

## CLINICAL REVIEW

### Clinical Review Section

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.

## CLINICAL REVIEW

### Clinical Review Section

- 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 to 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 to 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

## CLINICAL REVIEW

### Clinical Review Section

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  $\alpha = 0.05$  (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 to 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.

# CLINICAL REVIEW

## Clinical Review Section

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

## CLINICAL REVIEW

### Clinical Review Section

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

## CLINICAL REVIEW

### Clinical Review Section

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 proceeded 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  $\alpha$  was to be made. A log rank-based adjustment of the significance level  $\alpha$  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  $\alpha$ , 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  $\alpha$  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.

# CLINICAL REVIEW

## Clinical Review Section

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

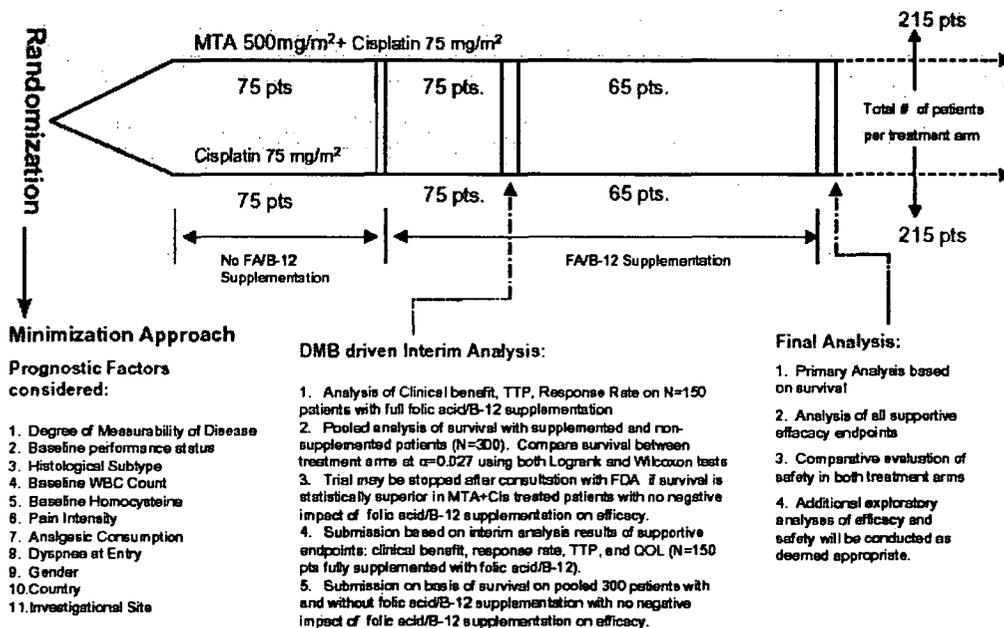
### Implications of the Planned Interim Study Results

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)



# CLINICAL REVIEW

## Clinical Review Section

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 <sub>12</sub> 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	L.Y231514 lyophilized formulation

# CLINICAL REVIEW

## Clinical Review Section

### 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 (<12 $\mu$ mol/L) and High ( $\geq$ 12 $\mu$ mol/L)
Disease Measurability	DM	Bidimensional and Unidimensional
Histology Subtype	HS	Epithelial and Others
Baseline WBC	WBC	Low (<8.3 $\times 10^9$ /L) and High ( $\geq$ 8.3 $\times 10^9$ /L)
Gender	Gender	M and F
Pain Intensity	PI	Low (<20mm) and High ( $\geq$ 20mm)
Analgesic Consumption	AC	Low (<60 morphine equivalents per day, only NSAIDS, or no analgesic consumption) High ( $\geq$ 60 morphine equivalents per day)
Dyspnea	Dyspnea	Low (<20mm) and High ( $\geq$ 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.

# CLINICAL REVIEW

## Clinical Review Section

**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 <sup>1</sup>
510-5109	LY/cis	Death (from study disease)
601-6014	Cisplatin	Patient decision

<sup>1</sup> 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.**

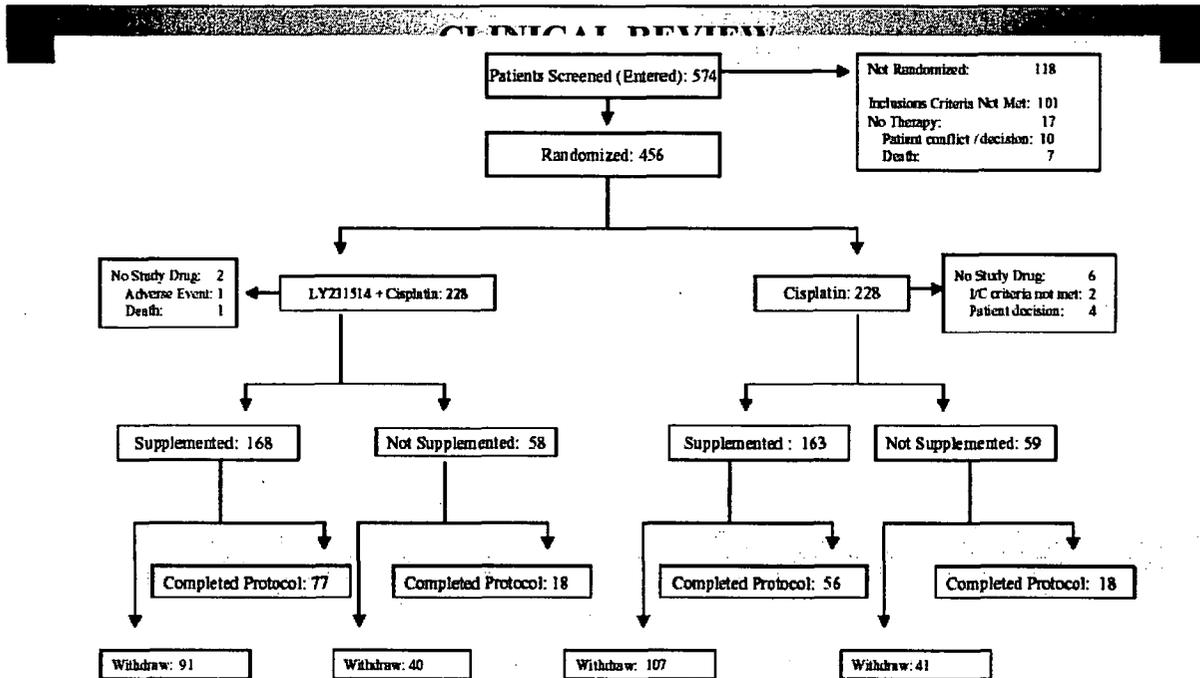
This was a multicenter trial that entered patients at 88 investigational sites (see the table below). Nineteen percent of the patients randomized (n=456) were from the United States; 81% of the patients randomized were from outside the United States. Among the 88 investigational sites, four centers (numbers 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 to 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	19	3.9
Italy	5	30	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
Slovenia	1	3	2	0.4
Singapore	1	1	0	0
Turkey	1	19	16	3.5
<b>Total</b>	<b>88</b>	<b>574</b>	<b>456</b>	<b>100%</b>

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<sup>1</sup>.**

<sup>1</sup> 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 <sup>1</sup>	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.

# CLINICAL REVIEW

## Clinical Review Section

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.
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:

## CLINICAL REVIEW

### Clinical Review Section

- 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**

Cycle Number	LY/cis (N=168)		Cisplatin (N=163)	
	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	--

# CLINICAL REVIEW

## Clinical Review Section

### 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)
<b>Sex</b>		
Male	184 (81.4%)	181 (81.5%)
Female	42 (18.6)	41 (18.5)
<b>Origin</b>		
Caucasian	204 (90.3)	206 (92.8)
Hispanic	11 (4.9)	12 (5.4)
Asian <sup>1</sup>	10 (4.4)	4 (1.9)
African	1 (0.4)	0
<b>Age</b>		
Median	61	60
Minimum	29	19
Maximum	85	84

<sup>1</sup> 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)
<b>Sex</b>				
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)
<b>Origin</b>				
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 <sup>1</sup>	7 (4.2)	3 (5.2)	3 (1.8)	1 (0.7)
African	1 (0.6)	0	0	0
<b>Age</b>				
Median	60	62	60	61
Minimum	29	32	19	35
Maximum	85	77	82	84

<sup>1</sup> Western and East/Southeast Asian have been combined.

# CLINICAL REVIEW

## Clinical Review Section

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)
<b>Diagnosis / Histology</b>		
Epithelial	154 (68.1%)	152 (68.9%)
Mixed	37 (16.4)	36 (16.2)
Sarcomatoid	18 (8.0)	25 (11.3)
Other	17 (7.5)	9 (4.1)
<b>Stage at Entry</b>		
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)
<b>Performance Status</b>		
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)
<b>Diagnosis / Histology</b>				
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)
<b>Stage at Entry</b>				
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
<b>Performance Status</b>				
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.**

# CLINICAL REVIEW

## Clinical Review Section

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 <sup>1</sup>	1 (0.4)	0
Unknown classification <sup>2</sup>	1 (0.4)	0

<sup>1</sup> Patient 502-5052 received IL-2.

<sup>2</sup> 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 <sup>1</sup>	1 (0.6)	0	0	0

<sup>1</sup> Patient 501-5001 received an unknown drug for the purpose of pleurodesis.

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# CLINICAL REVIEW

## Clinical Review Section

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 <sup>1</sup>	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)

<sup>1</sup> 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**

Disease Site <sup>1</sup>	LY/cis		Cisplatin	
	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)

<sup>1</sup> 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.

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# CLINICAL REVIEW

## Clinical Review Section

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 <sup>1</sup>	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)

<sup>1</sup> 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**

Event <sup>1</sup>	LY/cis		Cisplatin	
	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)

<sup>1</sup> Patients may have more than one historical illness. Percentages are defined as the involvement of a given illness among all patients in the group.

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# CLINICAL REVIEW

## Clinical Review Section

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)
<b>KPS</b>				
Low ( $\leq 80$ )	83 (49.4%)	26 (44.8)	69 (42.3%)	28 (47.5)
High ( $\geq 90$ )	85 (50.6)	32 (55.2)	94 (57.7)	31 (52.5)
<b>Degree of Measurability<sup>1</sup></b>				
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)
<b>Histologic Subtype</b>				
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)
<b>WBC</b>				
Low ( $< 8.3$ GL/L)	72 (42.9)	25 (43.1)	68 (41.7)	23 (39.0)
High ( $\geq 8.3$ GL/L)	96 (57.1)	33 (56.9)	95 (58.3)	36 (61.0)
<b>Pain Intensity<sup>2</sup></b>				
Low ( $< 20$ mm)	82 (49.4)	30 (51.7)	80 (49.1)	33 (55.9)
High ( $\geq 20$ mm)	84 (50.6)	28 (48.3)	83 (50.9)	26 (44.1)
<b>Analgesic Consumption</b>				
Low ( $< 60$ mg morph eq/day)	129 (76.8)	44 (75.9)	124 (76.1)	46 (78.0)
High ( $\geq 60$ mg morph eq/day)	39 (23.2)	14 (24.1)	39 (23.9)	13 (22.0)
<b>Dyspnea<sup>2</sup></b>				
Low ( $< 20$ mm)	66 (39.8)	25 (43.1)	68 (41.7)	24 (40.7)
High ( $\geq 20$ mm)	100 (60.2)	33 (56.9)	95 (58.3)	35 (59.3)
<b>Homocysteine</b>				
Low ( $< 12$ umol/L)	119 (70.8)	36 (62.1)	118 (72.4)	38 (64.4)
High ( $\geq 12$ umol/L)	49 (29.2)	22 (37.9)	45 (27.6)	21 (35.6)
<b>Sex</b>				
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)

<sup>1</sup> A single patient was missing their evaluable disease measurement at baseline.

<sup>2</sup> 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.

## CLINICAL REVIEW

### Clinical Review Section

**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.**

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# CLINICAL REVIEW

## Clinical Review Section

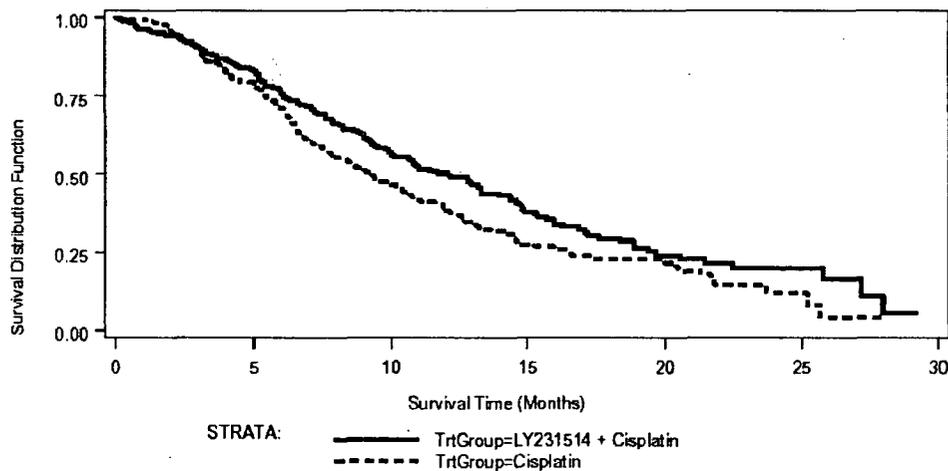
### Survival: The Primary Endpoint

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

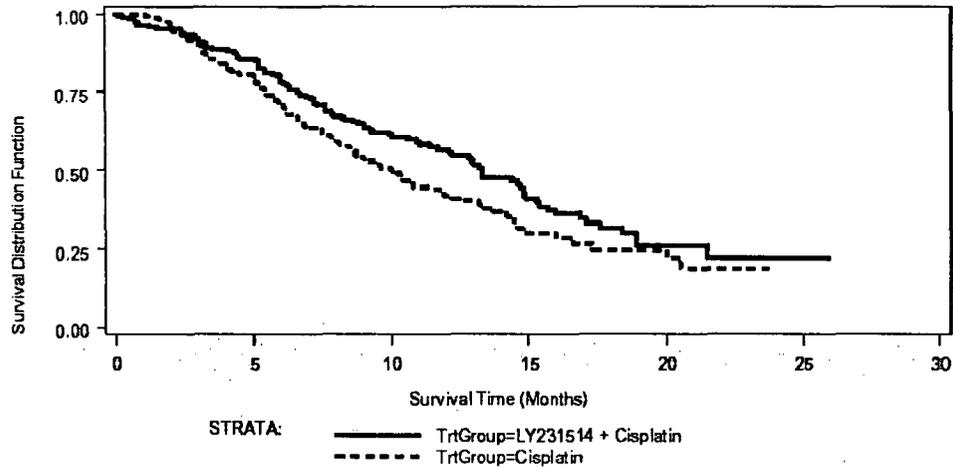
<sup>1</sup>n = number of patients known alive at indicated time.



Program name: ttevent4.SAS. Variable name: survtime. Population: All.

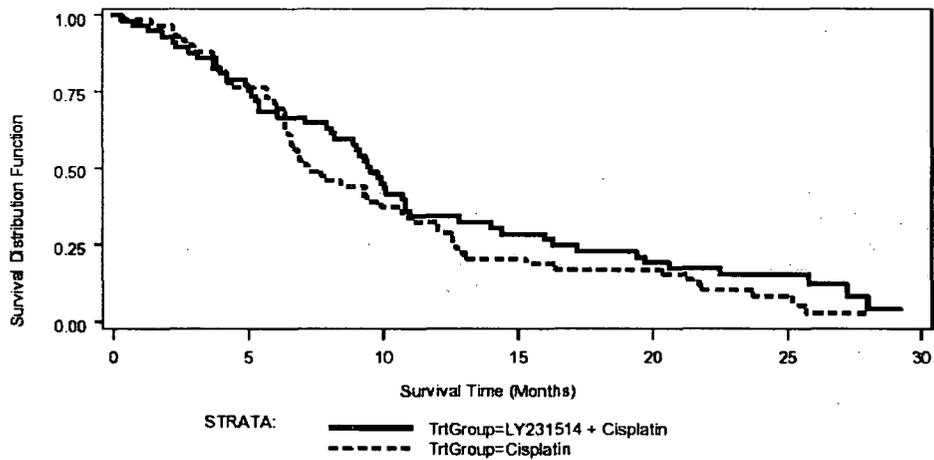
# CLINICAL REVIEW

## Clinical Review Section



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.

# CLINICAL REVIEW

## Clinical Review Section

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			HR <sup>2</sup>
	N	Median (mo)	% Censored	HR <sup>1</sup>	N	Median (mo)	% Censored	N	Median (mo)	% Censored	
<b>Supplementation Group</b>											
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
<b>KPS Group</b>											
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
<b>Disease Stage Group</b>											
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
<b>Histological Subtype</b>											
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
<b>WBC</b>											
<8.2 GI/L	176	13.2	41.5	0.67	92	14.4	43.5	84	12.7	39.3	0.88
≥8.2 GI/L	272	8.9	26.1	--	134	10.6	30.6	138	7.5	21.7	0.71
<b>Post study Chemo</b>											
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	N	Median (mo)	% Censored	HR <sup>1</sup>	N	Median (mo)	% Censored	N	Median (mo)	% Censored	HR <sup>2</sup>
<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

<sup>1</sup> Hazard ratio for subgroup relative to complementary subgroup. For Histological subtype, hazard ratio relative to sarcomatoid subgroup.  
<sup>2</sup> Hazard ratio for LY/cis relative to cisplatin alone.

## Clinical Review Section

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.

## CLINICAL REVIEW

**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

	IY/cis (N=216)	Cisplatin (N=218)
<b>Supplementation Group</b>		
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)
<b>Age*</b>		
<65	138 (63.9)	132 (60.6)
≥65	78 (36.1)	86 (39.5)
<b>Gender</b>		
Male	175 (81.0)	177 (81.2)
Female	41 (19.0)	41 (18.8)
<b>Geography</b>		
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)
<b>Race</b>		
Caucasian	194 (89.8)	202 (92.7)
Other	22 (10.2)	16 (7.3)
<b>KPS Group</b>		
70, 80	101 (46.8)	96 (44.0)
90, 100	115 (53.2)	122 (56.0)
<b>Disease Stage Group</b>		
I, II	49 (22.7)	47 (21.6)
III, IV	167 (77.3)	171 (78.4)
<b>Histological Subtype</b>		
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)
<b>Time from Diagnosis*</b>		
<1.0 months	34 (15.7)	34 (15.6)
≥1.0 months	182 (84.3)	184 (84.4)
<b>WBC*</b>		
<8.2 G/L	87 (40.3)	82 (37.6)
≥8.2 G/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)

	IY/cis (N=216)	Cisplatin (N=218)
<b>Prior Radiotherapy</b>		
Yes	22 (10.2)	29 (13.3)
No	194 (89.8)	189 (86.7)
<b>Poststudy Chemotherapy</b>		
Yes	82 (38.0)	104 (47.7)
No	134 (62.0)	114 (52.3)
<b>Other Poststudy Therapy</b>		
Yes	38 (17.6)	26 (11.9)
No	178 (82.4)	192 (88.1)
<b>Pre-FA Homocysteine*</b>		
<15 µmol/L	183 (84.7)	187 (85.8)
≥15 µmol/L	33 (15.3)	31 (14.2)
<b>Past-FA Homocysteine*</b>		
<15 µmol/L	202 (93.5)	204 (93.6)
≥15 µmol/L	14 (6.5)	14 (6.4)
<b>Pre-FA MMA*</b>		
<272 µmol/L	180 (83.3)	180 (82.6)
≥272 µmol/L	36 (16.7)	38 (17.4)
<b>Past-FA MMA*</b>		
<272 µmol/L	194 (89.8)	193 (88.5)
≥272 µmol/L	22 (10.2)	25 (11.5)
<b>Pre-FA Cystathionine*</b>		
<301 µmol/L	145 (67.1)	150 (68.8)
≥301 µmol/L	71 (32.9)	68 (31.2)
<b>Past-FA Cystathionine*</b>		
<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.

# CLINICAL REVIEW

## Clinical Review Section

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 supplementation 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**

Parameter	Wald Chi-Square p-values		
	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.

# CLINICAL REVIEW

## Clinical Review Section

### 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.**

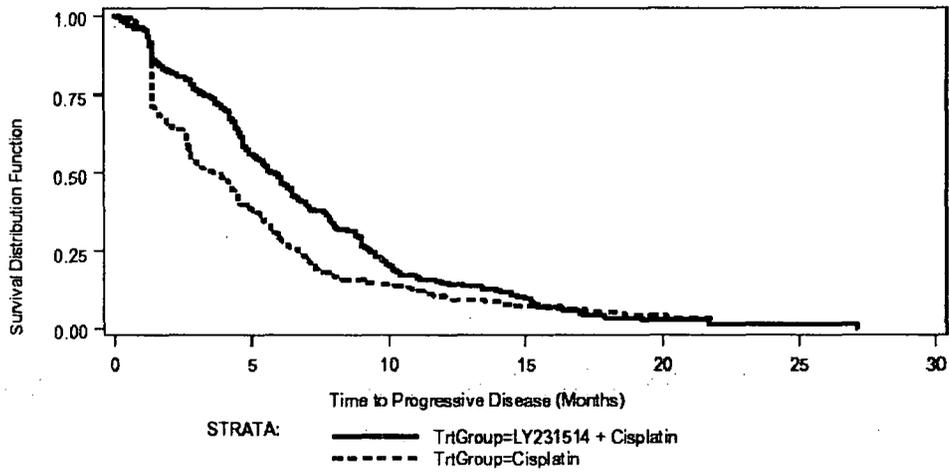
**Table JMCH.11.21. Summary of Time to Progressive Disease (Months)  
RT Population  
H3E-MC-JMCH**

	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 <sup>1</sup> ):						
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

<sup>1</sup>n = number of patients known to be progression-free at indicated time.

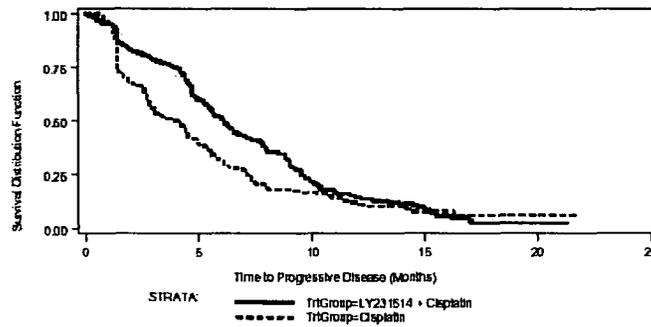
# CLINICAL REVIEW

## Clinical Review Section



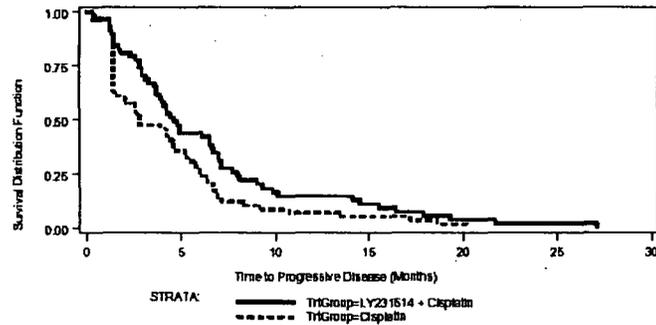
Program name: ttwent4.SAS. Variable name: timepdps. Population: All.

Figure JMCH.11.4. K-M estimates of TTPD for LY/cis and cisplatin alone, RT population.



Program name: ttwent4.SAS. Variable name: timepdps. Population: Supplemented.

Figure JMCH.11.5. K-M estimates of TTPD for LY/cis and cisplatin alone, FS subpopulation.



Program name: ttwent4.SAS. Variable name: timepdps. Population: Non-supplemented.

Figure JMCH.11.6. K-M estimates of TTPD for LY/cis and cisplatin alone, PS+NS subpopulation.

# CLINICAL REVIEW

## Clinical Review Section

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			HR <sup>2</sup>
	N	Median (mo)	% Censored	HR <sup>1</sup>	N	Median (mo)	% Censored	N	Median (mo)	% Censored	
<b>Supplementation Group</b>											
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
<b>Race</b>											
Caucasian	410	4.6	7.3	--	204	5.7	6.4	205	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
<b>KPS Group</b>											
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
<b>Disease Stage Group</b>											
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
<b>Histological Subtype</b>											
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
<b>Time from Diagnosis</b>											
<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**

<b>WBC</b>											
<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
<b>Pre-FA Homocysteine</b>											
<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
<b>Pre-FA Cystathionine</b>											
<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

<sup>1</sup> Hazard ratio for subgroup relative to complementary subgroup. For Histological subtype, hazard ratio relative to sarcomatoid subgroup.  
<sup>2</sup> Hazard ratio for LY/Cis relative to cisplatin alone.

# CLINICAL REVIEW

## Clinical Review Section

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	TTF
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 <sup>1</sup>	0.013	0.106	0.203	0.036
Methylmalonic Acid <sup>1</sup>	0.764	0.293	0.535	0.543
Cystathionine <sup>1</sup>	0.033	0.521	0.162	0.324

<sup>1</sup> Presupplementation.

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# CLINICAL REVIEW

## Clinical Review Section

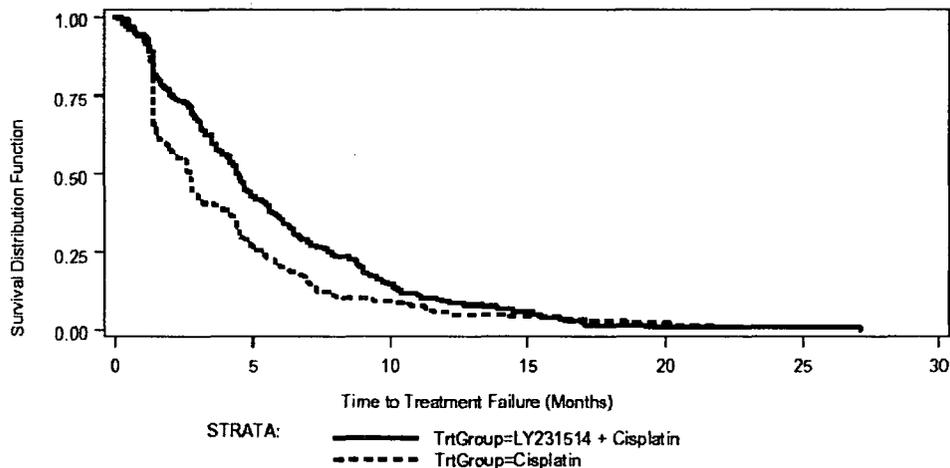
### Time to Treatment Failure

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**  
**HSE-MC-JMCH**

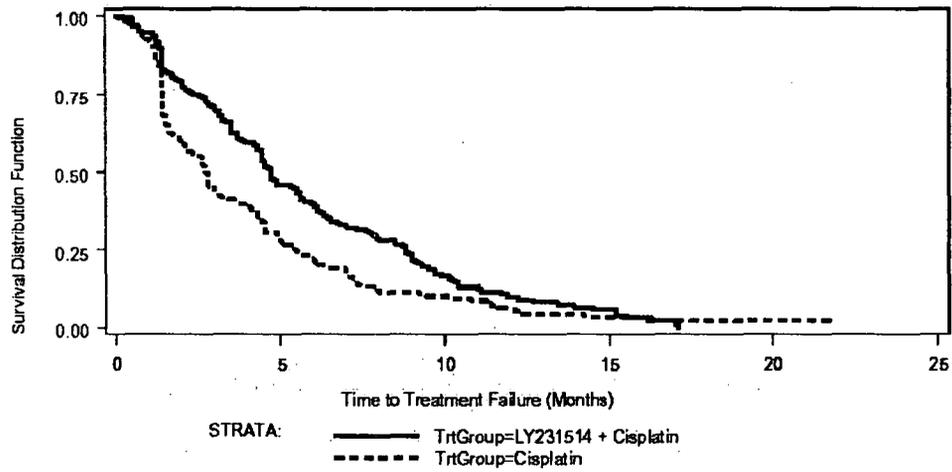
	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=168)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
Minimum						
25th percentile	2.1	1.4	2.4	1.4	1.6	1.4
Median	4.5	2.7	4.7	2.7	3.7	2.6
95% CI for median	3.9-4.9	2.1-2.9	4.3-5.6	2.2-3.1	2.8-4.6	1.4-3.0
75th percentile	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 <sup>1</sup> ):						
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

<sup>1</sup>n = number of patients who did not discontinue early and who are known alive and progression-free at indicated time.



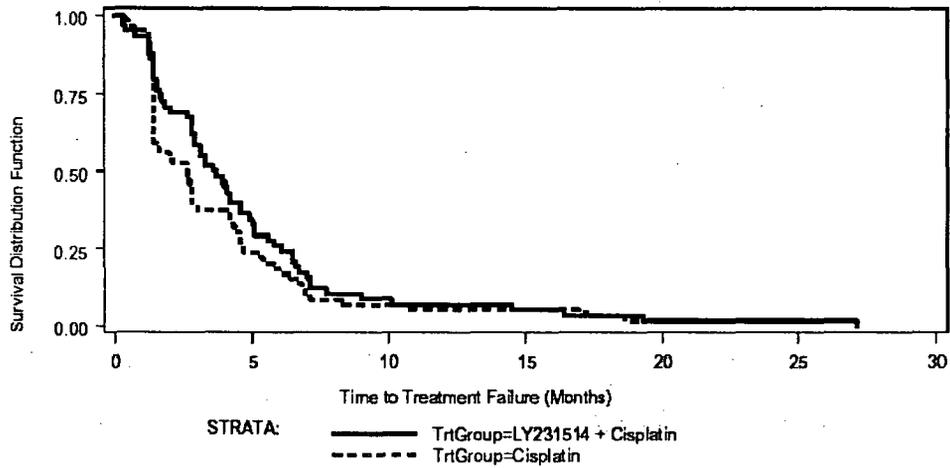
# CLINICAL REVIEW

## Clinical Review Section



Program name: ttevent4.SAS. Variable name: ttfswo. 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: ttfswo. Population: Nonsupplemented.

Figure JMCH.11.12. K-M curves for time to treatment failure for LY/cis and cisplatin alone, PS+NS subpopulation.

## CLINICAL REVIEW

### Clinical Review Section

#### 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%.

# CLINICAL REVIEW

## Clinical Review Section

**MEDICAL OFFICER NOTE: The list of responders sent by Lilly had 94 alimta/cisplatin responders and 37 cisplatin responders.<sup>138</sup>**

**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%.

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<sup>138</sup> Cover letter from Lilly dated 10/22/2002

# CLINICAL REVIEW

## Clinical Review Section

**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).

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# CLINICAL REVIEW

## Clinical Review Section

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**

Supplementation Group	All RT			LY/cis			Cisplatin Alone		
	N	Number of Responders	Rate (%)	N	Number of Responders	Rate (%)	N	Number of Responders	Rate (%)
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
<b>WBC</b>									
<8.2 GI/L	175	66	37.7	91	48	52.8	84	18	21.4
≥8.2 GI/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.

# CLINICAL REVIEW

## Clinical Review Section

**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 <sup>1</sup> ):						
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

<sup>1</sup>n = number of responding patients known to be progression-free at indicated time.

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# CLINICAL REVIEW

## Clinical Review Section

### 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/tis (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

## CLINICAL REVIEW

### Clinical Review Section

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%.

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ON ORIGINAL**

# CLINICAL REVIEW

## Clinical Review Section

**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**

CB Parameter	LY/cis		Cisplatin	
	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

# CLINICAL REVIEW

## Clinical Review Section

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**

		EVA/Cisp					Sal/Cisp				
		Clinical Benefit				Total	Clinical Benefit				Total
		Responder	Stable	Failure	Insufficient Data		Responder	Stable	Failure	Insufficient Data	
Overall	CR + PR	26	16	34	2	78	8	10	11	0	29
Study	SD	10	17	29	5	61	14	26	34	3	77
Tumor	PD	3	10	7	14	34	3	19	25	21	68
Response	Other	0	1	0	10	11	0	1	0	9	10
<b>Total</b>		<b>39</b>	<b>44</b>	<b>70</b>	<b>31</b>	<b>184</b>	<b>25</b>	<b>56</b>	<b>70</b>	<b>32</b>	<b>184</b>

Clinical Benefit Response Definition - HYBRID  
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# CLINICAL REVIEW

## Clinical Review Section

### Exposure

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/cisplatin 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	
	FS (N=168)	NS (N=32)	FS (N=163)	NS (N=38)
Completed Cycles				
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				

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## CLINICAL REVIEW

### Clinical Review Section

#### 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.

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## CLINICAL REVIEW

### Clinical Review Section

#### 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 <sup>139</sup>		
Randomized and treated	448		
Fully supplemented + (partially supplemented + not supplemented)		168 <sup>140</sup> + 58 <sup>141</sup> = 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 <sup>142</sup>	222
Independent review, 2/13/2002		194	195
Independent review 6/10/2002		197	200

<sup>139</sup> This should be the intent-to-treat population.

<sup>140</sup> This represents a 15% increase over the designed enrollment.

<sup>141</sup> Not supplemented: 32 alimta/cisplatin; 38 cisplatin alone

## CLINICAL REVIEW

### Clinical Review Section

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<sup>143</sup>; "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	STUDY REPORT, ORIGINAL PACKAGE INSERT, JCO ARTICLE
page number in JMCH study report	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. <sup>144</sup> p. 5
All enrolled patients meeting the following criteria will be evaluated for tumor response: <ul style="list-style-type: none"> <li>• Histologic diagnosis of malignant pleural mesothelioma.</li> <li>• No prior systemic chemotherapy.</li> <li>• No concurrent systemic chemotherapy or radiotherapy.</li> <li>• Presence of unidimensionally and/or bidimensionally measurable disease.</li> <li>• 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</li> </ul>	Enrolled patients who met the following criteria were included in the analyses of tumor response rate: <ul style="list-style-type: none"> <li>• histologic diagnosis of MPM</li> <li>• no prior systemic chemotherapy</li> <li>• no concurrent systemic chemotherapy or radiotherapy</li> <li>• presence of unidimensionally or bidimensionally measurable disease or both</li> <li>• treatment with at least one dose of LY231514 and cisplatin (Arm A) or one dose of cisplatin (Arm B).</li> </ul> p. 5

<sup>142</sup> 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."

<sup>143</sup> Vogelzang et al. J Clin Onc. 2003;21:2636-2649

<sup>144</sup> The JMCH study report acknowledges this discrepancy on p. 122.

## CLINICAL REVIEW

### Clinical Review Section

PROTOCOL	STUDY REPORT, ORIGINAL PACKAGE INSERT, JCO ARTICLE
page number in JMCH study report	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, <u>except</u> 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	

# CLINICAL REVIEW

## Clinical Review Section

<p>PROTOCOL</p> <p>page number in JMCH study report was to take precedence. p. 107</p>	<p>STUDY REPORT, ORIGINAL PACKAGE INSERT, JCO ARTICLE</p> <p>page number in JMCH study report</p>
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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 HBE-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 <sup>1</sup>
510-5109	LY/cis	Death (from study disease)
601-6014	Cisplatin	Patient decision

<sup>1</sup> 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.

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## CLINICAL REVIEW

### Clinical Review Section

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
<b>Total</b>	<b>574</b>	<b>456</b>	<b>79.44251%</b>	<b>20.55749</b>	
		Difference (not entered): <b>118</b>	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,<sup>145</sup> Lilly provided the information illustrated in the table below.<sup>146</sup> Again, no source documents were submitted and reviewed.

<sup>145</sup> FDA query sent 8/14/2003; Lilly response received 9/2/2003.

<sup>146</sup> No source documents, i.e., The ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT forms for the patients, were submitted.

## CLINICAL REVIEW

### Clinical Review Section

MOST IMPORTANT REASON THAT PATIENT WAS NOT ENROLLED ON JMCH	TOTAL NUMBER OF PATIENTS
No histologically proven diagnosis of mesothelioma <sup>147</sup>	7
Non-measurable disease <sup>148</sup>	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.

<sup>147</sup> 30 patients were enrolled (randomized and treated), in whom the pathology of malignant mesothelioma was not confirmed by the independent pathologist reviewers.

<sup>148</sup> 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.

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