate drugs, there is a potential for serious adverse reactions in nursing infants and nursing should be discontinued if the mother is treated with Alimta.

Alimta is eliminated primarily via the renal route. Patients with a creatinine clearance of < 45 ml/min, calculated with the mean body weight by the formula of Cockcroft and Gault, should not receive Alimta.

As with other antifolates, caution should be exercised when concomitant administration of Alimta with nonsteroidal anti-inflammatory drugs are used.

Patients with clinically significant pleural effusions have been excluded in studies performed with Alimta. Before starting treatment, pleural effusions should be drained.

The safety evaluation seems adequate for marketing for this indication. Areas of caution and limited safety experience have been noted above.

2. Description of Patient Exposure

All patients were randomly assigned to either the Alimta/ cisplatin arm or the cisplatin alone arm, defined as follows:
A. Alimta, 500 mg/ m^2, diluted in normal saline, 100 mL, 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.
B. Normal saline, 100 mL, that did not contain Alimta administered intravenously over approximately 10 minutes, followed approximately 30 minutes later by cisplatin, 75 mg/ m2, administered intravenously over approximately 2 hours on Day 1 of each 21- day cycle.
Both arms were treated as follows: Patients were pre- and post hydrated according to local practice. Patients were instructed to take dexamethasone 4 mg, or equivalent corticosteroid, orally twice per day on the day before, the day of, and the day after each dose of assigned treatment. Patients were instructed to take folic acid supplementation, 350 to 1000 µg or equivalent, orally each day beginning approximately 1 to 3 weeks before the first dose of treatment arm and continued daily until the patient discontinued from study therapy. A vitamin B_{12} injection, 1000 µg, was given intramuscularly approximately 1 to 3 weeks before the first dose of treatment and was repeated approximately every 9 weeks until the patient discontinued from study therapy. The primary analysis of this study was performed on the population of all patients who received study drug in the treatment arm. A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy.

The decision to add folic acid and vitamin B_{12} was made after the start of the study. At the time of the decision, approximately 117 patients had been accrued to the pivotal study. All patients still on study therapy (in both treatment arms) were given folic acid (350 to 1000 µg oral daily) and vitamin B_{12} (1000 µg intramuscular every 9 weeks). In addition, the same doses and schedules of these vitamins were routinely given to all subsequent new patients enrolled into the study.

2.1 Extent of Exposure

Drug Administration

Of the 456 patients randomly assigned to a treatment arm, 448 (98.2%) received Alimta/ cisplatin or cisplatin monotherapy. These patients constitute the randomized and treated (RT) population for this study. Of these, 226 patients were randomized to and treated with Alimta/cisplatin and 222 patients were randomized to the cisplatin alone arm and received at least one dose of cisplatin. Among these 448 patients, 331 patients were fully supplemented and constituted the fully supplemented (FS) population for this study. Of the 331 patients, 168 were randomized and treated with Alimta/cisplatin and 163 were randomized and treated with cisplatin alone.

Among the RT patients, a median of six cycles (range: 1 – 12 cycles) were completed on the Alimta/ cisplatin arm compared with four cycles (range: 1 – 9 cycles) completed on the cisplatin alone arm. A total of 120 (53.1%) patients on the Alimta/ cisplatin arm and 89 (40.1%) patients on the cisplatin alone arm completed at least six cycles of therapy while 18 (8.0%) patients on the Alimta/ cisplatin arm compared with 19 (8.6%) patients on the cisplatin alone arm completed only one cycle. The duration of treatment was greater in the Alimta/cisplatin arm than in the cisplatin alone arm.

Among the FS patients, a median of six cycles of therapy were delivered on the Alimta/ cisplatin arm compared with four cycles delivered on the cisplatin alone arm. In addition, among FS patients, a total of 97 (57.7%) patients on the Alimta/ cisplatin arm versus 66 (40.5%) patients on the cisplatin alone arm completed at least six cycles of therapy. Thirteen (7.7%) patients on the Alimta/ cisplatin arm compared with 15 (9.2%) patients on the cisplatin alone arm completed only one cycle.

The Table below summarizes the number of cycles of therapy administered by treatment arm by supplementation status. Within the Alimta/ cisplatin arm, FS patients received a median of six cycles compared with two cycles in the never-supplemented (NS) patients (p=< 0.001). For the cisplatin alone arm, there was also a difference favoring a larger number of cycles in the FS group (p= 0.049).

Table 7.1. Summary of Cycles Given RT Population FS and NS

	LY/cis		Cisplatin	
Completed Cycles	FS (N=168)	NS (N=32)	FS (N=163)	NS (N=38)
Mean	4.9	3.2	4.0	3.2
Median	6.0	2.0	4.0	2.0
Standard Deviation	2.2	1.8	2.1	1.8
Minimum				
Maximum				

Source: Section 12.1.7. Applicant's Table JMCH 12.13

Among RT patients, 1066 cycles were administered to patients on the Alimta/ cisplatin arm while 877 cycles were administered to patients on the cisplatin alone arm. On the Alimta/ cisplatin arm, 96.6% of the Alimta cycles and 96.5% of the cisplatin cycles were administered at full dose. On the cisplatin alone arm, 99.7% of cycles were given without any dose adjustment.

The following tables show the duration of exposure, doses and dose intensity in all the treatment groups. The FDA exposure analysis is consistent with that submitted by the applicant.

Alimta exposure was for a median of 18 weeks. The median doses of Alimta and cisplatin were higher in those fully supplemented. Patients in both arms received > 90% of the planned dose

intensity. Patients receiving Alimta in the RT group received a relative dose intensity of 92% of the protocol specified Alimta dose intensity and patients treated with cisplatin in the same group received 92.3% of the projected dose intensity with Alimta compared to 96.5% cisplatin alone. Similarly, after supplementation, 92.7% Alimta, 93% cisplatin when given with Alimta and 96.4% cisplatin when given alone were the relative dose intensities.

Table 7.2. Treatment Duration (weeks) (Reviewers Table)

	Randomized and treated patients			**Fully Supplemented Patients**		
	Alimta/cisplatin N=226		**Cisplatin** N=222	**Alimta/cisplatin** N=168		**Cisplatin** N=163
	Alimta	cisplatin	cisplatin	Alimta	cisplatin	cisplatin
Median duration	18	18	12	18	18	12
Mean duration	15	15	12	16	16	13
Max duration	39	39	27	39	39	27
Min duration	3	3	3	3	3	3

Table 7.3. Total Dose of Treatment Received (Reviewers Table)

	Randomized and treated patients			**Fully supplemented patients**		
	Alimta/cisplatin N=226		**Cisplatin** N=222	**Alimta/cisplatin** N=168		**Cisplatin** N=163
	Alimta Mg/m^2	Cisplatin Mg/m^2	Cisplatin Mg/m^2	Alimta Mg/m^2	Cisplatin Mg/m^2	Cisplatin Mg/m^2
Median dose	2614.5	399.4	300	2942	445	300
Mean dose	2289.7	343.6	295.3	2392.3	358.4	298.1
Max dose	6008	902	666	6008	902	666
Min dose	497	74	68	497	74	68

Table 7.4. Dose Intensity (DI) Per Week ($mg/m^{2)}$ (Reviewers Table)

	Randomized and treated patients			Fully supplemented patients		
	Alimta/cisplatin N=226		Cisplatin N=222	Alimta/cisplatin N=168		Cisplatin N=163
	Alimta	Cisplatin	Cisplatin	Alimta	Cisplatin	Cisplatin
Median DI	160.3	24.1	24.8	162	24.3	24.8
Mean DI	153.3	23.1	24.1	154.5	23.3	24.1
Max DI						
Min DI						
Relative dose intensity (%)*	91.9	92.3	96.5	92.7	93.1	96.4

*Dose delivered(mean)/dose planned

Reviewers Comment:
The median duration of treatment was the same in the RT and FS groups. The median doses for Alimta and cisplatin were higher in those fully supplemented. The planned dose for Alimta was 166 mg/m^2/week, and the mean dose delivered was 153 mg/m^2/week for a relative dose intensity of 92%. Relative dose intensity of cisplatin given alone was higher than that of cisplatin when given with Alimta. However, the relative dose intensity for both Alimta and cisplatin in the Alimta/cisplatin arm with and without supplementation was greater than 90%. Folate and vitamin B_{12} supplementation allowed the administration of more cycles of chemotherapy.

Dose Delays

In the RT population, 308 (28.9%) dose delays were reported for the patients treated on the Alimta/ cisplatin arm, and 171 (19.5%) were reported for patients treated with cisplatin alone. Scheduling conflicts constituted the majority of the dosing delays with a total of 172 (55.8%) delays on the Alimta/cisplatin arm and131 (76.6%) delays on the cisplatin alone arm. The most common clinical cause of delay on both arms was neutropenia, followed by reduced creatinine clearance, leukopenia, anemia, stomatitis and infection. On both treatment arms, Cycle 4 was the cycle of therapy with the most clinical delays.

In the FS arm, there were 231 dose delays in the Alimta/cisplatin arm and 124 reported in patients treated with cisplatin alone. As in the RT population, scheduling conflicts caused the majority of dose delays and the reasons for the delays were similar.

Table 7.5. Most Common Clinical Reasons for Dose Delay-All Cycles (Reviewers Table)

Reason	Randomized and treated patients		Fully supplemented patients	
	Alimta/cisplatin N (%)	Cisplatin N (%)	Alimta/cisplatin N (%)	Cisplatin N (%)
Scheduling conflict	172 (55.8)	131 (76.6)	134 (58.0)	91 (73.4)
Neutropenia	68 (22.1)	11 (6.4)	50 (21.6)	7 (5.6)
CrCl decreased	20 (6.5)	12 (7.0)	13 (5.6)	12 (9.7)
Anemia	11 (3.6)	1 (0.6)	5 (2.2)	1 (0.8)
Leukopenia	9 (2.9)	3 (1.8)	8 (3.5)	3 (2.4)
Stomatitis	3 (1.0)	0	3 (1.3)	0
Infection	1 (0.3)	2 (1.2)	1 (0.4)	1 (0.8)
Fatigue	2 (0.6)	0	1 (0.4)	0
Rash	2 (0.6)	0	1 (0.4)	0
Diarrhea	1 (0.3)	1 (0.6)	0	1 (0.8)
Dyspnea	1 (0.3)	1 (0.6)	1 (0.4)	1 (0.8)
URI	1 (0.3)	1 (0.6)	1 (0.4)	1 (0.8)
Vomiting	1 (0.3)	1 (0.6)	0	0

CrCl: creatinine clearance; URI: upper respiratory infection

Reviewers Comment:
There were more dose delays in patients treated with the Alimta and cisplatin combination. Scheduling conflict caused the most dose delays. Of the drug related toxicity neutropenia caused the most dose delays.

Dose Reductions/Omissions

Dose reductions on the Alimta/cisplatin arm were reported in 27 (2.5%) for Alimta and cisplatin, 9 (0.8%) for Alimta alone and 1 (0.1%) for cisplatin alone in the randomized and treated population. The most frequent reason for dose reduction was neutropenia, followed by diarrhea, thrombocytopenia, and stomatitis. On the cisplatin alone arm, 3 (0.3%) dose reductions were reported. On both arms, dose reductions occurred most frequently in Cycle 2. In the fully supplemented patients on the Alimta/ cisplatin arm, the most frequent reasons for Alimta dose reductions were diarrhea, neutropenia, and stomatitis (each 17.4%). The most frequent reasons for cisplatin dose reductions were attributed to neutropenia (4 [23.5%]), diarrhea (3 [17.6%]) and thrombocytopenia (3 [17.6%]). The Tables below summarize these findings.
Two patients (Patients #136- 1631 and #720- 7200) omitted cisplatin at some time during therapy. One patient received the last eight cycles of therapy with cisplatin omitted because of deafness; another patient omitted cisplatin in the last cycle because of vomiting. Both were on the Alimta/cisplatin arm.

Table 7.6. Reasons for Dose Reduction – All Doses Delivered RT Population

	LY/cis		Cisplatin
Reason	LY231514	Cisplatin	Cisplatin
Total Reductions	36	28	3
Neutropenia	9 (25.0%)	9 (32.1%)	1 (33.3%)
Thrombocytopenia	5 (13.9)	5 (17.9)	0
Diarrhea	5 (13.9)	4 (14.3)	0
Stomatitis	6 (16.7)	1 (3.6)	0
Blood cr increased	1 (2.8)	1 (3.6)	0
CrCl decreased	1 (2.8)	1 (3.6)	0
Nausea	2 (5.6)	2 (7.1)	0
Fatigue	2 (5.6)	1 (3.6)	0
Vomiting	2 (5.6)	1 (3.6)	0
Dehydration	1 (2.8)	1 (3.6)	0
GGT increased	1 (2.8)	1 (3.6)	0
Rash	1 (2.8)	0	0
Deafness	0	1 (3.6)	0
Hyponatremia	0	0	1 (33.3)
Neurotoxicity	0	0	1 (33.3)

Source: Section 12.1.3 Applicant Table JMCH.12.8.

Table 7.7. Reasons for Dose Reduction – All Doses Delivered RT Population by Supplementation Status

	LY/cis				Cisplatin	
Drug Associated	LY231514		Cisplatin		Cisplatin	
Reason	FS	PS+NS	FS	PS+NS	FS	PS+NS
Total Reductions	23	13	17	11	2	1
Neutropenia	4 (17.4%)	5 (38.5%)	4 (23.5%)	5 (45.5%)	1 (50.0%)	0
Thrombocytopenia	3 (13.0)	2 (15.4)	3 (17.6)	2 (18.2)	0	0
Diarrhea	4 (17.4)	1 (7.7)	3 (17.6)	1 (9.1)	0	0
Stomatitis	4 (17.4)	2 (15.4)	0	1 (9.1)	0	0
Blood cr increased	1 (4.3)	0	1 (5.9)	0	0	0
CrCl decreased	1 (4.3)	0	1 (5.9)	0	0	0
Nausea	2 (8.7)	0	2 (11.8)	0	0	0
Fatigue	2 (8.7)	0	1 (5.9)	0	0	0
Vomiting	1 (4.3)	1 (7.7)	0	1 (9.1)	0	0
Dehydration	0	1 (7.7)	0	1 (9.1)	0	0
GGT increased	1 (4.3)	0	1 (5.9)	0	0	0
Rash	0	1 (7.7)	0	0	0	0
Deafness	0	0	1 (5.9)	0	0	0
Hyponatremia	0	0	0	0	1 (50.0)	0
Neurotoxicity	0	0	0	0	0	1 (100%)

Source: Section 12.1.3, Applicant Table JMCH.12.9

Protocol Violations

While dose escalations were not permitted according to protocol, 2 patients were given dose escalations in violation of the protocol. On the Alimta/ cisplatin arm, a single dose escalation (Patient # 403- 4047) occurred in which the Alimta dose was escalated in error from 250 mg/ m^2 to 500 mg/ m^2 in Cycle 5. On the cisplatin alone arm, 1 patient (Patient #502- 5014) received a reduced cisplatin dose in Cycle 2 which was subsequently escalated to the full dose (75 mg/ m^2) in Cycle 3 and all remaining cycles.

3. Methods and Specific Findings of Safety Review

The definition of the safety population was any patient who received at least one dose of the drug. A clinical trial adverse event was defined as any undesirable experience that occurred after the patient had received the first dose of study drug without regard to the possibility of a causal relationship, and without regard to treatment group assignment. The occurrence or nature of adverse events were acquired by study site personnel and recorded on the patient's case report forms (CRF). Unless otherwise indicated, all AE rates are reported on a per patient basis.

The safety review was conducted using the electronic datasets from the randomized controlled trial comparing Alimta in combination with cisplatin and cisplatin alone for treatment of patients with MPM. All adverse events after the patient had received the first dose of study drug without regard to the possibility of a causal relationship were considered. Study datasets were constructed by deriving datasets from the raw datasets provided. The study used the Medical Dictionary for Regulatory Activities (MedDRA Version 3.0) translation dictionary for the reporting of the adverse event data. MedRA was used to code the investigators adverse event terms to actual term or CTC text. Adverse events were graded using the NCI Common Toxicity Criteria.

3.1 Summary of Adverse Events

A total of 226 patients on the Alimta/cisplatin arm and 222 patients on the cisplatin alone arm qualified for safety analysis. On the Alimta/cisplatin arm, 223 (98.7%) patients reported at least one adverse event (AE). On the cisplatin alone arm, a total of 218 (98.2%) patients reported at least one AE.

Tables 7.8 and 7.9 summarize the adverse events (≥5%) reported for all patients who received study drug, regardless of drug causality.

On both treatment arms in both populations nausea, fatigue and dyspnea were the most commonly reported AEs of all grades.

In the RT population, in the Alimta/cisplatin arm, neutropenia, fatigue and leucopenia were the most commonly reported grade 3/4 AEs. In the cisplatin alone arm, hypertension, fatigue and

dyspnea were the most commonly reported grade 3/4 AEs. The incidence of grade 3/4 neutropenia was much higher (28.8%) when Alimta and cisplatin were used in combination than when cisplatin was used alone (2.3 %). The incidence of leucopenia (18 vs. 1.4 %), nausea (14.6 vs. 6.3%), vomiting (13.7 vs. 3.6%), anemia (6.2 vs. 0.5%), thrombocytopenia (5.8 vs. 0%), and anorexia (3.2 vs. 0.5%) were also higher in the Alimta/cisplatin arm. In the cisplatin alone arm, the incidence of hypertension was higher (16.2%) than in the Alimta/cisplatin arm (9.3%). Other AEs higher in the cisplatin alone arm were dyspnea, tumor pain, pleuritic pain, edema, depression and insomnia. In the Alimta/cisplatin arm, grade 3/4 neutropenia, leucopenia, nausea and vomiting occurred in 15% or more of the patients.

In the FS population, neutropenia, fatigue and leucopenia were the most commonly reported grade 3/4 AEs in the Alimta/cisplatin arm while hypertension, fatigue and dyspnea were most common in the cisplatin alone arm. The incidence of grade 3/4 neutropenia in the Alimta/cisplatin arm (24.4%) was higher than the cisplatin alone arm (3.1%). The incidence of fatigue (17.3 vs. 12.9%), leucopenia (15.5% vs. 0.6%), nausea (11.9 vs. 5.5%), dyspnea (11.3 vs. 9.2%), vomiting (10.7 vs. 4.3%), chest pain (8.3 vs. 6.7%), anemia (6.0 vs. 0.6%), thrombocytopenia (5.4 vs. 0.0 %), and anorexia (2.4 vs. 0.6%) were also higher in the Alimta/cisplatin arm. In the cisplatin alone arm, the incidence of hypertension was higher (17.8%) than in the Alimta/cisplatin arm (11.3%). Other AEs more common in the cisplatin alone arm are pain, decreased creatinine and hearing loss. In the Alimta/cisplatin arm, grade 3/4 neutropenia, leucopenia and fatigue occurred in more than 15% of the patients.

Table 7.10 shows the incidence of grade 3/4 toxicities in patients who were fully supplemented with folic acid and vitamin B_{12} from the time of enrollment in the study and patients who never received vitamin supplementation during the study in the Alimta/cisplatin arm. Compared to patients never supplemented, grade 3/4 hypertension, thrombosis/embolism and chest pain were more frequent among those supplemented.

As expected, there were more AEs experienced by patients on the Alimta/ cisplatin arm than on the cisplatin alone arm in both treatment populations. Overall, even after vitamin supplementation, there were more AEs with the Alimta/cisplatin combination although both populations have a reduced incidence of adverse events on supplementation. Severe toxicities reported on the Alimta/ cisplatin arm were less frequent among FS patients.

Myelosuppression was the most common toxicity of Alimta. Myelosuppression was manifested predominantly as neutropenia. In the fully supplemented Alimta/cisplatin arm, the initial incidence of grades 3/4 neutropenia was 24.4%. The incidence of febrile neutropenia and neutropenic sepsis were relatively infrequent. The incidences of grade 3/4 anemia and thrombocytopenia were 6% and 5.4% respectively.

Figures 7.1-7.3 shows the percentage of the ten commonest grade 3/4 adverse events in the RT population, FS population and the group never supplemented.

There were 2 hospitalizations for febrile neutropenia (Patient # 111-1347 and #804-8040), one of whom died while on-study (#804-840). The death of one patient (patient #510-5100) was

attributed to febrile neutropenia. The death of another patient with febrile neutropenia (patient #214-2148) could be study-drug related.

Table 7.8. Adverse Events Summary (≥5% Incidence) in RT Population (Reviewers Table)

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	139	61.5	65	28.8	33	14.9	5	2.3
Fatigue	187	82.7	41	18.1	167	75.2	34	15.3
Leukocytes	130	57.5	41	18.1	45	20.3	3	1.4
Nausea	195	86.3	33	14.6	177	79.7	14	6.3
Vomiting	145	64.2	31	13.7	117	52.7	8	3.6
Dyspnea	149	65.9	25	11.1	146	65.8	32	14.4
Hypertension	56	24.8	21	9.3	74	33.3	36	16.2
Chest pain	90	39.8	18	8.0	69	31.1	16	7.2
Hemoglobin	73	32.3	14	6.2	34	15.3	1	0.5
Platelets	66	29.2	13	5.8	19	8.6	0	0.0
Thrombosis/embolism	14	6.2	12	5.3	10	4.5	9	4.1
Diarrhea without colostomy	64	28.3	11	4.9	35	15.8	1	0.5
Tumor pain	42	18.6	11	4.9	37	16.7	12	5.4
Dehydration	20	8.8	10	4.4	2	0.9	2	0.9
Stomatitis/pharyngitis	81	35.8	9	4.0	20	9.0	0	0.0
Anorexia	87	38.5	8	3.5	61	27.5	1	0.5
Constipation	103	45.6	8	3.5	90	40.5	3	1.4
Renal/Genitourinary-Other	73	32.3	8	3.5	66	29.7	6	2.7
Constitutional Symptoms-Other	22	9.7	6	2.7	18	8.1	2	0.9
Pleuritic pain	39	17.3	6	2.7	39	17.6	10	4.5
Other pain	33	14.6	5	2.2	46	20.7	7	3.2
Pulmonary-Other	42	18.6	5	2.2	37	16.7	4	1.8
Febrile neutropenia	4	1.8	4	1.8	0	0.0	0	0.0
Infection with grade 3 or 4 Neutropenia	20	8.8	4	1.8	13	5.9	1	0.5
Infection without Neutropenia	25	11.1	4	1.8	12	5.4	2	0.9
Other Gastrointestinal	44	19.5	4	1.8	30	13.5	1	0.5
Dysphagia, esophagitis, odynophagia	12	5.3	3	1.3	11	5.0	1	0.5
Mood alteration-anxiety agitation	26	11.5	3	1.3	24	10.8	1	0.5

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Other endocrine	18	8.0	3	1.3	18	8.1	0	0.0
Rash/desquamation	61	27.0	3	1.3	26	11.7	0	0.0
Abdominal pain or cramping	21	9.3	2	0.9	16	7.2	1	0.5
Edema	34	15.0	2	0.9	33	14.9	5	2.3
Fever	36	15.9	2	0.9	18	8.1	0	0.0
Infection/Febrile Neutropenia-Other	5	2.2	2	0.9	4	1.8	0	0.0
Inner ear/hearing	21	9.3	2	0.9	30	13.5	2	0.9
Mood alteration-depression	28	12.4	2	0.9	21	9.5	3	1.4
Other auditory/hearing	15	6.6	2	0.9	11	5.0	0	0.0
Other musculoskeletal	18	8.0	2	0.9	18	8.1	2	0.9
Alopecia	31	13.7	1	0.4	15	6.8	0	0.0
Cough	90	39.8	1	0.4	82	36.9	2	0.9
Creatinine	39	17.3	1	0.4	26	11.7	2	0.9
Dizziness/lightheadedness	20	8.8	1	0.4	19	8.6	0	0.0
Dyspepsia/heartburn	26	11.5	1	0.4	10	4.5	0	0.0
Headache	29	12.8	1	0.4	24	10.8	1	0.5
Hypercholesterolemia	10	4.4	1	0.4	20	9.0	1	0.5
Other metabolic/laboratory	7	3.1	1	0.4	14	6.3	0	0.0
Other neurology	18	8.0	1	0.4	13	5.9	1	0.5
SGPT(ALT)	17	7.5	1	0.4	20	9.0	1	0.5
Sweating	29	12.8	1	0.4	27	12.2	0	0.0
Tearing	15	6.6	1	0.4	1	0.5	0	0.0
Weight loss	42	18.6	1	0.4	31	14.0	2	0.9
Insomnia	36	15.9	0	0.0	40	18.0	3	1.4
Neuropathy-sensory	36	15.9	0	0.0	30	13.5	1	0.5
SGOT(AST)	18	8.0	0	0.0	12	5.4	1	0.5
Allergic rhinitis	20	8.8	0	0.0	8	3.6	0	0.0
Conjunctivitis	21	9.3	0	0.0	1	0.5	0	0.0
Other Dermatology/Skin	16	7.1	0	0.0	15	6.8	0	0.0
Other ocular/visual	12	5.3	0	0.0	6	2.7	0	0.0
Taste disturbance	21	9.3	0	0.0	15	6.8	0	0.0
Urinary frequency/urgency	16	7.1	0	0.0	9	4.1	0	0.0

Table 7.9. Adverse Events Summary (≥ 5% Incidence) in RT Fully Supplemented Population (Reviewers Table)

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	96	57.1	41	24.4	22	13.5	5	3.1
Fatigue	137	81.5	29	17.3	120	73.6	21	12.9
Leukocytes	92	54.8	26	15.5	30	18.4	1	0.6
Nausea	142	84.5	20	11.9	128	78.5	9	5.5
Dyspnea	110	65.5	19	11.3	103	63.2	15	9.2
Hypertension	44	26.2	19	11.3	56	34.4	29	17.8
Vomiting	99	58.9	18	10.7	83	50.9	7	4.3
Chest pain	68	40.5	14	8.3	50	30.7	11	6.7
Hemoglobin	57	33.9	10	6.0	24	14.7	1	0.6
Thrombosis/embolism	12	7.1	10	6.0	6	3.7	6	3.7
Platelets	44	26.2	9	5.4	15	9.2	0	0.0
Tumor pain	31	18.5	8	4.8	24	14.7	7	4.3
Dehydration	12	7.1	7	4.2	2	1.2	2	1.2
Constipation	78	46.4	6	3.6	66	40.5	1	0.6
Diarrhea without colostomy	43	25.6	6	3.6	25	15.3	1	0.6
Other pain	26	15.5	5	3.0	42	25.8	7	4.3
Pulmonary-Other	34	20.2	5	3.0	31	19.0	4	2.5
Renal/Genitourinary-Other	52	31.0	5	3.0	50	30.7	4	2.5
Stomatitis/pharyngitis	47	28.0	5	3.0	13	8.0	0	0.0
Anorexia	59	35.1	4	2.4	44	27.0	1	0.6
Constitutional Symptoms-Other	18	10.7	4	2.4	14	8.6	2	1.2
Infection without Neutropenia	21	12.5	4	2.4	7	4.3	0	0.0
Other Gastrointestinal	33	19.6	3	1.8	26	16.0	1	0.6
Pleuritic pain	29	17.3	3	1.8	31	19.0	8	4.9
Dysphagia, esophagitis, odynophagia	10	6.0	2	1.2	9	5.5	0	0.0
Edema	24	14.3	2	1.2	25	15.3	4	2.5
Hyperglycemia	8	4.8	2	1.2	11	6.7	6	3.7
Infection/Febrile Neutropenia-Other	5	3.0	2	1.2	3	1.8	0	0.0
Mood alteration-depression	23	13.7	2	1.2	15	9.2	2	1.2
Other	19	11.3	2	1.2	19	11.7	3	1.8

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
cardiovascular/general								
Other musculoskeletal	14	8.3	2	1.2	13	8.0	2	1.2
Cough	64	38.1	1	0.6	61	37.4	2	1.2
Creatinine	26	15.5	1	0.6	18	11.0	2	1.2
Dizziness/lightheadedness	16	9.5	1	0.6	16	9.8	0	0.0
Dyspepsia/heartburn	20	11.9	1	0.6	6	3.7	0	0.0
Headache	21	12.5	1	0.6	18	11.0	1	0.6
Hypercholesterolemia	7	4.2	1	0.6	19	11.7	1	0.6
Infection with grade 3 or 4 Neutropenia	10	6.0	1	0.6	6	3.7	0	0.0
Mood alteration-anxiety agitation	22	13.1	1	0.6	14	8.6	0	0.0
Other auditory/hearing	11	6.5	1	0.6	8	4.9	0	0.0
Other endocrine	12	7.1	1	0.6	16	9.8	0	0.0
Other metabolic/laboratory	7	4.2	1	0.6	11	6.7	0	0.0
Rash/desquamation	37	22.0	1	0.6	16	9.8	0	0.0
Sweating	24	14.3	1	0.6	17	10.4	0	0.0
Abdominal pain or cramping	13	7.7	0	0.0	13	8.0	1	0.6
Cardiac-ischemia/infarction	7	4.2	0	0.0	10	6.1	4	2.5
Inner ear/hearing	13	7.7	0	0.0	21	12.9	2	1.2
Insomnia	28	16.7	0	0.0	31	19.0	1	0.6
Neuropathy-sensory	29	17.3	0	0.0	24	14.7	1	0.6
Other neurology	14	8.3	0	0.0	11	6.7	1	0.6
SGOT(AST)	14	8.3	0	0.0	10	6.1	1	0.6
SGPT(ALT)	10	6.0	0	0.0	17	10.4	1	0.6
Weight loss	32	19.0	0	0.0	18	11.0	1	0.6

Table 7.10. Grade 3/4 Adverse Events in Fully Supplemented versus Never Supplemented Patients treated with Alimta/Cisplatin (Reviewers Table)

Adverse Events	Fully Supplemented % N=168	Never Supplemented % N=32
Neutrophils/granulocytes	24.4	37.5
Fatigue	17.3	31.3
Leukocytes	15.5	34.4
Nausea	11.9	31.3
Dyspnea	11.3	12.5
Hypertension	11.3	3.1
Vomiting	10.7	34.4
Chest pain	8.3	6.3
Hemoglobin	6.0	9.4
Thrombosis/embolism	6.0	3.1
Platelets	5.4	9.4
Tumor pain	4.8	6.3
Dehydration	4.2	9.4
Constipation	3.6	3.1
Diarrhea without colostomy	3.6	9.4
Febrile neutropenia	0.6	9.4
Infection with Grade3/4 Neutropenia	0.6	6.3

Figure 7.1. Alimta/Cisplatin: % of Ten Commonest Grade 3/4 Adverse Events RT Population (Reviewers Chart)

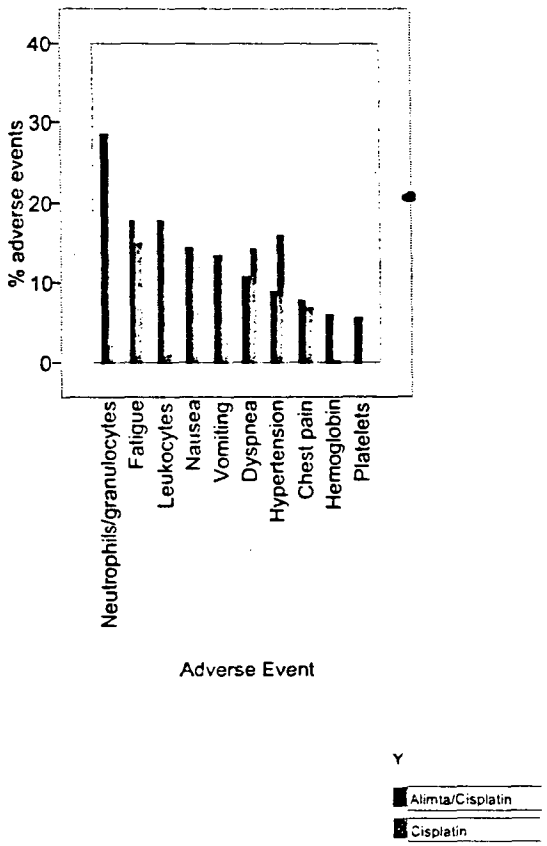


Figure 7.2. Alimta/Cisplatin: % of Ten Commonest Grade 3/4 Adverse Events RT Fully Supplemented Population (Reviewers Chart)

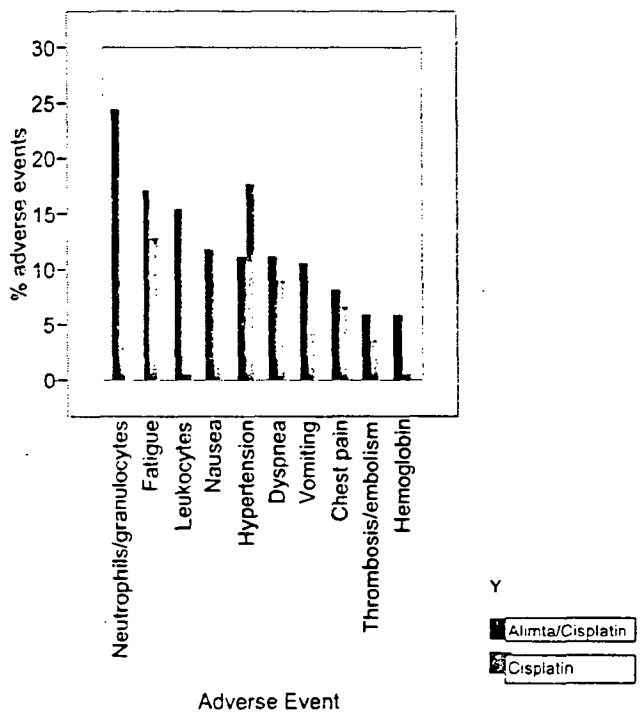
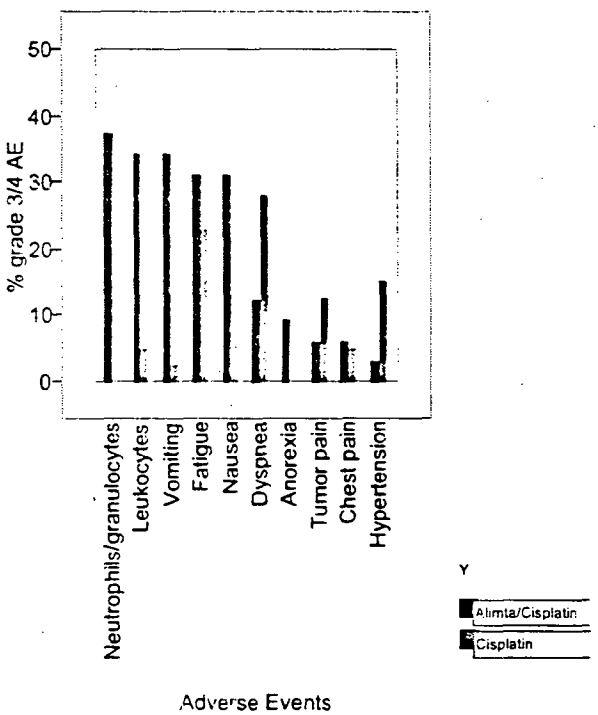


Figure 7.3. Alimta/Cisplatin: % of Ten Commonest Grade 3/4 Adverse Events RT Never-Supplemented Group (Reviewers Chart)



The following adverse events were selected to be discussed individually.

1. **Neutropenia**

There were 1066 cycles of Alimta delivered to the 226 patients in the Alimta/cisplatin arm. For these patients, the median nadir ANC was 1,928 cells/mm^3.
Twenty-three of these patients had nadir ANC below 500 in a total of 31 cycles (threshold for dose adjustment), with the median nadir count of 274 cells/mm^3. For these 23 patients, the median duration of neutropenia to recovery above 500 cells/mm^3 was 7 days.

There were 877 cycles of cisplatin delivered to the 222 patients in the cisplatin arm. For these patients, the median nadir ANC was 3,443 cells/mm^3. Only 1 patient had nadir ANC below 500 and this occurred in only 1 cycle, (440 cells/mm^3).

Five patients had febrile neutropenia, 4 in the Alimta/cisplatin arm, of which one was in the supplemented group. One death was attributed to febrile neutropenia (Patient # 510-5100). Two other deaths while on-study therapy also had febrile neutropenia (Patient # 804-8040 and # 150-1580). There were no deaths in the supplemented group. Two patients were hospitalized for febrile neutropenia (Patient # 111-1347 and # 804-8040).

Granulocyte colony-stimulating factors (CSFs) were given to 5 patients, all for the purpose of treating established severe neutropenia. Of the 4 patients on the Alimta/ cisplatin arm, 3 patients were in the PS+ NS subgroup. The patient on the cisplatin alone arm was also in that subgroup.

Table 7.12 shows the patients with febrile neutropenia and infection with and without neutropenia.

Table 7.11. Incidence and Severity of Neutropenia (Reviewers Table)

Neutropenia grade	RT patients				Fully Supplemented patients			
	Alimta/cisplati n N	%	Cisplatin N	%	Alimta/cisplati n N	%	Cisplatin N	%
1	31	13.7	15	6.8	23	13.7	9	5.5
2	43	19.0	13	5.9	32	19.0	8	4.9
3	47	20.8	4	1.8	32	19.0	4	2.5
4	18	8.0	1	0.5	9	5.4	1	0.6

Table 7.12. Safety: Neutropenia/Infection (Reviewers Table)

Event	Randomized and treated patients				Fully supplemented patients			
	Alimta/cisplati n N	%	Cisplatin N	%	Alimta/cisplati n N	%	Cisplatin N	%
Febrile neutropenia	4	1.8	1	0.5	1	0.6	0	0
Infection with G3/4 neutropenia	3	1.3	1	0.5	0	0	0	0
Infection without neutropenia	1	0.4	0	0	1	0.6	0	0

2. Anemia

There were no protocol restrictions to the use of erythrocyte CSFs. Of the 24 patients who received erythrocyte CSFs, 17 patients were treated for anemia. A total of 7 patients received erythrocyte CSFs prophylactically, 5 patients on the Alimta/ cisplatin fully supplemented arm and 2 patients on the cisplatin alone partially or nonsupplemented arm.
There were no patients who were transfused due to bleeding.

Table 7.13. Incidence and Severity of Anemia (Reviewers Table)

Anemia grade	RT population				Fully Supplemented			
	Alimta/cisplatin N	%	Cisplatin N	%	Alimta/cisplatin N	%	Cisplatin N	%
1	51	22.6	28	12.6	39	23.2	21	12.9
2	52	23.0	19	8.6	41	24.4	14	8.6
3	14	6.2	1	0.5	10	6.0	1	0.6
4	1	0.4	0	0.0	1	0.6	0	0.0

3. Fatigue

Grade 3 fatigue was high and not lessened by supplementation in the Alimta/cisplatin arm. Fatigue together with co-existing nausea or mild vomiting leads to decreased quality of life and may not allow most patients to maintain relatively normal function while receiving treatment.

Table 7.14. Incidence and Severity of Fatigue (Reviewers Table)

Fatigue grade	RT population				Fully Supplemented			
	Alimta/cisplatin N	%	Cisplatin N	%	Alimta/cisplatin N	%	Cisplatin N	%
1	75	33.2	71	43.6	57	33.9	50	30.7
2	71	31.4	62	38.0	51	30.4	49	30.1
3	39	17.3	33	20.2	29	17.3	20	12.3
4	2	0.9	1	0.6	0	0.0	1	0.6

5. Nausea

Both treatment arms were treated with 5-HT3 antagonists and many received additional treatments. Both treatment arms also received dexamethasone.
In the Alimta/cisplatin arm, the most frequently reported serious adverse event was nausea (8.4%) and vomiting (8.4%).

In the Alimta/cisplatin arm the median time to start of nausea after chemotherapy was one day (range of 0 to 22 days) and the median duration of nausea was 6 days. Excluding episodes of nausea recorded as intermittent, the maximum duration of nausea was 37 days.

For the cisplatin alone arm, the median time to start of nausea after chemotherapy was one day (range of 0 to 31 days), and the median duration of nausea was 5 days. Excluding episodes of nausea recorded as intermittent, the maximum duration of nausea was 58 days.

Table 7.15. Incidence and Severity of Nausea (Reviewers Table)

Nausea grade	RT population				Fully Supplemented			
	Alimta/cisplatin n		Cisplatin		Alimta/cisplatin n		Cisplatin	
	N	%	N	%	N	%	N	%
1	69	30.5	86	38.7	50	29.8	64	39.3
2	93	41.2	77	34.7	72	42.9	55	33.7
3	31	13.7	14	6.3	19	11.3	9	5.5
4	2	0.9	0	0.0	1	0.6	0	0.0

6. Vomiting

Vomiting was the most frequently reported serious adverse event reported in both the Alimta/cisplatin arm (8.4%) and the cisplatin alone arm (2.3%). It was also one of the main reasons for discontinuation.

Table 7.16. Incidence and Severity of Vomiting (Reviewers Table)

Vomiting grade	RT population				Fully Supplemented			
	Alimta/cisplatin n		Cisplatin		Alimta/cisplatin n		Cisplatin	
	N	%	N	%	N	%	N	%
1	49	21.7	57	25.7	37	22.0	43	26.4
2	65	28.8	52	23.4	44	26.2	33	20.2
3	29	12.8	7	3.2	17	10.1	6	3.7
4	2	0.9	1	0.5	1	0.6	1	0.6

7. Renal

Table 7.17 shows the incidence of renal-related adverse events. The incidence of renal-related events are higher in the Alimta/cisplatin combination arm compared to the cisplatin alone arm in both the RT and FS populations. The incidence of increased creatinine and decreased creatinine clearance are higher in the Alimta/cisplatin arm. There is a slight decrease with supplementation.

Table 7.17. Incidence of Renal Events (Reviewers Table)

Renal AE	RT patients				Fully Supplemented patients			
	Alimta/cisplatin N=248		Cisplatin N=222		Alimta/cisplatin N=168		Cisplatin N=163	
	N	%	N	%	N	%	N	%
Creatinine renal clearance decreased	61	27.0	49	22.1	40	23.8	36	22.1
Blood creatinine increased	39	17.3	26	11.7	26	15.5	18	11.0
Nocturia	1	0.4	0	0.0	1	0.6	0	0.0
Hydronephrosis	1	0.4	1	0.5	1	0.6	1	0.6
Polyuria	1	0.4	0	0.0	1	0.6	0	0.0
Blood urea increased	2	0.9	3	1.4	2	1.2	3	1.8
Renal impairment NOS	2	0.9	1	0.5	1	0.6	1	0.6
Renal failure NOS	0	0.0	1	0.5	0	0.0	1	0.6
Acute pre-renal failure	1	0.4	0	0.0	0	0.0	0	0.0

Reviewer's Comments:
All adverse events are discussed without regard to the possibility of a causal relationship. All safety reviewers' results are based on the analysis data sets provided by the sponsor.
The Alimta and cisplatin combination is more toxic than cisplatin alone.
The data suggest that Alimta has a relatively high emetogenic potential in this treatment setting, given the similarity in the frequency of 5- HT3 administration across both treatment arms. Of note is that both treatment arms also received dexamethasone.
The most frequent toxicity of Alimta, myelosuppression, was reduced by folate and vitamin B_{12} supplementation.

Supplementation resulted in overall less toxicity including grade 3/4 toxicity in the Alimta/cisplatin arm. Patients receiving cisplatin alone also seemed to benefit from vitamin

supplementation, although to a lesser degree. Despite supplementation, however, the combination of Alimta and cisplatin produces a high degree of toxicity.

Serious Adverse Events

Serious adverse events (SAE) were defined as any event that resulted in death, initial or prolonged hospitalization, severe or permanent injury, congenital anomaly, was life-threatening or significant for any other reason. Table 7.18 summarizes the serious adverse events for patients enrolled into the study, regardless of drug causality. There were 36.7% SAE on the Alimta/cisplatin arm and 21.6 % on the cisplatin arm alone.

Table 7.18. Summary of Serious Adverse Events (> 2% Incidence) Regardless of Drug Causality RT Population

Event Classification	LY231514/CISPLATIN (N=226) n (%)	CISPLATIN (N=222) n (%)	TOTAL (N=448) n (%)	p-value
PATIENT WITH >= 1 EVENT	83 (36.7)	48 (21.6)	131 (29.2)	<.001
Vomiting NOS	19 (8.4)	5 (2.3)	24 (5.4)	0.005
Nausea	19 (8.4)	3 (1.4)	22 (4.9)	0.001
Dehydration	14 (6.2)	1 (0.5)	15 (3.3)	0.001
Dyspnoea NOS	9 (4.0)	6 (2.7)	15 (3.3)	0.601
Fatigue	9 (4.0)	3 (1.4)	12 (2.7)	0.141
Diarrhoea NOS	8 (3.5)	1 (0.5)	9 (2.0)	0.037
Neutrophil count decreased	9 (4.0)	0 (0.0)	9 (2.0)	0.004
Stomatitis	8 (3.5)	0 (0.0)	8 (1.8)	0.007
Anaemia NOS	7 (3.1)	0 (0.0)	7 (1.6)	0.015
Anorexia	5 (2.2)	0 (0.0)	5 (1.1)	0.061
White blood cell count decreased	5 (2.2)	0 (0.0)	5 (1.1)	0.061

Frequencies analyzed using a Fisher's Exact test

Source: Applicant Table JMCH.12.23.

The most frequently reported SAEs in the Alimta/ cisplatin arm were nausea (8.4%), vomiting (8.4%), and dehydration (6.2%). The most frequently reported SAEs in the cisplatin alone arm were dyspnea (2.7%) and vomiting (2.3%).

3.2 Discontinuations

Table 7.19 summarizes the reasons for discontinuations due to SAEs. A total of 15 (6.6%) patients on the Alimta/ cisplatin arm and 5 (2.3%) patients on the cisplatin alone arm discontinued from the study because of a SAE in the RT population. In the Alimta/ cisplatin arm, 4% patients discontinued because of possibly drug-related serious adverse events and, except for diarrhea that occurred twice, these were all single types of events.

Table 7.19. Serious Adverse Events that Led to Discontinuation RT Population

	Number of Patients with an Event Regardless of Drug Causality		Number of Patients with an Event Possibly Drug Related	
Reason	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=226)	Cisplatin (N=222)
Cerebral ischemia	2 (0.9%)	0	0	0
Diarrhea	2 (0.9)	0	2 (0.9%)	0
Anemia	1 (0.4)	0	1 (0.4)	0
Blood creatinine increased	1 (0.4)	0	1 (0.4)	0
Vomiting	1 (0.4)	0	1 (0.4)	0
Angina pectoris	1 (0.4)	0	1 (0.4)	0
Atrial fibrillation	1 (0.4)	0	0	0
Condition aggravated	1 (0.4)	0	1 (0.4)	0
Depression	1 (0.4)	0	0	0
Pulmonary embolism	1 (0.4)	0	1 (0.4)	0
Tumor pain	1 (0.4)	0	0	0
WBC decreased	1 (0.4)	0	1 (0.4)	0
Hypertension NOS	1 (0.4)	0	0	0
Cardiac failure	0	1 (0.5%)	0	1 (0.5%)
Dehydration	0	1 (0.5)	0	0
Fluid overload	0	1 (0.5)	0	0
Jugular vein thrombosis	0	1 (0.5)	0	0
Right ventricular failure	0	1 (0.5)	0	1 (0.5)
Total	15 (6.6)	5 (2.3)	9 (4.0)	2 (0.9)

Source: Applicant Table JMCH.12.26.

A nonserious clinically significant event was defined as any non- serious adverse event that led to discontinuation from the study. Thirteen patients discontinued on both the Alimta/ cisplatin arm as well as the cisplatin alone arm. In both treatment arms, the most frequent reason for discontinuation was decreased creatinine clearance (7 [3.1%] on the Alimta/ cisplatin arm, 9 [4.1%] on the cisplatin alone arm). A decrease in creatinine clearance was the only event occurring in > 1% of patients, occurring with similar frequency (3.1% versus 3.6%) in the two arms. Table 7.20 summarizes these patient discontinuations.

Table 7.21 shows the number of patients discontinuing treatment for grade 3/4 toxicity in each treatment group.

Table 7.20. Discontinuations Because of Nonserious, Clinically Significant Adverse Events RT Population

	Number of Patients with an Event Regardless of Drug Causality		Number of Patients with an Event Possibly Drug Related	
Reason	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=226)	Cisplatin (N=222)
CrCl decreased	7 (3.1%)	9 (4.1%)	7 (3.1%)	8 (3.6%)
Anemia	1 (0.4)	0	1 (0.4)	0
Deafness	1 (0.4)	0	1 (0.4)	0
Nausea	1 (0.4)	0	1 (0.4)	0
Neuropathy NOS	1 (0.4)	0	1 (0.4)	0
Vomiting	1 (0.4)	0	1 (0.4)	0
Pneumonitis NOS	1 (0.4)	0	1 (0.4)	0
Fatigue	0	1 (0.5)	0	1 (0.5)
Hypoasthesia	0	1 (0.5)	0	1 (0.5)
Tinnitus	0	1 (0.5)	0	1 (0.5)
Weight decreased	0	1 (0.5)	0	0
Total	13 (5.8)	13 (5.9)	13 (5.8)	11 (5.0)

Source: Section 12.3.1.2. Applicant Table JMCH 12.27.

Table 7.21. Discontinuations for Grade 3/4 AE (Reviewer's Table)

Adverse Events	No. of patients with each AE							
	RT population				Fully Supplemented			
	Alimta/Cisplatin		Cisplatin		Alimta/Cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
Leukocytes	8	3.5	0	0	4	2.4	0	0
Fatigue	5	2.2	1	0.5	4	2.4	1	0.6
Dyspnea	4	1.8	5	2.3	4	2.4	5	3.1
Neutrophils/granulocytes	9	4.0	0	0	3	1.8	0	0
Nausea	6	2.7	1	0.5	3	1.8	1	0.6
Vomiting	6	2.7	0	0	3	1.8	0	0
Platelets	4	1.8	0	0	2	1.2	0	0
Chest pain	2	0.9	3	1.4	2	1.2	3	1.8
Hypertension	2	0.9	4	1.8	2	1.2	4	2.5
Renal/Genitourinary-Other	2	0.9	1	0.5	2	1.2	1	0.6

Adverse Events	No. of patients with each AE							
	RT population				Fully Supplemented			
	Alimta/Cisplatin		Cisplatin		Alimta/Cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
Hemoglobin	3	1.3	0	0	1	0.6	0	0
Constitutional Symptoms-Other	2	0.9	0	0	1	0.6	0	0
Cushingoid appearance	1	0.4	0	0	1	0.6	0	0
Dehydration	1	0.4	1	0.5	1	0.6	1	0.6
Hypokalemia	1	0.4	0	0	1	0.6	0	0
Mood alteration-anxiety agitation	1	0.4	0	0	1	0.6	0	0
Mood alteration-depression	1	0.4	0	0	1	0.6	0	0
Other cardiovascular/arrhythmia	1	0.4	0	0	1	0.6	0	0
Other cardiovascular/general	1	0.4	1	0.5	1	0.6	1	0.6
Pulmonary-Other	1	0.4	1	0.5	1	0.6	1	0.6
Supraventricular arrhythmias	1	0.4	0	0	1	0.6	0	0
Thrombosis/embolism	1	0.4	1	0.5	1	0.6	1	0.6
Tumor pain	1	0.4	0	0	1	0.6	0	0
CNS Cerebrovascular ischemia	2	0.9	0	0	0	0	0	0
Diarrhea without colostomy	2	0.9	0	0	0	0	0	0
Abdominal pain or cramping	1	0.4	0	0	0	0	0	0
Alopecia	1	0.4	0	0	0	0	0	0
Fever	1	0.4	0	0	0	0	0	0
Hyperglycemia	1	0.4	2	0.9	0	0	2	1.2
Hypoglycemia	1	0.4	0	0	0	0	0	0
Inner ear/hearing	1	0.4	0	0	0	0	0	0
Other auditory/hearing	1	0.4	0	0	0	0	0	0
Other endocrine	1	0.4	0	0	0	0	0	0
Other neurology	1	0.4	0	0	0	0	0	0
Syncope	1	0.4	0	0	0	0	0	0

3.3 Deaths

Among patients who were randomized and treated, 22 died while on study or within 30 days of end of study or discontinuation, 14 of whom had been treated with Alimta/ cisplatin and 8 with cisplatin alone. Eight deaths in the Alimta/ cisplatin arm and three in the cisplatin alone arm occurred in the first two cycles of therapy and five deaths in the Alimta/ cisplatin arm and three in the cisplatin alone arm occurred in the 30 days following the last infusion of study drug. The on-study death rates in the RT group were 6.2% in the Alimta/cisplatin arm and 3.6% in the cisplatin alone arm.

In the FS subgroups, the death-rates were 4.8% in the Alimta/cisplatin arm and 3.7% in the cisplatin alone arm.

Tables 7.22 and 7.23 summarize deaths that occurred while patients were on-study. The deaths were fewer in the Alimta/cisplatin arm of the FS group.

Table 7.22. Summary of on- study Deaths RT Population

Reasons for Death	LY/cis (N=226)	Cisplatin (N=222)
Study Drug Toxicity		
Febrile neutropenia	1 (0.4%)	0
Study Disease		
Study disease[1]	11 (4.9)	5 (2.3%)
Other Causes		
Cerebrovascular accident NOS	1 (0.4)	0
Myocardial infarction	0	1 (0.5)
Septic shock	1 (0.4)	0
Sudden death unexplained	0	1 (0.5)
Thrombosis NOS	0	1 (0.5)
Total	14 (6.2)	8 (3.6)

[1] Two of the 11 deaths on the LY/cis arm are considered to be study disease-related by investigators, but were considered to be possibly study drug-related, in the opinion of the Lilly physician.

Source: Section 12.3.1.1. Applicant Table JMCH. 12.21.

Table 7.23. Summary of on- study Deaths RT Population by Supplementation Status

	LY/cis		Cisplatin	
Reason	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Study Drug Toxicity				
Febrile neutropenia	0	1 (1.7%)	0	0
Study Disease				
Study disease[1]	6 (3.6%)	5 (8.6)	4 (2.5%)	1 (1.7%)
Other Causes				
Cerebrovascular accident NOS	1 (0.6)	0	0	0
Myocardial infarction	0	0	0	1 (1.7)
Septic shock	1 (0.6)	0	0	0
Sudden death unexplained	0	0	1 (0.6)	0
Thrombosis NOS	0	0	1 (0.6)	0
Total	8 (4.8)	6 (10.3)	6 (3.7)	2 (3.4)

[1] Two of the 6 deaths on the LY/cis arm are considered to be study disease-related by investigators, but were considered to be possibly study drug-related, in the opinion of the Lilly physician.

Source: Section 12.3.1.1. Applicant Table JMCH 12.22.

Only one on-study death was thought by investigators to be possibly related to study drug (patient 510-5100). However, the symptoms leading to two other deaths warranted a closer examination of the circumstances. All cases discussed below were reviewed from the applicant's death summary and CRF.

Patient 510- 5100 (on the Alimta/ cisplatin arm and never supplemented) was a 75-year male diagnosed with stage IV epithelial MPM scar lesions and cranial and chest lymph nodes. The patient had undergone decortication and pleurectomy in June 1998. His KPS score was 90 with dyspnea on exertion as the only symptom. He started the first treatment of Alimta/cisplatin on 16 June 1999 and the last infusion was on 26 July 1999. He completed two cycles of therapy. Side effects in cycle 1 were CTC grade 1 rash, fever, nausea, anorexia, fatigue, and grade 3 neutropenia, leukopenia and thrombocytopenia. Cycle 2 was delayed because of poor appetite and generally feeling unwell. A blood transfusion was given because of low levels of hemoglobin on 26 July in cycle 2. The patient was seen in a clinic on day 8. He complained of grade 1 nausea but appeared well. One week later the patient's general practitioner informed the investigator that the patient had experienced fever, diarrhea, and stomatitis 13 days after the last dose of study drug. He was given morphine and had planned to come to the hospital the next day. He died at home on 09 August 1999. An autopsy was not performed.

Patient 214-2148 (Alimta/cisplatin arm, supplemented) was a 58-year old male with stage IV mixed cell MPM who was randomly assigned to receive Alimta/cisplatin and received only one cycle on 02 February 2000. On ——— he was hospitalized for stomatitis and anorexia. A chest x-ray did not show disease progression. His condition worsened and he died on ———. An autopsy was not performed. Although the investigator felt that the study drug was not related to his death, a relationship to study drug cannot be completely excluded.

Patient 804-8040 (Alimta/cisplatin, never supplemented) was a 59-year old male with Stage IV mixed cell MPM randomly assigned to receive Alimta/cisplatin. He received one cycle on 08 September 1999. Three days later, he experienced grade 3 nausea, vomiting, exertional dyspnea as well as grade 4 febrile neutropenia, leukocytes and neutrophils and died on 16 September 1999. An autopsy was not performed. A relationship to study drug cannot be excluded.

The cause of death in all other patients could be attributed to the underlying disease or to complications thereof.

Reviewers comment:
According to the sponsor and investigator, only one death was due to study drug toxicity. However, based on the above, 3 deaths in patients treated with Alimta/cislatin were possibly treatment related, the common thread being febrile neutropenia.
One death occurred in the Alimta/cisplatin arm with vitamin supplementation.

3.4 Serious, Unexpected, Reportable Adverse Events

Serious, unexpected, reportable adverse events were those events that were not described or listed in the clinical investigator's brochure and considered by the investigator or sponsor to be possibly or probably related to the study drug. Table 7.24 details these events.

Six patients on the Alimta/ cisplatin arm and 3 patients on the cisplatin alone arm experienced a serious, unexpected, reportable event. Except for constipation, all events were unique to a specific patient. Two events, ulcerative esophagitis and death, were attributable to Alimta.

Table 7.24. Serious, Unexpected, Reportable Adverse Events RT Population

LY/cis N=226				Cisplatin N=222			
Patient Number	FS/PS+NS	Drug Associated	Event	Patient Number	FS/PS+NS	Drug Associated	Event
101-1018	FS	Cisplatin	Hypovolemia	136-1632	FS	Cisplatin	Urinary retention
130-1196	FS	Cisplatin	Polyneuropathy	409-4178	FS	Cisplatin	Subileus and constipation
141-1461	FS	LY/cis	Ulcerative esophagitis	720-7208	FS	Cisplatin	Headache
216-2161	PS+NS	Cisplatin	Constipation				
510-5100	PS+NS	LY/cis	Death[1]				
554-5516	FS	Cisplatin	Angina pectoris				

[1] This patient death was possibly related to other events such as diarrhea, stomatitis and fever that are associated with LY231514 therapy.

Source: Sponsors Table JMCH.12.28.

3.5 Hospitalizations

In the RT population, 100 patients were hospitalized, 67 in the Alimta/cisplatin arm and 33 in the cisplatin alone arm. In the FS population, 67 patients were hospitalized, 46 in the Alimta/cisplatin arm and 21 in the cisplatin alone arm. More patients were hospitalized in the Alimta/cisplatin arm than the cisplatin alone arm.

Table 7.25 details the common reasons for hospitalization. The most common reasons were neutropenia, febrile neutropenia, infection, decreased renal function, stomatitis, nausea, vomiting, fatigue and diarrhea.

Table 7.25. Most Common Reasons for Hospitalization (Reviewers Table)

Reason for Hospitalization	No. of patients with each event							
	RT population				Fully Supplemented			
	Alimta/Cisplatin		Cisplatin		Alimta/Cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
Neutrophil count decreased	67	29.6	33	14.9	46	27.4	21	12.9
Febrile neutropenia	67	29.6	33	14.9	46	27.4	21	12.9
Infection NOS	67	29.6	33	14.9	46	27.4	21	12.9
Nausea	67	29.6	33	14.9	46	27.4	21	12.9
Blood creatinine increased	67	29.6	33	14.9	46	27.4	21	12.9
Creatinine renal clearance decreased	67	29.6	33	14.9	46	27.4	21	12.9
Fatigue	67	29.6	33	14.9	46	27.4	21	12.9
Diarrhoea NOS	67	29.6	33	14.9	46	27.4	21	12.9
Stomatitis	67	29.6	33	14.9	46	27.4	21	12.9
Vomiting NOS	67	29.6	33	14.9	46	27.4	21	12.9
White blood cell count decreased	67	29.6	32	14.4	46	27.4	21	12.9
Platelet count decreased	67	29.6	33	14.9	46	27.4	21	12.9
Pneumonitis NOS	67	29.6	33	14.9	46	27.4	21	12.9
Rash NOS	67	29.6	33	14.9	46	27.4	21	12.9
Alanine aminotransferase increased	67	29.6	33	14.9	46	27.4	21	12.9
Aspartate aminotransferase increased	67	29.6	33	14.9	46	27.4	21	12.9
Blood bilirubin increased	67	29.6	33	14.9	46	27.4	21	12.9
Dyspnoea NOS	49	21.7	28	12.6	35	20.8	18	11.0

	No. of patients with each event							
	RT population				Fully Supplemented			
	Alimta/Cisplatin		Cisplatin		Alimta/Cisplatin		Cisplatin	
Constipation	38	16.8	16	7.2	30	17.9	9	5.5
Cough	34	15.0	11	5.0	25	14.9	6	3.7
Anaemia NOS	27	11.9	6	2.7	21	12.5	4	2.5
Anorexia	25	11.1	9	4.1	16	9.5	3	1.8
Chest pain	19	8.4	10	4.5	15	8.9	7	4.3
Pyrexia	18	8.0	7	3.2	15	8.9	4	2.5
Hypertension NOS	19	8.4	8	3.6	14	8.3	5	3.1
Dehydration	19	8.4	1	0.5	12	7.1	1	0.6
Weight decreased	15	6.6	5	2.3	12	7.1	3	1.8
Tumour pain	12	5.3	4	1.8	10	6.0	1	0.6
Pulmonary embolism[1]	12	5.2	5	2.3	10	6.0	3	1.8
Anxiety NEC	9	4.0	6	2.7	8	4.8	2	1.2
Depression NOS	10	4.4	4	1.8	8	4.8	3	1.8
Oedema NOS	10	4.4	2	0.9	8	4.8	2	1.2
Oedema lower limb	9	4.0	5	2.3	8	4.8	3	1.8
Dizziness (excl vertigo)	8	3.5	2	0.9	6	3.6	2	1.2
Insomnia	9	4.0	6	2.7	6	3.6	3	1.8
Paraesthesia	6	2.7	1	0.5	6	3.6	1	0.6
Sweating increased	7	3.1	3	1.4	6	3.6	2	1.2
Breath sounds decreased	6	2.7	1	0.5	5	3.0	1	0.6
Diabetes mellitus NOS	8	3.5	3	1.4	5	3.0	3	1.8
Hypotension NOS	6	2.7	0	0.0	5	3.0	0	0.0
Pain NOS	13	5.8	7	3.2	5	3.0	4	2.5
Pleural effusion	5	2.2	0	0.0	5	3.0	0	0.0
Pleuritic pain	6	2.7	6	2.7	5	3.0	5	3.1
Weakness	7	3.1	3	1.4	5	3.0	2	1.2
Abdominal distension	4	1.8	1	0.5	4	2.4	1	0.6
Abdominal pain NOS	6	2.7	4	1.8	4	2.4	3	1.8
Renal events[2]	4	1.7	2	1.0	3	1.2	2	1.2

[1] includes pulmonary embolism, venous thrombosis, deep venous thrombosis, subclavian vein thrombosis, thrombosis

[2] Includes renal failure NOS, renal failure acute, renal impairment

3.6 Transfusions

On the Alimta/ cisplatin arm, 41 patients (18.1%) received a total of 138 units of red blood cell transfusions, two units of plasma transfusions, and four units of platelet transfusions, compared

with 17 patients (7.7%) on the cisplatin alone arm who received a total of 42 units of red blood cell transfusions and three units of plasma transfusions.
In the supplemented group, in both treatment arms, the incidence of red blood cell transfusions was lower among patients in the FS group when compared with the PS+ NS group. This supports data above showing a trend toward a lower incidence of grade 3/ 4 anemia in FS patients. The incidences of platelet and plasma transfusions were too low to justify any conclusions.

In the RT population, 19 (8.4%) patients used erythrocyte CSFs in those treated with Alimta/cisplatin while 5 (2.3%) patients used them in the cisplatin alone arm. In the supplemented subgroup, patients who used erythrocyte CSFs in the Alimta/cisplatin arm were 17 (10.1%) fully supplemented and 2 (3.4%) partially or never supplemented. In the cisplatin alone arm, 2 (1.2%) patients were fully supplemented and 3 (5.1%) were in the partially or never supplemented.

Table 7.26. Summary of Patients Who Received Transfusions On- study RT Population

Type of Transfusion	LY/cis (N=226)		Cisplatin (N=222)	
Patient with ≥1 Transfusion	41 (18.1%)		17 (7.7%)	
	Units	Patients	Units	Patients
RBC Transfusions	138	40 (17.7%)	42	16 (7.2%)
Platelet Transfusions	4	2 (0.9)	0	0
Plasma Transfusions	2	1 (0.4)	3	1 (0.5)

Patient could have received more than one type of transfusion.

Source: Section 12.5.2. Applicant Table JMCH.12.47

Table 7.27. Summary of patients Who received Transfusions On-Study RT population by Supplementation Status

	LY/cis				Cisplatin			
	FS		PS+NS		FS		PS+NS	
Type of Transfusion	(N=168)		(N=58)		(N=163)		(N=59)	
Patient with ≥1 Transfusion	26 (15.5%)		15 (25.9%)		11 (6.7%)		6 (10.2%)	
	Units	Patients	Units	Patients	Units	Patients	Units	Patients
RBC Transfusions	91	26 (15.5%)	47	14 (24.1%)	27	10 (6.1%)	15	6 (10.2%)
Platelet Transfusion	0	0	4	2 (3.4)	0	0	0	0
Plasma Transfusions	2	1 (0.6)	0	0	3	1 (0.6)	0	0

Patient could have received more than one type of transfusion.

Source: Section 12.5.2. Applicant Table JMCH.12.48.

Table 7.28. Summary of Reasons for Transfusions (Reviewers Table)

Reasons	RT Group				FS Subgroup			
	Alimta/cisplatin		Cisplatin		Alimta/cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
ANEMIA[1]	43	18.8	18	7.4	29	17.3	12	7.3
PLATELETS	2	0.9	0	0.0	0	0	0	0
DYSPNEA	1	0.4	0	0.0	1	0.6	0	0.0
FATIGUE	1	0.4	0	0.0	0	0	0	0
PROTHROMBIN TIME ELEVATED	1	0.4	0	0.0	1	0.6	0	0.0
SHORTNESS BREATH	1	0.4	0	0.0	0	0	0	0
LOW ALBUMIN	0	0.0	1	0.5	0	0.0	1	0.6

[1] Anemia and decreased hemoglobin have been combined.

3.7 Concomitant Drugs

The requirements for 5-HT_3 antagonists and other antiemetics did not change with the use of vitamin supplementation; however the use of anti-diarrheals decreased.

Table 7.29. Selected Concomitant Drug Therapy RT Population

	LY/cis (N=226)	Cisplatin (N=222)
Patients receiving at least 1 concomitant drug	226 (100%)	222 (100%)
Categories[1, 2]		
Corticosteroids (systemic)	224 (99.1)	221 (99.5)
5-HT_3 antagonists	215 (95.1)	211 (95.0)
Prokinetics (e.g., metoclopramide)	127 (56.2)	118 (53.2)
Other antiemetics (e.g., prochlorperazine)	86 (38.1)	67 (30.2)
H_2-antagonists	74 (32.7)	60 (27.0)
Proton pump inhibitors	66 (29.2)	46 (20.7)
Benzodiazepines	123 (54.4)	113 (50.9)
Morphine	60 (26.5)	43 (19.4)
Fentanyl	27 (11.9)	29 (13.1)
Codeine-containing products	58 (25.7)	51 (23.0)
Other narcotic-containing products	102 (45.1)	98 (44.1)
NSAIDs	86 (38.1)	79 (35.6)
Aspirin-containing products	35 (15.5)	32 (14.4)
Paracetamol-containing products	76 (33.6)	83 (37.4)
Anti-diarrheals	16 (7.1)	7 (3.2)
Erythrocyte colony-stimulating factors (CSFs)	19 (8.4)	5 (2.3)
Granulocyte CSFs	4 (1.8)	1 (0.5)
Folinic acid (leucovorin)	7 (3.1)	0

1 Patients may have taken more than one of the medications in the category.

2 Any particular drug product was only included in one category.

Source: Applicant Table JMCH. 11.16.

Table 7.30. Selected Concomitant Drug Therapy RT Population by Supplementation Status

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Patients receiving at least 1 concomitant drug	168 (100%)	58 (100%)	163 (100%)	59 (100%)
Categories[1,2]				
Corticosteroids (systemic)	166 (98.8)	58 (100)	162 (99.4)	59 (100)
5-HT_3 antagonists	160 (95.2)	55 (94.8)	157 (96.3)	54 (91.5)
Prokinetics (e.g., metoclopramide)	92 (54.8)	35 (60.3)	83 (50.9)	35 (59.3)
Other antiemetics (e.g., prochlorperazine)	64 (38.1)	22 (37.9)	46 (28.2)	21 (35.6)
H_2-antagonists	46 (27.4)	28 (48.3)	43 (26.4)	17 (28.8)
Proton pump inhibitors	49 (29.2)	17 (29.3)	35 (21.5)	11 (18.6)
Benzodiazepines	87 (51.8)	36 (62.1)	83 (50.9)	30 (50.8)
Morphine	43 (25.6)	17 (29.3)	31 (19.0)	12 (20.3)
Fentanyl	17 (10.1)	10 (17.2)	19 (11.7)	10 (16.9)
Codeine-containing products	41 (24.4)	17 (29.3)	36 (22.1)	15 (25.4)
Other narcotic-containing products	74 (44.0)	28 (48.3)	65 (39.9)	33 (55.9)
NSAIDs	59 (35.1)	27 (46.6)	59 (36.2)	20 (33.9)
Aspirin-containing products	22 (13.1)	13 (22.4)	22 (13.5)	10 (16.9)
Paracetamol-containing products	53 (31.5)	23 (39.7)	60 (36.8)	23 (39.0)
Anti-diarrheals	11 (6.5)	5 (8.6)	3 (1.8)	4 (6.8)
Erythrocyte colony-stimulating factors (CSFs)	17 (10.1)	2 (3.4)	2 (1.2)	3 (5.1)
Granulocyte CSFs	1 (0.6)	3 (5.2)	1 (0.6)	0
Folinic acid (leucovorin)	3 (1.8)	4 (6.9)	0	0

1 Patients may have taken more than one of the medications in the category.

2 Any particular drug product was only included in one category.

Source: Applicant Table JMCH. 11.17.

3.8 Supportive Studies

Table 7.31. Clinical Studies Discussed in the Integrated Summary of Safety

Study	Phase	Design	Status	Indication	No. Patients	Treatment[a]	Vitamin Suppl.	Dexamethasone Prophylaxis
LY231514 plus Cisplatin								
JMCH	3	Single-blind, randomized	Completed	MPM	Enrolled=456 Safety evaluable=448	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2 vs cisplatin, 75 mg/m^2	Yes. 331 patients (both arms)	primary
JMAY	2	Open-label, nonrandomized	Completed	NSCLC	Enrolled=36 Safety evaluable=36	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2	No	primary
JMBZ[b]	2	Open-label, nonrandomized	Completed	NSCLC	Enrolled=31 Safety evaluable=31	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2	No	primary
JMAP	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=51 Safety evaluable=51	LY231514, 300 to 600 mg/m^2 plus Cisplatin, 60 to 100 mg/m^2	No	secondary
LY231514 Single-Agent Studies								
Integrated data on supplemented patients[c]	2	Open-label, nonrandomized	Completed	Breast and MPM	Enrolled=207 Safety evaluable=207	LY231514, 500 mg/m^2	Yes	primary
Integrated data on nonsupplemented patients[d]	2/3[h]	Open-label, randomized (JMBQ) and nonrandomized	Completed	Various cancers	Enrolled=608 Safety evaluable=608	LY231514, 500 and 600 mg/m^2, presented by starting dose	No	primary and secondary (specified per study in Table ISS.5.1)
Other – LY231514 Dose- and Schedule-Finding Studies								
JMAA	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=37 Safety evaluable=37	LY231514, 50 to 700 mg/m^2	No	none recommended
BP-001[f]	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=38 Safety evaluable=38	LY231514, 0.2 to 5.2 mg/m^2	No	none recommended
JMAB[g]	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=25 Safety evaluable=25	LY231514, 10 to 40 mg/m^2	No	none recommended

Abbreviations: AUC = area under the curve; MPM = malignant pleural mesothelioma; NSAIDs = nonsteroidal anti-inflammatory drugs; NSCLC = non-small cell lung cancer.

[a] One dose of the study drug(s) administered once every 21 days defined one cycle of therapy, unless otherwise noted.

[b] Studies conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Data cannot be integrated with studies conducted by Lilly.

[c] Data from supplemented patients in studies JMBT, JMDM, JMDR, and JMDS.

[d] Data from nonsupplemented patients in studies JMAC, JMAD, JMAG, JMAH, JMAI, JMAJ, JMAK, JMAL, JMBB, JMBM, JMBP, JMBQ, JMBR, JMBT, JMDM, and JMDR.

[e] Supplementation regimen: 5 mg folic acid daily for 5 days beginning 2 days before each cycle; no vitamin B_{12} was given.

[f] A cycle was defined as LY231514 given daily for 5 days every 21 days.

[g] A cycle was defined as LY231514 given once per week for 28 days followed by a 14-day rest period.

[h] Three patients from a prematurely terminated Phase 3 study are included.

Source: Safety Update. Applicant Table 3.1.

Study JMDR

In the supporting Phase 2 study, Alimta was administered as a single agent to chemo-naïve patients with malignant pleural mesothelioma. The dose was 500 mg/m^2 given as an approximately 10- minute intravenous infusion on Day 1 of a 21- day period. This 21- day period defined one cycle of therapy. Dexamethasone, 4 mg (or an equivalent corticosteroid), was to be taken by all patients orally BID 1 day before, on the day of, and 1 day after the administration of Alimta.

Sixty- four patients were enrolled in the study. Forty- three patients were supplemented with folic acid and vitamin B_{12} and 21 were nonsupplemented.

The median age of patients at the time of enrollment was 65 years. The median age of supplemented patients was 63 years compared with 68 years for nonsupplemented patients.

All 64 patients received at least one cycle of Alimta. Enrolled patients completed a median of six cycles of therapy. The supplemented patients completed a median of six cycles and nonsupplemented patients completed a median of two cycles.

Three doses were reduced among the supplemented patients because of elevated febrile neutropenia, alkaline phosphatase levels and hypokinesia respectively. The adverse events that resulted in the four reductions among nonsupplemented patients were neutropenia (2 patients), febrile neutropenia, and stomatitis.

Nineteen dose delays occurred during the study. Thirteen delays occurred because of scheduling conflicts. Six were done for reasons that were considered clinically relevant. Five of these delays occurred in supplemented patients and were attributed to herpes zoster infection (2 patients), pain, asthenia, and myocardial infarction. A pleural disorder accounted for the single dose delay among the nonsupplemented patients.

All 64 patients were included in the safety analysis. Grade 3 or grade 4 neutropenia was reported in 15 patients. Eleven of these 15 patients were nonsupplemented and included 8 patients (38.1%) with grade 4 toxicity. Two supplemented patients (4.7%) reported grade 3 and 2 patients (4.7%) reported grade 4 neutropenia. Grade 3 or grade 4 leukopenia was reported in 12 patients. Eight of the 12 reports were in nonsupplemented patients, and included 2 patients (9.5%) with grade 4 toxicity. Four supplemented patients (9.3%) reported grade 3 leukopenia.

Fatigue and febrile neutropenia were the most commonly reported toxicities for nonlaboratory data. There were two reports each of these toxic events for supplemented and nonsupplemented patients. In general, the incidence of grade 4 toxicity was low for nonlaboratory data. Only one grade 4 event (chest pain) was reported in a nonsupplemented patient. In addition, ten grade 3 events were reported in 21 nonsupplemented patients, compared with fifteen grade 3 events in the 43 supplemented patients.

There were twenty- three reports of serious adverse events, thirteen among the nonsupplemented patients and ten among the supplemented patients. Fever (9 patients) was the most commonly reported overall. Fever in these 9 patients included five events reported verbatim as fever, three events of febrile neutropenia, and one event reported as fever without neutropenia. Fever was the most commonly reported SAE for supplemented patients. Six reports of fever included four events reported verbatim as fever, one as febrile neutropenia, and one as fever without neutropenia. Fever and leukopenia (three reports each) were most commonly reported serious adverse events for nonsupplemented patients. Three reports of fever among nonsupplemented patients included two events reported verbatim as febrile neutropenia, and one event reported as fever. The three reports of leukopenia included two events reported verbatim as neutropenia, and one reported as leukopenia with associated neutropenia.

Three supplemented and 4 nonsupplemented patients had adverse events that resulted in their discontinuation of treatment and study withdrawal. These events included arthralgia, deafness and elevated creatinine levels for the supplemented patients and cerebrovascular accident, dyspnea, abnormal kidney function, and stomatitis for the nonsupplemented patients.

Two patients died during the treatment phase (Cycle 1) of the study, and two additional deaths were reported within 30 days of administration of the last dose of the study drug. These deaths were attributed to disease progression.

The data showed that patients receiving low- dose folic acid and vitamin B_{12} for supplementation in this setting were able to receive more Alimta therapy. Supplemented patients had an improved safety profile with a lower incidence of hematologic toxicity, particularly grade 3 and grade 4 neutropenia and leucopenia but not with nonlaboratory toxicities. However, the relatively small number of patients included in these analyses precluded any firm conclusions on toxicity observations.

Safety Data from Phase 2 and 3 Single-Agent Alimta Studies

For all studies, the objective relating to patient safety was to characterize the qualitative and quantitative toxicities of Alimta, 500 mg/ m2 administered once every 21 days. Patients received prophylactic dexamethasone and folic acid and vitamin B_{12} supplementation. Dose adjustments and delays were allowed based on laboratory and nonlaboratory toxicities.

The original integrated analysis of 207 supplemented patients from single- agent Alimta studies submitted in the Integrated Summary of Safety (ISS) included data from four studies: H3E- MC- JMBT, H3E- MC- JMDM, H3E- MC- JMDR, and H3E- MC- JMDS. These studies were completed at the time the ISS was created. The subsequent analysis included two new studies: H3E- MC- JMEI, which was complete; and H3E- MC- JMEU, which was ongoing. Both of these studies began after the implementation of vitamin supplementation; therefore, all patients in these two studies are supplemented.

Data are presented for the subsequent analysis, followed by the data presented in the ISS on the 207 supplemented patients for comparison.

Table 7.32 summarizes other key aspects of the studies discussed in this section.

Table 7.32. Studies of Alimta as a Single Agent (n= 517)

Study	Tumor Type	Prior Therapy	N[a]	Max. Cycles[b]
JMEI	NSCLC	At least one prior chemotherapy regimen	265	NS
JMBT[c]	Breast	Prior anthracycline or anthracenedione and a taxane required	43	NS
JMDM[c]	Breast	JMBT requirements plus capecitabine	60	NS
JMDR[c]	MPM	None	43	6[d]
JMDS	Breast	None	61	3[e]
JMEU	Bladder	One prior regimen	45	NS

Abbreviations: MPM = malignant pleural mesothelioma; NS = not specified.

a N = number of supplemented patients who received at least one dose of LY231514.

b Maximum number of cycles allowed if there was no evidence of disease progression or unacceptable toxicity, and if the physician and patient agreed it was in the patient's best interest to continue.

c These studies had additional patients who did not receive supplementation.

d More cycles were allowed if the patient was experiencing a clinical benefit.

e Only three cycles were given. Patients then underwent local therapy.

Source: Safety Update. Applicant Table 4.1.

Among the 517 patients who received Alimta as a single agent at a dose of 500 mg/ m^2 every 21 days, with dexamethasone treatment and folic acid and vitamin B_{12} supplementation, the most common reasons for discontinuation were disease progression and completion of protocol-allowed therapy. Because JMEU is an ongoing study with patients still on study and not all data available, a complete account of the reasons for discontinuation from the study was not provided by the sponsors. Twenty- six (26) of the 517 patients (5.0%) discontinued because of adverse events, compared with 3.9% in the ISS database. Nine patients discontinued because of death (excluding study disease- related; 1.7%) and 1 additional patient because of death from study drug toxicity (0.2%), compared with 0.5% (1 patient) because of death (not study disease-related or study drug- related) in the ISS database. Some of these differences could be because of the overall poorer health and poorer prognoses of bladder cancer and previously treated NSCLC patients. However, the overall pattern of reasons for discontinuation was similar to that reported in the ISS.

Only 29 dose reductions were reported of the 2246 doses of Alimta given (1.3%). Thrombocytopenia was the most common reason for dose reduction. Most reductions occurred in Cycle 2 or 3. These results are comparable with those previously reported in the ISS, where 1.2%

of 893 doses of Alimta were reduced; again, thrombocytopenia was most common reason for dose reduction in that database.

Scheduling conflicts accounted for 81% of the 436 dose delays reported. Eighty- four delays were for clinical reasons. The most common clinical reasons for delay were decreased creatinine clearance, respiratory infections (including pneumonia), fatigue, and neutropenia . In the ISS database, fatigue and neutropenia were the most common clinical reasons for dose delay. The large number of patients (265) with previously treated NSCLC, more than 90% of whom had been treated with a platinum- based regimen, may account for the increased reporting of decreased creatinine clearance resulting in dose delay.

Most patients (96.1%) had at least one treatment- emergent adverse event (TEAE), with 82.4% of patients having at least one TEAE considered at least remotely related to study therapy. The most common TEAEs, regardless of causality, were nausea, fatigue, anorexia, and vomiting. The most common drug- related TEAEs were nausea, fatigue, vomiting, and anorexia.

One hundred fifty- nine (159) of the 517 patients (30.8%) experienced one or more of 361 serious adverse events (SAEs), regardless of drug causality. Of these, only 89 SAEs in 48 (9.3%) patients were considered at least remotely related to study therapy. Each of these related SAEs occurred in less than 2% of the patients. The frequencies and patterns of all SAEs and study drug- related SAEs are similar to those reported in the ISS.

As of 18 April 2003, 34 patients who received Alimta on Study JMEI and Study JMEU died while on- study or within 30 days of discontinuing study therapy . Of these, 3 patients from Study JMEI died of study drug- related causes (cardiac arrest, hepatic failure, and pneumonia/ sepsis). All 3 patients from JMEU died because of study disease.

Only 18 of 310 patients (5.8%) in Study JMEI and Study JMEU who received Alimta discontinued study therapy because of an adverse event as of 18 April 2003. All patients were from Study JMEI. Seven of the patients discontinued because of events considered related to study therapy. Events related to renal function were the most common drug- related cause for discontinuation.

Ten serious, unexpected, and reportable adverse events (SURs) were reported in 8 patients who received Alimta in Study JMEI (5 patients) and Study JMEU (3 patients). In Study JMEI, these events were arthralgia and myalgia (both events in the same patient), cytolytic hepatitis (1 patient), pneumonia and sepsis (both events in the same patient), bacterial pneumonia (1 patient), and supraventricular arrhythmia (1 patient). In Study JMEU, the SURs were lower gastrointestinal hemorrhage, hypoglycemia, and migraine (occurring in 1 patient each).

The pattern of CTC laboratory toxicities (Version 2) in the updated safety database was similar to that reported in the ISS database. Grade 3 and 4 transaminase elevations occurred in fewer than 10% of patients. Neutropenia rarely resulted in clinical sequelae; the rate of febrile neutropenia was only 1.9%, very similar to the previously reported rate of 2%.

The pattern of CTC nonlaboratory toxicities (Version 2) in the updated safety database was similar to that reported in the ISS database. Fatigue was the most common grade 3 or 4 toxicity, occurring in 4.7% of patients.

Subgroup analyses of clinically relevant TEAEs showed that decreased creatinine clearance and anemia were reported more commonly in older patients. Anorexia, decreased hemoglobin, and rash occurred significantly more frequently in men, while vomiting and diarrhea occurred more often in women. Analyses of clinically relevant CTC grade 3 and 4 toxicities showed no significant differences between either age or sex subgroups. These results differed slightly from the ISS; however, the conclusion that no particular clinical concern exists for any subgroup remained the same.

The integrated analysis illustrated that the safety profile of single- agent Alimta with folic acid and vitamin B_{12} supplementation and prophylactic dexamethasone was manageable and consistent with increased patient exposure over time. Alimta had predictable toxicities that were mostly mild to moderate, even in patients who had previously received chemotherapy.

Phase 1 Single-Agent Alimta Studies:

Study JMAS

Study JMAS is an Alimta plus folic acid Phase I study which evaluated the maximum tolerated dose of single- agent Alimta administered every 3 weeks, concurrent with two different regimens of supplementation:
• folic acid only, 5 mg oral dose daily for 5 days beginning 2 days before Alimta dose, or
• a multivitamin containing 350 to 600 µg folic acid and vitamin B_{12}, to be taken orally daily.

In addition, there were two cohorts of patients within each vitamin cohort:
• lightly pretreated patients (no prior therapy, 2 courses of mitomycin- C, 6 courses of an alkylating agent, or 4 courses of carboplatin)
• heavily pretreated patients (anything beyond treatments listed above, or radiation to the pelvis).
Planned doses of Alimta could reach 1700 mg/ m^2.

Eighty- seven (87) patients have enrolled in this study as of 18 April 2003.

The most common serious adverse events reported on JMAS thus far, regardless of causality, were neutropenia, vomiting, anemia, nausea, pyrexia, and thrombocytopenia, which were the same as the most common drug-related serious adverse events. Febrile neutropenia occurred in 3.4% of patients thus far.
Two patients experienced severe toxicity during cycle 1. One of these patients was on stable doses of naproxen (500 mg twice per day) concurrent with Alimta at 800 mg/m^2. The other was on stable doses of a long acting NSAID concurrent with 900 mg/m^2 of Alimta.

Only one patient died on- study thus far (of coronary artery disease). No patient deaths had been reported within 30 days of discontinuation of study therapy.
To date, 10 patients had discontinued from Study JMAS because of adverse events.
The serious, unexpected and reportable adverse event of subdural hematoma was reported in one patient. This patient had deep vein thrombosis, was receiving anticoagulants, and also experienced chemotherapy- related thrombocytopenia.
The rate of certain serious adverse events and the rate of discontinuation because of adverse events reported thus far were higher than the rate seen in the Phase 2 and Phase 3 integrated studies. Heavy pretreatment, greater tumor burden, and testing of dose levels of Alimta higher than 500 mg/ m^2 in the study was thought to have contributed to increased rates of certain adverse events and discontinuations because of adverse events.

Reviewers Comment:
In study JMAS, increased toxicity possibly due to the use of NSAIDS with Alimta cannot be excluded.

Study JE-1001

Study JE-1001 was a Phase 1 dose- finding study of single- agent Alimta (plus supplementation and dexamethasone) in Japanese cancer patients. Dose levels to be tested were 300, 500, 600, 700, 800, 900, and 1000 mg/ m^2, with escalation continuing in 100 mg/ m^2- increments, if the listed doses were tolerated. The objective related to safety was to determine the qualitative and quantitative toxicities of this regimen in these patients. Data for this study was not currently in Lilly's database.

Twenty- one (21) patients had enrolled in this study as of 18 April 2003. Eighteen (18) were eligible for safety analyses as of the same date.
As of the data cutoff date, no deaths on study or within 30 days of discontinuation of therapy had been reported.
As of the data cutoff date, no patients discontinued study therapy because of adverse events.
No serious unexpected reportable adverse events had been reported thus far.
The few data available for this ongoing Phase 1 study suggested that therapy was well- tolerated.

4. Adequacy of Safety Testing

The safety population in the randomized trial (study JMCH) represents a population of chemo-naïve patients with MPM, ranging in age from 19-85, average age 60 years, who received Alimta together with cisplatin. Most patients received folic acid and vitamin B_{12} supplementation. Adverse events were more common in the combination treatment group and reduced with vitamin supplementation. The sample of patients is likely to represent the usual MPM patient population. As such, for the specific labeled indication, the safety testing appears appropriate and credible.

5. Summary of Critical Safety Findings and Limitations of Data

This study underwent two distinct stages that evolved because of safety concerns. During the treatment of the first 117 patients, the number of on- study deaths were high. Therefore, an extensive review of the data on these patients and the full safety database of the Alimta development program were done and Lilly decided to add low- dose folic acid and vitamin B_{12} supplementation to all patients. A total of 70 patients had come off study therapy by that date and thus never received the supplementation, while 47 patients continued to receive treatment and were partially supplemented. The decision to add supplementation also resulted in an increase in the sample size as part of a decision to power the subgroup that received supplementation throughout their treatment at the same level as the population in the original design. The results in these supplement-defined subgroups in the safety analyses are of considerable importance because the labeled use is with vitamin supplementation.

Because this was a two- drug versus a one- drug trial, the toxicity of the Alimta/ cisplatin arm was greater than the cisplatin alone control arm as expected.
The frequency of grade 3 and 4 laboratory toxicity was higher in the Alimta/ cisplatin arm when compared to the control arm. The frequency of grade 3/ 4 hematologic toxicity in the fully supplemented Alimta/ cisplatin arm were neutropenia (24.4%), anemia (6%) and thrombocytopenia (5.4%). The uses of colony-stimulating factors were infrequent. Twenty-six patients (15.5%) received RBC transfusions, but platelet and plasma transfusions were infrequent. The frequency of grade 4 toxicity was lower than grade 3 (for neutropenia, 19% Grade 3 versus 5.4% Grade 4). Despite dose reductions and dose delays > 92% of planned doses were delivered.

Nausea, vomiting, and fatigue were the most commonly reported grade 3/ 4 nonlaboratory toxicities in both treatment arms. Nausea and vomiting were more frequent in the Alimta/ cisplatin arm despite the equal frequency of therapy with 5- HT3 antagonists and dexamethasone in the two arms (nausea, 11.3% grade 3 versus 0.6% grade 4).

Supplementation was added to both treatment arms in an effort to maintain blinding of treatment assignments for patients. Analyses by supplementation status were done across treatment arms as well as within treatment arms.
Within the Alimta/ cisplatin arm, supplementation resulted overall in less toxicity, including less grade 3/ 4 toxicity; this was associated with a statistically significant increase in the median number of cycles administered in the fully supplemented subgroup.The frequencies of adverse events were mostly lower in the fully supplemented subgroup when compared to the nonsupplemented subgroup.

Supplementation was also given in the cisplatin alone arm, allowing similar comparisons as in the Alimta/ cisplatin arm. There was a general trend toward fewer adverse events in the fully supplemented subgroup, though the differences were generally less than those seen in the Alimta/ cisplatin arm.

Death rates from all causes while on study drugs between treatment arms were higher in the Alimta/cisplatin group and were reduced with the implementation of supplementation. The FDA review indicated that three deaths in the Alimta/ cisplatin arm could be attributed to be possibly study drug- related, one of which was in the fully supplemented subgroup. There were no study related deaths in the control arm.

The frequencies of discontinuations because of adverse events were low in both arms. Many of the discontinuations in both arms were because of reduced creatinine clearance; the remaining discontinuations thought due to study drugs were distributed over both arms and each had a different cause.

The toxicity profile of Alimta/cisplatin appears consistent with other cytotoxic drugs. The safety population primarily reflects the phase 3 study in chemo-naïve patients.
In this population, Alimta/cisplatin appears to have a high incidence of toxicities that are mostly mild to moderate, even in patients who have received vitamin supplementation.
Adverse events were commonly encountered, suggesting that near maximal dosing was achieved. The toxicities were consistent across the phase 1 and 2 studies done with single –agent Alimta and combination with platinums. Also, most toxicities predicted by the animal studies were confirmed in patients. The adverse event profile of Alimta was judged to be acceptable for patients with MPM. The frequency and severity of adverse events observed during the study were consistent with the clinical course of patients with MPM and with the predicted and known effects of the study drug. Supplemented patients had a better safety profile with a lower incidence of toxicities.

VIII. Dosing, Regimen, and Administration Issues

1. Introduction

The results of the pivotal trial, JMCH, provided confidence in the efficacy and safety of alimta + cisplatin (plus folic acid and vitamin B12) in patients with malignant pleural mesothelioma. However, the underlying science of the addition of folic acid and B12 to an antifolate regimen did not provide confidence with known *in vitro* and *in vivo* antifolate pharmacology. This issue is discussed in detail in section 5 (Important Issues with Pharmacologically Related Agents) of this review.

2. Safety

The recommended dose of Alimta is 500 mg/m^2/dose administered IV over 10 minutes on day 1 with cisplatin in a 21-day cycle. Vitamin supplementation is started prior to starting chemotherapy and continued with treatment. This 21-day cycle is considered a treatment cycle.

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 (H3EMC- 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. 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. 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. 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. 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 grade 4 thrombocytopenia occurred in 4 and 1 patients, respectively, during the first cycle. 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 4 patients with partial responses had failed previous treatment with thymidylate synthase inhibitors including either 5- FU, FUDR, or raltitrexed.

In a Canadian study in metastatic colorectal cancer, 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%). In a 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%).

A multi- institutional study in NSCLC completed in Canada 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 grade 3 mucositis and grade 4 vomiting and myalgia. Seven partial responses were observed in 30 evaluable patients for an overall response rate of 23.3% (95% CI 9.9 to 42.3%). All responding patients were treated at the 500 mg/ m^2 dose level.

A total of 646 patients were treated on the once every 3 weeks schedule in the Phase 2 setting at 600 mg/ m^2. The most frequent, serious toxicity was hematologic in nature. Grade 3 and 4 hematologic toxicity included neutropenia (23% and 24%, respectively) and thrombocytopenia (7% and 5%, respectively). Although severe neutropenia was common, the frequency of serious infection was low (CTC Grade 4 infection 2%). Likewise, thrombocytopenia had been apparent, and yet serious episodes of bleeding were rare (< 1%). While 6% of patients experienced CTC Grade 3 (5% with Grade 4) skin rash, prophylactic dexamethasone was reported to ameliorate or prevent the rash in subsequent cycles. Other grade 3 and 4 nonhematologic toxicities included stomatitis, diarrhea, vomiting, and infection. Transient grade 3 and 4 elevation of liver transaminases were common but not dose- limiting. There were no cases of persistent transaminase elevation.

Toxicity at 600 mg/ m^2 was recently compared to that at 500 mg/ m^2. For hematologic parameters there appeared to be no difference between the incidence of grade 3 and 4 toxicity or grade 4 toxicity alone. For nonhematologic parameters rash, fatigue, and stomatitis appeared to be less severe at 600 mg/ m^2. Of note, patients who were administered Alimta 500 mg/ m^2 in previous trials had 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 was thus likely a result of concomitant corticosteroid administration, and was not considered a dose response effect of Alimta treatment.

Because of toxicities seen in two Phase 2 studies (H3E- MC- JMAN and H3E-MCJMAO), the dose of Alimta used in these two studies was reduced from 600 mg/ m^2 to 500 mg/ m^2. With little evidence that a 600 mg/ m^2 dose had an efficacy advantage over a 500 mg/ m^2 dose, the 500 mg/m^2 dose was used in all subsequent single- agent Phase 2 Alimta studies. This decision was made after a discussion with the FDA in September of 1998.

In a Phase 1 trial of Alimta in combination with cisplatin, patients with solid tumors were enrolled into one of two cohorts. The first cohort received both Alimta and cisplatin on Day 1 of a 21- day cycle, and the second cohort received Alimta 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 the split schedule, which included two therapy- related deaths, led to the conclusion that the second schedule was clinically inferior.

Early clinical trials of Alimta recommended the use of dexamethasone as secondary prophylaxis, that is, as pretreatment in future cycles of Alimta after patients experienced troublesome skin rash. After many patients required this secondary prophylaxis, a programmatic decision was made to recommend the use of dexamethasone as primary prophylaxis. A minimum of 3 days of dexamethasone therapy or clinical equivalent was required, but additional days of therapy were allowed as antiemetic prophylaxis.

Pretreatment homocysteine levels significantly predicted severe thrombocytopenia and neutropenia with or without associated grade 3/ 4 diarrhea, mucositis, or infection. Patients with elevated baseline levels of homocysteine alone, or of both homocysteine and methylmalonic acid, were found to have a high risk of severe toxicity. These findings formed the basis to postulate that reducing homocysteine would result in a reduction of severe toxicity. Another finding was that baseline homocysteine levels behaved as a continuous risk factor for toxicity. In addition, no homocysteine level could be identified below which the risk of severe toxicity was low enough to not recommend supplementation. As a consequence, even some patients with normal or near- normal homocysteine levels could have been at an increased risk and, therefore, could benefit from supplementation. It was thus decided to add folic acid and vitamin B_{12} supplementation to all patients receiving Alimta to minimize the risk of severe toxicity.

IX. Use in Special Populations

Table 9.1 summarizes the categories of subgroups analyzed for clinically significant safety variables. CTC toxicities were evaluated by gender and age. There were insufficient numbers of minority patients to evaluate toxicity by race.

Table 9.1. Categorization of Subgroups RT Population

Subgroup	Category	LY/cis (N=226)	Cisplatin (N=222)	Total (N=448)
Gender	Female	42	41	83
	Male	184	181	365
Age	<65 Years	143	136	279
	≥65 Years	83	86	169

Source: Section 2.6. Applicant table JMCH.12.49.

1. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

1.1 FDA's Efficacy Analyses for Gender Effects

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388

The under-powered female subgroup demonstrated in randomized and treated and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in

favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm.[192]

1.2 Evaluation of Gender Effects on Safety

Each summary represents the proportion of patients with specific treatment- emergent adverse event without regard to relationship to drug and pairwise comparisons within each subgroup strata.

Table 9.2 is a summary of the subgroup analysis for TEAEs by gender. A statistically significant subgroup- by- treatment interaction was observed in rash (p= 0.025). Male patients in the Alimta/ cisplatin group demonstrated a greater frequency of events when compared with males in the cisplatin alone treatment arm. However, events reported for female patients occurred at similar frequencies among treatment groups.

Table 9.2. Summary of Subgroup Analysis for TEAEs by Gender

Event	Subgroup	Subcategory	Therapy	N (%)	Therapy p-value	Interaction p-value
Nausea	Gender	Female	LY/cis	34 (81.0%)	0.592	0.153
			Cisplatin	35 (85.4)		
		Male	LY/cis	156 (84.8)	0.022	
			Cisplatin	136 (75.1)		
Rash NOS	Gender	Female	LY/cis	6 (14.3)	0.964	0.025
			Cisplatin	6 (14.6)		
		Male	LY/cis	52 (28.3)	<0.001	
			Cisplatin	14 (7.7)		
WBC count decreased	Gender	Female	LY/cis	20 (47.6)	0.053	0.058
			Cisplatin	11 (26.8)		
		Male	LY/cis	109 (59.2)	<0.001	
			Cisplatin	32 (17.7)		

Source: Section12.6. Applicant table JMCH.12.50.

Table 9.3 is a summary of the CTC toxicities for the Alimta/cisplatin treatment group by gender. The sample sizes between the two sex subgroups are imbalanced. Caution should be taken when interpreting the results of the analysis. There were no statistically significant differences between the genders for events.

[192] Lilly did a multifactorial survival analysis considering prognostic factors and there was no gender effect; ISE document submitted 3/24/2003.

Table 9.3. Analysis of CTC toxicities for the Alimta/cisplatin Group by Gender (Reviewers Table)

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	21	65.6	75	55.1	9	28.1	32	23.5
Hypertension	10	31.3	34	25.0	6	18.8	13	9.6
Vomiting	23	71.9	76	55.9	6	18.8	12	8.8
Nausea	29	90.6	113	83.1	5	15.6	15	11.0
Chest pain	18	56.3	50	36.8	5	15.6	9	6.6
Leukocytes	16	50.0	76	55.9	4	12.5	22	16.2
Fatigue	26	81.3	111	81.6	3	9.4	26	19.1
Dyspnea	17	53.1	93	68.4	3	9.4	16	11.8
Diarrhea without colostomy	11	34.4	32	23.5	3	9.4	3	2.2
Hemoglobin	13	40.6	44	32.4	2	6.3	8	5.9
Tumor pain	5	15.6	26	19.1	2	6.3	6	4.4
Constipation	16	50.0	62	45.6	2	6.3	4	2.9
Renal/Genitourinary-Other	10	31.3	42	30.9	2	6.3	3	2.2
Constitutional Symptoms-Other	6	18.8	12	8.8	2	6.3	2	1.5
Thrombosis/embolism	1	3.1	11	8.1	1	3.1	9	6.6
Platelets	5	15.6	39	28.7	1	3.1	8	5.9
Dehydration	1	3.1	11	8.1	1	3.1	6	4.4
Pulmonary-Other	4	12.5	30	22.1	1	3.1	4	2.9
Hypokalemia	1	3.1	4	2.9	1	3.1	1	0.7
Hyponatremia	1	3.1	3	2.2	1	3.1	1	0.7
Other auditory/hearing	5	15.6	6	4.4	1	3.1	0	0.0
Cushingoid appearance	1	3.1	0	0.0	1	3.1	0	0.0
Dysmenorrhea	1	3.1	1	0.7	1	3.1	0	0.0
GGT	1	3.1	1	0.7	1	3.1	0	0.0
Hypoxia	1	3.1	0	0.0	1	3.1	0	0.0
Prothrombin time	1	3.1	0	0.0	1	3.1	0	0.0
Urticaria	1	3.1	1	0.7	1	3.1	0	0.0
Stomatitis/pharyngitis	13	40.6	34	25.0	0	0.0	5	3.7
Other pain	6	18.8	20	14.7	0	0.0	5	3.7
Anorexia	12	37.5	47	34.6	0	0.0	4	2.9
Infection without Neutropenia	5	15.6	16	11.8	0	0.0	4	2.9
Other Gastrointestinal	7	21.9	26	19.1	0	0.0	3	2.2

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
Pleuritic pain	1	3.1	28	20.6	0	0.0	3	2.2
Pleural effusion	0	0.0	6	4.4	0	0.0	3	2.2
Supraventricular arrhythmias	0	0.0	5	3.7	0	0.0	3	2.2
Edema	6	18.8	18	13.2	0	0.0	2	1.5
Other musculoskeletal	4	12.5	10	7.4	0	0.0	2	1.5
Mood alteration-depression	3	9.4	20	14.7	0	0.0	2	1.5
Confusion	1	3.1	4	2.9	0	0.0	2	1.5
Dysphagia, esophagitis, odynophagia	1	3.1	9	6.6	0	0.0	2	1.5
Other cardiovascular/general	1	3.1	18	13.2	0	0.0	2	1.5
Hyperglycemia	0	0.0	8	5.9	0	0.0	2	1.5
Ileus	0	0.0	2	1.5	0	0.0	2	1.5
Infection/Febrile Neutropenia-Other	0	0.0	5	3.7	0	0.0	2	1.5
Other cardiovascular/arrhythmia	0	0.0	4	2.9	0	0.0	2	1.5
Pneumonitis/pulmonary infiltrates	0	0.0	4	2.9	0	0.0	2	1.5
Cough	8	25.0	56	41.2	0	0.0	1	0.7
Headache	6	18.8	15	11.0	0	0.0	1	0.7
Mood alteration-anxiety agitation	5	15.6	17	12.5	0	0.0	1	0.7
Rash/desquamation	5	15.6	32	23.5	0	0.0	1	0.7
Creatinine	4	12.5	22	16.2	0	0.0	1	0.7
Dizziness/lightheadedness	4	12.5	12	8.8	0	0.0	1	0.7
Sweating	4	12.5	20	14.7	0	0.0	1	0.7
Arthralgia	3	9.4	5	3.7	0	0.0	1	0.7
Hypomagnesemia	3	9.4	4	2.9	0	0.0	1	0.7
Dyspepsia/heartburn	2	6.3	18	13.2	0	0.0	1	0.7
Incontinence	1	3.1	1	0.7	0	0.0	1	0.7
Infection with grade 3 or 4 Neutropenia	1	3.1	9	6.6	0	0.0	1	0.7
Neuropathic pain	1	3.1	4	2.9	0	0.0	1	0.7
Other endocrine	1	3.1	11	8.1	0	0.0	1	0.7
Salivary gland changes	1	3.1	2	1.5	0	0.0	1	0.7
Tearing	1	3.1	6	4.4	0	0.0	1	0.7
Adult Respiratory Distress	0	0.0	1	0.7	0	0.0	1	0.7

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
Syndrome								
Ascites	0	0.0	1	0.7	0	0.0	1	0.7
Blood/Bone Marrow-Other	0	0.0	7	5.1	0	0.0	1	0.7
Depressed level of consciousness	0	0.0	2	1.5	0	0.0	1	0.7
Erectile impotence	0	0.0	3	2.2	0	0.0	1	0.7
Febrile neutropenia	0	0.0	1	0.7	0	0.0	1	0.7
Hepatic enlargement	0	0.0	1	0.7	0	0.0	1	0.7
Hepatic pain	0	0.0	1	0.7	0	0.0	1	0.7
Hypercholesterolemia	0	0.0	7	5.1	0	0.0	1	0.7
Hypophosphatemia	0	0.0	1	0.7	0	0.0	1	0.7
Hypotension	0	0.0	5	3.7	0	0.0	1	0.7
Lymphopenia	0	0.0	1	0.7	0	0.0	1	0.7
Muscle weakness	0	0.0	6	4.4	0	0.0	1	0.7
Neuropathy-motor	0	0.0	5	3.7	0	0.0	1	0.7
Operative injury of vein/artery	0	0.0	1	0.7	0	0.0	1	0.7
Other metabolic/laboratory	0	0.0	7	5.1	0	0.0	1	0.7
Pericardial effusion/pericarditis	0	0.0	2	1.5	0	0.0	1	0.7
Renal failure	0	0.0	4	2.9	0	0.0	1	0.7
Vasovagal episode	0	0.0	1	0.7	0	0.0	1	0.7
Insomnia	7	21.9	21	15.4	0	0.0	0	0.0
Fever	5	15.6	23	16.9	0	0.0	0	0.0
Alopecia	4	12.5	15	11.0	0	0.0	0	0.0
Neuropathy-sensory	4	12.5	25	18.4	0	0.0	0	0.0
SGOT(AST)	4	12.5	10	7.4	0	0.0	0	0.0
Abdominal pain or cramping	3	9.4	10	7.4	0	0.0	0	0.0
Conjunctivitis	3	9.4	9	6.6	0	0.0	0	0.0
Other ocular/visual	3	9.4	7	5.1	0	0.0	0	0.0
Pruritus	3	9.4	3	2.2	0	0.0	0	0.0
Weight loss	3	9.4	29	21.3	0	0.0	0	0.0
Allergic rhinitis	2	6.3	9	6.6	0	0.0	0	0.0
Dysuria	2	6.3	2	1.5	0	0.0	0	0.0
Other Dermatology/Skin	2	6.3	12	8.8	0	0.0	0	0.0
Other neurology	2	6.3	12	8.8	0	0.0	0	0.0
Pigmentation changes	2	6.3	4	2.9	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
SGPT(ALT)	2	6.3	8	5.9	0	0.0	0	0.0
Taste disturbance	2	6.3	13	9.6	0	0.0	0	0.0
Vaginal bleeding	2	6.3	0	0.0	0	0.0	0	0.0
Weight gain	2	6.3	3	2.2	0	0.0	0	0.0
Alkaline phosphatase	1	3.1	1	0.7	0	0.0	0	0.0
Allergic reaction/hypersenitivity	1	3.1	3	2.2	0	0.0	0	0.0
Bone pain	1	3.1	5	3.7	0	0.0	0	0.0
Bruising	1	3.1	2	1.5	0	0.0	0	0.0
Cardiac-ischemia/infarction	1	3.1	6	4.4	0	0.0	0	0.0
Dry eye	1	3.1	2	1.5	0	0.0	0	0.0
Dry skin	1	3.1	4	2.9	0	0.0	0	0.0
Epistaxis	1	3.1	4	2.9	0	0.0	0	0.0
Gastric ulcer	1	3.1	2	1.5	0	0.0	0	0.0
Glaucoma	1	3.1	2	1.5	0	0.0	0	0.0
Hematuria	1	3.1	0	0.0	0	0.0	0	0.0
Hot flashes/flushes	1	3.1	1	0.7	0	0.0	0	0.0
Hyperkalemia	1	3.1	1	0.7	0	0.0	0	0.0
Hypoalbuminemia	1	3.1	3	2.2	0	0.0	0	0.0
Hypocalcemia	1	3.1	1	0.7	0	0.0	0	0.0
Hypothyroidism	1	3.1	2	1.5	0	0.0	0	0.0
Inner ear/hearing	1	3.1	12	8.8	0	0.0	0	0.0
Memory loss	1	3.1	1	0.7	0	0.0	0	0.0
Middle ear/hearing	1	3.1	0	0.0	0	0.0	0	0.0
Myalgia	1	3.1	6	4.4	0	0.0	0	0.0
Neuropathy-cranial	1	3.1	0	0.0	0	0.0	0	0.0
Nystagmus	1	3.1	1	0.7	0	0.0	0	0.0
Other allergy/immunology	1	3.1	6	4.4	0	0.0	0	0.0
Other hepatic	1	3.1	1	0.7	0	0.0	0	0.0
Palpitations	1	3.1	0	0.0	0	0.0	0	0.0
Radiation recall reaction	1	3.1	0	0.0	0	0.0	0	0.0
Rigors, chills	1	3.1	5	3.7	0	0.0	0	0.0
Secondary Malignancy-Other	1	3.1	0	0.0	0	0.0	0	0.0
Tremor	1	3.1	3	2.2	0	0.0	0	0.0
Urinary frequency/urgency	1	3.1	11	8.1	0	0.0	0	0.0
Vision-blurred vision	1	3.1	1	0.7	0	0.0	0	0.0
Voice	1	3.1	6	4.4	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
changes/stridor/larynx								
Acidosis	0	0.0	1	0.7	0	0.0	0	0.0
Apnea	0	0.0	1	0.7	0	0.0	0	0.0
Arthritis	0	0.0	8	5.9	0	0.0	0	0.0
Bicarbonate	0	0.0	1	0.7	0	0.0	0	0.0
Bilirubin	0	0.0	2	1.5	0	0.0	0	0.0
CNS Cerebrovascular ischemia	0	0.0	1	0.7	0	0.0	0	0.0
Cardiac left ventricular function	0	0.0	1	0.7	0	0.0	0	0.0
Catheter-related infection	0	0.0	1	0.7	0	0.0	0	0.0
Coagulation-Other	0	0.0	2	1.5	0	0.0	0	0.0
Cognitive disturbance/learning problems	0	0.0	1	0.7	0	0.0	0	0.0
Conduction abnormality/A/V heart block	0	0.0	1	0.7	0	0.0	0	0.0
Duodenal ulcer	0	0.0	2	1.5	0	0.0	0	0.0
Earache	0	0.0	1	0.7	0	0.0	0	0.0
Erythema multiforme	0	0.0	3	2.2	0	0.0	0	0.0
Flatulence	0	0.0	3	2.2	0	0.0	0	0.0
Flushing	0	0.0	3	2.2	0	0.0	0	0.0
Gastritis	0	0.0	3	2.2	0	0.0	0	0.0
Gynecomastia	0	0.0	1	0.7	0	0.0	0	0.0
Haptoglobin	0	0.0	1	0.7	0	0.0	0	0.0
Hemolysis	0	0.0	3	2.2	0	0.0	0	0.0
Hemoptysis	0	0.0	2	1.5	0	0.0	0	0.0
Hiccoughs	0	0.0	6	4.4	0	0.0	0	0.0
Hyperuricemia	0	0.0	2	1.5	0	0.0	0	0.0
Hypoglycemia	0	0.0	1	0.7	0	0.0	0	0.0
Injection site reaction	0	0.0	1	0.7	0	0.0	0	0.0
Mouth dryness	0	0.0	5	3.7	0	0.0	0	0.0
Nail changes	0	0.0	1	0.7	0	0.0	0	0.0
Nodal/junctional arrhythmia/dysrhythmia	0	0.0	2	1.5	0	0.0	0	0.0
Other hemorrhage	0	0.0	2	1.5	0	0.0	0	0.0
Other lymphatics	0	0.0	1	0.7	0	0.0	0	0.0
Peripheral arterial ischemia	0	0.0	1	0.7	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
Phlebitis	0	0.0	1	0.7	0	0.0	0	0.0
Photosensitivity	0	0.0	1	0.7	0	0.0	0	0.0
Pneumothorax	0	0.0	1	0.7	0	0.0	0	0.0
Proctitis	0	0.0	1	0.7	0	0.0	0	0.0
Proteinuria	0	0.0	1	0.7	0	0.0	0	0.0
Pulmonary fibrosis	0	0.0	1	0.7	0	0.0	0	0.0
Pyramidal tract dysfunction	0	0.0	1	0.7	0	0.0	0	0.0
Rectal bleeeding/hematochezia	0	0.0	2	1.5	0	0.0	0	0.0
Sense of smell	0	0.0	1	0.7	0	0.0	0	0.0
Sinus bradycardia	0	0.0	1	0.7	0	0.0	0	0.0
Sinus tachycardia	0	0.0	4	2.9	0	0.0	0	0.0
Syndromes-Other	0	0.0	1	0.7	0	0.0	0	0.0
Transfusion: pRBCs	0	0.0	3	2.2	0	0.0	0	0.0
Urinary retention	0	0.0	1	0.7	0	0.0	0	0.0
Ventricular arrhythmia	0	0.0	1	0.7	0	0.0	0	0.0
Vertigo	0	0.0	2	1.5	0	0.0	0	0.0

2. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

2.1 FDA's Efficacy Analyses for Age and Race

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Race White Randomized and treated (n=410)	12.2 months	9.3 monts	0.024
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white	8.8 months	9.55 months	0.619

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Fully folic acid/vitamin B12 supplemented (n=28)			
Age < 65 years Randomized and treated ()n=279)	13.3 months	10.2 months	0.02
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The white subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the randomized and treated group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age ≥ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

2.2 Evaluation of Evidence for Age Effects on Safety

Table 9.4 is a summary of the subgroup analysis for TEAEs by age. Patients randomized to the Alimta/ cisplatin treatment arm who were ≥ 65 years of age demonstrated a significantly greater frequency of nausea (p= 0.009) when compared with patients on the cisplatin alone arm.

Table 9.4. Summary of Subgroup Analysis for TEAEs by Age

Event	Subgroup	Subcategory	Therapy	N	n (%)	Therapy p-value	Interaction p-value
		≥65	LY/cis	83	72 (86.7%)	0.009	0.053
			Cisplatin	86	60 (69.8)		
		<65	LY/cis	143	118 (82.5)	0.845	
Nausea	Age		Cisplatin	136	111 (81.6)		

Source: Section12.6. Applicant table JMCH.12.51.

Table 9.5 is a summary of the analysis of CTC toxicities in the Alimta/cisplatin group by age. The sample sizes between the two age subgroups were imbalanced, with the majority of patients younger than 65 yrs old. Caution should be taken when interpreting the results of the analysis.

Of the adverse events examined, grade 3/4 leucopenia occurred significantly more often in older patients >65 years.

Table 9.5. Analysis of CTC toxicities in the Alimta/cisplatin group by Age (Reviewers Table)

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	57	53.3	39	63.9	19	17.8	22	36.1
Nausea	91	85.0	51	83.6	13	12.1	7	11.5
Dyspnea	69	64.5	41	67.2	13	12.1	6	9.8
Vomiting	64	59.8	35	57.4	13	12.1	5	8.2
Fatigue	84	78.5	53	86.9	12	11.2	17	27.9
Chest pain	44	41.1	24	39.3	12	11.2	2	3.3
Leukocytes	52	48.6	40	65.6	8	7.5	18	29.5
Hypertension	21	19.6	23	37.7	8	7.5	11	18.0
Diarrhea without colostomy	25	23.4	18	29.5	5	4.7	1	1.6
Thrombosis/embolism	5	4.7	7	11.5	5	4.7	5	8.2
Hemoglobin	30	28.0	27	44.3	4	3.7	6	9.8
Tumor pain	19	17.8	12	19.7	4	3.7	4	6.6
Dehydration	5	4.7	7	11.5	4	3.7	3	4.9
Constipation	45	42.1	33	54.1	3	2.8	3	4.9
Anorexia	35	32.7	24	39.3	3	2.8	1	1.6
Stomatitis/pharyngitis	31	29.0	16	26.2	3	2.8	2	3.3
Other Gastrointestinal	20	18.7	13	21.3	3	2.8	0	0.0
Pulmonary-Other	16	15.0	18	29.5	3	2.8	2	3.3
Infection without Neutropenia	14	13.1	7	11.5	3	2.8	1	1.6

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Constitutional Symptoms-Other	10	9.3	8	13.1	3	2.8	1	1.6
Pleural effusion	4	3.7	2	3.3	3	2.8	0	0.0
Other pain	17	15.9	9	14.8	2	1.9	3	4.9
Dysphagia, esophagitis, odynophagia	6	5.6	4	6.6	2	1.9	0	0.0
Hyponatremia	3	2.8	1	1.6	2	1.9	0	0.0
Pneumonitis/pulmonary infiltrates	2	1.9	2	3.3	2	1.9	0	0.0
Renal/Genitourinary-Other	24	22.4	28	45.9	1	0.9	4	6.6
Platelets	17	15.9	27	44.3	1	0.9	8	13.1
Sweating	15	14.0	9	14.8	1	0.9	0	0.0
Edema	14	13.1	10	16.4	1	0.9	1	1.6
Headache	14	13.1	7	11.5	1	0.9	0	0.0
Dyspepsia/heartburn	13	12.1	7	11.5	1	0.9	0	0.0
Pleuritic pain	13	12.1	16	26.2	1	0.9	2	3.3
Mood alteration-anxiety agitation	11	10.3	11	18.0	1	0.9	0	0.0
Mood alteration-depression	11	10.3	12	19.7	1	0.9	1	1.6
Dizziness/lightheadedness	10	9.3	6	9.8	1	0.9	0	0.0
Other musculoskeletal	10	9.3	4	6.6	1	0.9	1	1.6
Other auditory/hearing	9	8.4	2	3.3	1	0.9	0	0.0
Creatinine	8	7.5	18	29.5	1	0.9	0	0.0
Other cardiovascular/general	6	5.6	13	21.3	1	0.9	1	1.6
Other endocrine	5	4.7	7	11.5	1	0.9	0	0.0
Tearing	5	4.7	2	3.3	1	0.9	0	0.0
Hypercholesterolemia	4	3.7	3	4.9	1	0.9	0	0.0
Hypomagnesemia	4	3.7	3	4.9	1	0.9	0	0.0
Muscle weakness	4	3.7	2	3.3	1	0.9	0	0.0
Neuropathic pain	4	3.7	1	1.6	1	0.9	0	0.0
Hyperglycemia	3	2.8	5	8.2	1	0.9	1	1.6
Hypokalemia	3	2.8	2	3.3	1	0.9	1	1.6
Blood/Bone Marrow-Other	2	1.9	5	8.2	1	0.9	0	0.0
GGT	2	1.9	0	0.0	1	0.9	0	0.0

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Hypotension	2	1.9	3	4.9	1	0.9	0	0.0
Other cardiovascular/arrhythmia	2	1.9	2	3.3	1	0.9	1	1.6
Renal failure	2	1.9	2	3.3	1	0.9	0	0.0
Salivary gland changes	2	1.9	1	1.6	1	0.9	0	0.0
Urticaria	2	1.9	0	0.0	1	0.9	0	0.0
Adult Respiratory Distress Syndrome	1	0.9	0	0.0	1	0.9	0	0.0
Ascites	1	0.9	0	0.0	1	0.9	0	0.0
Cushingoid appearance	1	0.9	0	0.0	1	0.9	0	0.0
Dysmenorrhea	1	0.9	1	1.6	1	0.9	0	0.0
Febrile neutropenia	1	0.9	0	0.0	1	0.9	0	0.0
Hepatic enlargement	1	0.9	0	0.0	1	0.9	0	0.0
Hypophosphatemia	1	0.9	0	0.0	1	0.9	0	0.0
Ileus	1	0.9	1	1.6	1	0.9	1	1.6
Operative injury of vein/artery	1	0.9	0	0.0	1	0.9	0	0.0
Pericardial effusion/pericarditis	1	0.9	1	1.6	1	0.9	0	0.0
Prothrombin time	1	0.9	0	0.0	1	0.9	0	0.0
Supraventricular arrhythmias	1	0.9	4	6.6	1	0.9	2	3.3
Vasovagal episode	1	0.9	0	0.0	1	0.9	0	0.0
Cough	37	34.6	27	44.3	0	0.0	1	1.6
Rash/desquamation	23	21.5	14	23.0	0	0.0	1	1.6
Insomnia	21	19.6	7	11.5	0	0.0	0	0.0
Fever	18	16.8	10	16.4	0	0.0	0	0.0
Neuropathy-sensory	17	15.9	12	19.7	0	0.0	0	0.0
Weight loss	17	15.9	15	24.6	0	0.0	0	0.0
Alopecia	13	12.1	6	9.8	0	0.0	0	0.0
Taste disturbance	10	9.3	5	8.2	0	0.0	0	0.0
Abdominal pain or cramping	8	7.5	5	8.2	0	0.0	0	0.0
Conjunctivitis	8	7.5	4	6.6	0	0.0	0	0.0
Inner ear/hearing	8	7.5	5	8.2	0	0.0	0	0.0
Other Dermatology/Skin	8	7.5	6	9.8	0	0.0	0	0.0
Other neurology	8	7.5	6	9.8	0	0.0	0	0.0
SGOT(AST)	8	7.5	6	9.8	0	0.0	0	0.0
SGPT(ALT)	8	7.5	2	3.3	0	0.0	0	0.0
Other ocular/visual	7	6.5	3	4.9	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Urinary frequency/urgency	7	6.5	5	8.2	0	0.0	0	0.0
Myalgia	6	5.6	1	1.6	0	0.0	0	0.0
Bone pain	5	4.7	1	1.6	0	0.0	0	0.0
Infection with grade 3 or 4 Neutropenia	5	4.7	5	8.2	0	0.0	1	1.6
Pigmentation changes	5	4.7	1	1.6	0	0.0	0	0.0
Pruritus	5	4.7	1	1.6	0	0.0	0	0.0
Voice changes/stridor/larynx	5	4.7	2	3.3	0	0.0	0	0.0
Weight gain	5	4.7	0	0.0	0	0.0	0	0.0
Hiccoughs	4	3.7	2	3.3	0	0.0	0	0.0
Other allergy/immunology	4	3.7	3	4.9	0	0.0	0	0.0
Other metabolic/laboratory	4	3.7	3	4.9	0	0.0	1	1.6
Allergic rhinitis	3	2.8	8	13.1	0	0.0	0	0.0
Arthritis	3	2.8	5	8.2	0	0.0	0	0.0
Confusion	3	2.8	2	3.3	0	0.0	2	3.3
Dry skin	3	2.8	2	3.3	0	0.0	0	0.0
Epistaxis	3	2.8	2	3.3	0	0.0	0	0.0
Infection/Febrile Neutropenia-Other	3	2.8	2	3.3	0	0.0	2	3.3
Mouth dryness	3	2.8	2	3.3	0	0.0	0	0.0
Neuropathy-motor	3	2.8	2	3.3	0	0.0	1	1.6
Sinus tachycardia	3	2.8	1	1.6	0	0.0	0	0.0
Arthralgia	2	1.9	6	9.8	0	0.0	1	1.6
Cardiac-ischemia/infarction	2	1.9	5	8.2	0	0.0	0	0.0
Dysuria	2	1.9	2	3.3	0	0.0	0	0.0
Erectile impotence	2	1.9	1	1.6	0	0.0	1	1.6
Erythema multiforme	2	1.9	1	1.6	0	0.0	0	0.0
Flatulence	2	1.9	1	1.6	0	0.0	0	0.0
Flushing	2	1.9	1	1.6	0	0.0	0	0.0
Gastric ulcer	2	1.9	1	1.6	0	0.0	0	0.0
Gastritis	2	1.9	1	1.6	0	0.0	0	0.0
Hot flashes/flushes	2	1.9	0	0.0	0	0.0	0	0.0
Hyperuricemia	2	1.9	0	0.0	0	0.0	0	0.0
Hypoalbuminemia	2	1.9	2	3.3	0	0.0	0	0.0
Hypothyroidism	2	1.9	1	1.6	0	0.0	0	0.0
Nystagmus	2	1.9	0	0.0	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Other hemorrhage	2	1.9	0	0.0	0	0.0	0	0.0
Other hepatic	2	1.9	0	0.0	0	0.0	0	0.0
Rigors, chills	2	1.9	4	6.6	0	0.0	0	0.0
Tremor	2	1.9	2	3.3	0	0.0	0	0.0
Vaginal bleeding	2	1.9	0	0.0	0	0.0	0	0.0
Vertigo	2	1.9	0	0.0	0	0.0	0	0.0
Alkaline phosphatase	1	0.9	1	1.6	0	0.0	0	0.0
Allergic reaction/hypersenitivity	1	0.9	3	4.9	0	0.0	0	0.0
Bruising	1	0.9	2	3.3	0	0.0	0	0.0
CNS Cerebrovascular ischemia	1	0.9	0	0.0	0	0.0	0	0.0
Dry eye	1	0.9	2	3.3	0	0.0	0	0.0
Earache	1	0.9	0	0.0	0	0.0	0	0.0
Hematuria	1	0.9	0	0.0	0	0.0	0	0.0
Hemolysis	1	0.9	2	3.3	0	0.0	0	0.0
Hemoptysis	1	0.9	1	1.6	0	0.0	0	0.0
Hyperkalemia	1	0.9	1	1.6	0	0.0	0	0.0
Hypocalcemia	1	0.9	1	1.6	0	0.0	0	0.0
Incontinence	1	0.9	1	1.6	0	0.0	1	1.6
Injection site reaction	1	0.9	0	0.0	0	0.0	0	0.0
Memory loss	1	0.9	1	1.6	0	0.0	0	0.0
Middle ear/hearing	1	0.9	0	0.0	0	0.0	0	0.0
Nail changes	1	0.9	0	0.0	0	0.0	0	0.0
Neuropathy-cranial	1	0.9	0	0.0	0	0.0	0	0.0
Nodal/junctional arrhythmia/dysrhythmia	1	0.9	1	1.6	0	0.0	0	0.0
Other lymphatics	1	0.9	0	0.0	0	0.0	0	0.0
Photosensitivity	1	0.9	0	0.0	0	0.0	0	0.0
Pneumothorax	1	0.9	0	0.0	0	0.0	0	0.0
Proctitis	1	0.9	0	0.0	0	0.0	0	0.0
Proteinuria	1	0.9	0	0.0	0	0.0	0	0.0
Pulmonary fibrosis	1	0.9	0	0.0	0	0.0	0	0.0
Pyramidal tract dysfunction	1	0.9	0	0.0	0	0.0	0	0.0
Radiation recall reaction	1	0.9	0	0.0	0	0.0	0	0.0
Rectal bleeeding/hematochezia	1	0.9	1	1.6	0	0.0	0	0.0
Secondary Malignancy-Other	1	0.9	0	0.0	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Sense of smell	1	0.9	0	0.0	0	0.0	0	0.0
Sinus bradycardia	1	0.9	0	0.0	0	0.0	0	0.0
Acidosis	0	0.0	1	1.6	0	0.0	0	0.0
Apnea	0	0.0	1	1.6	0	0.0	0	0.0
Bicarbonate	0	0.0	1	1.6	0	0.0	0	0.0
Bilirubin	0	0.0	2	3.3	0	0.0	0	0.0
Cardiac left ventricular function	0	0.0	1	1.6	0	0.0	0	0.0
Catheter-related infection	0	0.0	1	1.6	0	0.0	0	0.0
Coagulation-Other	0	0.0	2	3.3	0	0.0	0	0.0
Cognitive disturbance/learning problems	0	0.0	1	1.6	0	0.0	0	0.0
Conduction abnormality/A/V heart block	0	0.0	1	1.6	0	0.0	0	0.0
Depressed level of consciousness	0	0.0	2	3.3	0	0.0	1	1.6
Duodenal ulcer	0	0.0	2	3.3	0	0.0	0	0.0
Glaucoma	0	0.0	3	4.9	0	0.0	0	0.0
Gynecomastia	0	0.0	1	1.6	0	0.0	0	0.0
Haptoglobin	0	0.0	1	1.6	0	0.0	0	0.0
Hepatic pain	0	0.0	1	1.6	0	0.0	1	1.6
Hypoglycemia	0	0.0	1	1.6	0	0.0	0	0.0
Hypoxia	0	0.0	1	1.6	0	0.0	1	1.6
Lymphopenia	0	0.0	1	1.6	0	0.0	1	1.6
Palpitations	0	0.0	1	1.6	0	0.0	0	0.0
Peripheral arterial ischemia	0	0.0	1	1.6	0	0.0	0	0.0
Phlebitis	0	0.0	1	1.6	0	0.0	0	0.0
Syndromes-Other	0	0.0	1	1.6	0	0.0	0	0.0
Transfusion: pRBCs	0	0.0	3	4.9	0	0.0	0	0.0
Urinary retention	0	0.0	1	1.6	0	0.0	0	0.0
Ventricular arrhythmia	0	0.0	1	1.6	0	0.0	0	0.0

3. **Evaluation of Pediatric Program**

There is a full waiver for the mesothelioma indication. The safety of alimta in pediatric patients has not been established. Malignant pleural mesothelioma is a disease of adults.

4. **Comments on Data Available or Needed in Other Populations**

4.1 Pregnancy and Nursing

As a class, folic acid antimetabolites have been demonstrated to produce manifestations of developmental toxicity such as growth retardation, embryo lethality, and malformations. Alimta was found to be embryo toxic at doses of 10 mg/ kg (30 mg/ m^2) and fetotoxic causing fetal malformations (cleft palate) at doses of 5 mg/ kg (15 mg/ m^2). There are no studies of Alimta in pregnant women. If Alimta is used during pregnancy, or if the patient becomes pregnant while taking Alimta, the patient should be apprised of the potential hazard to the fetus.

As with other anti-folate drugs, there is a potential for serious adverse reactions in nursing infants and nursing should be discontinued if the mother is treated with Alimta.

4.2 Renal, Nonsteroidal Anti-Inflammatory Drugs, and Pleural Effusions

Alimta is eliminated primarily via the renal route. Patients with a creatinine clearance of < 45 ml/min, calculated with the mean body weight by the formula of Cockcroft and Gault, should not receive Alimta.

As with other antifolates, caution should be exercised when concomitant administration of Alimta with nonsteroidal anti-inflammatory drugs are used.

Patients with clinically significant pleural effusions have been excluded in studies performed with Alimta. Before starting treatment, pleural effusions should be drained.

X. Conclusions and Recommendations

1. Conclusions

One single-blind, randomized, controlled trial, demonstrating the efficacy and safety of Alimta in combination with cisplatin for the treatment of malignant pleural mesothelioma patients whose disease is either unresectable or who are not candidates for curative surgery has been submitted and reviewed. The pivotal trial was multicenter with United States and non-US sites. The combination of Alimta plus cisplatin is the first chemotheraupetic regimen to demonstrate a survival benefit in malignant pleural mesothelioma in comparison to a control regimen.

The overall survival analyses of the randomized and treated (RT) and the intent-to-treat populations demonstrated a statistically significant improvement in survival in favor of the alimta/cisplatin arm compared to cisplatin alone. In the fully folic acid/vitamin B12 supplemented group, the alimta/cisplatin arm was favored and was marginally statistically significant. Sixty-seven percent of the patients enrolled on study had pathologically confirmed mesothelioma; in the confirmed mesothelioma subset, survival analyses of the RT and the fully folic acid/vitamin B12 supplemented groups demonstrated a marginally significant survival advantage in favor of the alimta/cisplatin arm. The under-powered female subgroup demonstrated in RT and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm.[193] The white subgroup demonstrated, in the RT and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the RT group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the RT and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age ≥ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

Alimta in combination with cisplatin has satisfactorily demonstrated a consistent survival advantage compared to cisplatin alone in patients with pleural malignant mesothelioma in a randomized, single-blinded study.

The common grade 3 or grade 4 laboratory toxicities in the RT group treated with Alimta plus cisplatin were neutropenia (28.8%), leucopenia (18.1%), thrombocytopenia (5.8%) and anemia (6.2%). In a subgroup analysis of patients fully supplemented with folic acid + vitamine B12 (FS), the Alimta + cisplatin treated arm had neutropenia (24.4%), leucopenia (15.5%), anemia (6%), thrombocytopenia (5.4%) while the cisplatin only arm had neutropenia (3.1%), leucopenia (0.6%) and decreased creatinine (1%). The common

[193] Lilly did a multifactorial survival analysis considering prognostic factors and there was no gender effect; ISE document submitted 3/24/2003.

nonlaboratory grade 3 and grade 4 adverse events in the RT group treated with Alimta + cisplatin were fatigue (18.1%), nausea (14.6%), vomiting (13.7%), diarrhea (4.9%), dehydration (4.4%), stomatitis (4%), anorexia (3.5%) and rash (1.3%). In the FS group, the patients treated with Alimta + cisplatin had fatigue (17.3%), nausea (11.9%), vomiting (10.7%), dehydration (4.2%), diarrhea (3.6%), stomatitis (3%) and anorexia (2.4%). Supplementation with folic acid + vitamin B12 reduced many of the laboratory and non-laboratory toxicities in comparison to a never supplemented subgroup.

However, the demonstration of the survival benefit is based on only one randomized, control trial which had challenges with regard to pathology confirmation, eligibility based on measurable disease, response evaluation, the addition of folic acid plus vitamin B12 into the ongoing pivotal trial, and financial disclosure. In view that these deficiencies could be the result of bias and affect the survival benefit, replication of the survival benefit in another randomized, controlled trial appears desirable although not required for approval.

2. Recommendations

Based on this review of NDA 21-462, Alimta in combination with cisplatIn is clinically approvable for the treatment of malignant pleural mesothelioma patients whose disease is either unresectable or who are not candidates for curative surgery.

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/s/

Robert White
1/28/04 02:37:20 PM
MEDICAL OFFICER

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1/28/04 04:20:46 PM
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John Johnson
1/29/04 09:22:47 AM
MEDICAL OFFICER
See also my Clinical Team Leader Review

MEDICAL OFFICER CONSULTATION

Date: November 13, 2003

To: P. Garvey, Project Manager, HFD-150

From: Sally Seymour, MD
Medical Officer
Division of Pulmonary and Allergy Drug Products (HFD-570)

Through: Eugene Sullivan, MD, FCCP
Medical Team Leader (Acting), DPADP

Badrul Chowdhury, MD, PhD
Director, DPADP

Subject: Consultation regarding pulmonary function in a Phase 3 clinical trial conducted to gain marketing approval of Alimta (pemetrexed)

General Information

NDA #	21-462
Sponsor	Eli Lilly & Company
Protocol	H3E-MC-JMCH (g)
Drug Product	Alimta (pemetrexed)
Request From	Division of Oncology Drug Products (HFD-150)
Materials	Proposed label; Protocol H3E-MC-JMCH(g); Pulmonary function results from trial comparing alimta/cisplatin and cisplatin alone

Background

The Division of Oncology Drug Products consulted the Division of Pulmonary and Allergy Drug Products to comment on ——— pulmonary function for alimta (NDA 21-462) in the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who were not candidates for curative surgery and who had not received prior chemotherapeutic regimens.

Malignant mesothelioma is a tumor of the pleura or the peritoneum associated with prior exposure to asbestos. The disease is refractory to current therapeutic options and consequently the prognosis is poor with median survival < 18 months.

Alimta is an antifolate that exerts antineoplastic activity by disrupting folate-dependent metabolic processes that are essential for cell replication. The Sponsor conducted a multicenter single-blinded randomized Phase 3 trial of alimta plus cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. Two hundred twenty-six

patients received alimta plus cisplatin while 222 patients received only cisplatin on day 1 of a 21 day cycle. Six cycles were administered with the option of additional cycles at the discretion of the investigator.

The primary endpoint of the trial was survival. The secondary endpoints pertinent to this consult were pulmonary function tests. Per protocol, the Sponsor chose to measure forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and slow vital capacity (SVC) at baseline and prior to every other treatment cycle. According to the protocol, FVC, SVC and FEV1 were measured using standard apparatus and following ATS or European Respiratory guidelines.

Table 1 and Table 2 summarize the results of the forced vital capacity for the Phase 3 clinical trial. Per the Sponsor's protocol, to be included in the analysis of a particular PFT parameter, a patient must have had data from the baseline period and data from at least one cycle among cycles 2, 4, and 6.

Table 1

Forced Vital Capacity
(Liters, % predicted)
RT Population **

		Alimta/Cisplatin		Cisplatin
Cycle	**N**	**LS Mean**	**N**	**LS Mean**
Baseline	167	2.37 (61.52)	156/155	2.45 (62.12)
Cycle 2	152	2.51 (65.37)	141/139	2.44(63.21)
Cycle 4	117	2.57 (67.11) *	89/88	2.41 (63.44) *
Cycle 6	66	2.55 (67.12) *	54/53	2.33 (60.72) *
Average	167	2.54 (66.53) *	156/155	2.40 (62.45) *

**Randomized & Treated * $p < 0.05$

Table 2

Forced Vital Capacity - Change from Baseline
Liters (% predicted)
RT Population **

		Alimta/Cisplatin		Cisplatin
Cycle	**N**	**LS Mean**	**N**	**LS Mean**
Cycle 2	152	0.08 (2.90)	141/139	0 (0.67)
Cycle 4	117	0.14 (4.62) *	89/88	-0.03 (0.70) *
Cycle 6	66	0.12 (4.57) *	54/53	-0.11 (-2.01) *
Average	167	0.11 (4.03) *	156/155	-0.05 (-0.21) *

**Randomized & Treated * $p < 0.05$

The Sponsor would like to make the following claim in the —— section of the label:

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J

Specific Comments

The Division of Oncology Drug Products has asked the following questions:

1. What are the appropriate pulmonary function tests to demonstrate benefit in this disease?

   Malignant mesothelioma causes a loss of lung volume and therefore would be expected to produce a restrictive pattern on pulmonary function tests. Measurement of lung volumes such as total lung capacity and vital capacity would be the most appropriate variables to monitor a restrictive disease, while FEV1 is less useful. Unless a significant amount of obstruction and/or air trapping is present, the FVC and SVC should be similar and performing analysis on both is redundant. Although the FVC can suggest restriction, it is effort dependent and lung volumes are necessary to confirm the restrictive defect. Therefore, the ideal parameter for assessing restrictive physiology would be lung volume measurements, which can be performed using helium dilution or body plethysmography. However, of the variables the Sponsor measured, the FVC could reasonably be used to monitor and analyze trends. Therefore, the remainder of this consult will focus on the FVC results.

2. What degree of improvement in pulmonary function is clinically important?

   The degree of improvement in pulmonary function that is clinically important is not well defined. Therefore even though the data shows a statistically significant difference between groups in FVC, the clinical relevance of the magnitude of change is unclear.

   When measuring FVC, several acceptable maneuvers are recorded to show reproducibility. According to the American Thoracic Society, the two largest FVCs from acceptable maneuvers can vary up to 200 mL.[1] In addition, serial measurement of FVC is subject to a certain amount of variability often termed the coefficient of variation. The amount of within subject variability is not well defined but is often estimated to be around 5% over the course of day-to-day measurement.[2]

   The Sponsor's data for FVC reported in Table JMCH.11.69 and Table JMCH.11.70 is summarized in Table 1 and Table 2, above. The average mean increase in FVC from baseline in the alimta/cisplatin arm was 110mL while the average mean decrease from baseline in the cisplatin arm was 50mL. Thus, the difference between groups in average mean change in FVC totals 160mL.

[1] Am J Respir Crit Care Med 1995; 152:1107-1136.
[2] Am Rev Respir Dis 1991; 144:1202-1218.

Because the difference between groups in mean change from baseline FVC in this trial is less than the range of variability allowed by the ATS in a single test session and less than generally accepted day-to-day variability, it is the opinion of this Reviewer that the difference in FVC is not clinically significant.

If the effects of multiple cycles of alimta are felt to be cumulative, one could argue that it would be more appropriate to base conclusions on the Cycle 6 data, rather than the data representing the average values over multiple cycles. One difficulty with this approach is that the numbers of patients for which data are available become quite small with successive cycles. That said, the largest change in FVC was in cycle 6 in which the alimta/cisplatin arm showed a mean increase from baseline FVC of 120mL while the cisplatin arm showed a mean decrease from baseline FVC of 110mL. The difference between groups in mean change from baseline FVC was 230mL. Although this is a larger increase in FVC, the value is only slightly out of the range of variability allowed by the ATS in a single test session. In addition, as mentioned above, the significant decline in patient data available during the course of the trial makes any interpretation of the data very difficult. Therefore, it remains the opinion of this Reviewer that the difference in FVC is not clinically significant.

3. Does the data on pulmonary function support the label claims of improvement in pulmonary function

It doesn't appear that appropriate statistical methods were specified to account for multiplicity among the various secondary endpoints. DPADP defers to DODP in regards to whether this alone would preclude inclusion of the proposed claims in the label.

Although the data on pulmonary function does support a statistically significant difference between the two treatment groups (issues of multiplicity aside), the effect size is not considered clinically meaningful

The observation that we see in this study is interesting. To support a specific labeling claim of an improvement in lung function which is clinically meaningful, the Sponsor should do a 'second' trial where assessment of lung function is declared as the primary variable. A 'second' trial is recommended because of the secondary nature of the observation in this trial as well as lack of control of multiplicity. Furthermore, the choice of variables to be measured would need further explanation with a detailed discussion in the protocol of what would constitute a favorable response. Finally, in the design of the 'second' trial, the Sponsor would need to address the significant decline in the numbers

of patients for which data are available, which was noted during the course of this trial.

cc: HFD-570/Sullivan/Medical Team Leader (Acting)
HFD-570/Chowdhury/Division Director
HFD-570/Barnes/Chief Project Management Staff

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