CENTER FOR DRUG EVALUATION AND RESEARCH

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Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL DIVISION: Oncology Drug Products (HFD-150)
BIOMETRICS DIVISION: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-462

DRUG NAME: ALIMTA® (pemetrexed, LY231514) 500 mg Vials

INDICATION: Treatment of Malignant Pleural Mesothelioma

SPONSOR: Eli Lilly and Company

DOCUMENTS REVIEWED:
1. Cover letter and documents (CDER REC'D Dates: 24-OCT-2002, 22-NOV-2002 and 26-NOV-2002) including SAS data base
2. Cover letter (CDER REC'D Dates: 6-DEC-2002) including the pdf file for review's aids, SAS data sets, and SAS programs for the efficacy analyses

STATISTICAL KEY WORDS: Log-rank test, proportional hazard model, Kaplan-Meier estimate, hazard ratio, multiple comparison, Bonferroni adjustment

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Table of Contents

1 Executive Summary of Statistical Findings

1.1 Recommendations and Conclusions

Based on the collective evidences and findings, in this statistical reviewer's opinion the data and results of the Phase III Study H3E-MC-JMCH support the sponsor's efficacy claim of ALIMTA® (pemetrexed, LY231514) 500 mg Vials with respect to the survival endpoint for the patients with Malignant Pleural Mesothelioma. The data and results of the study show that the primary endpoint, survival, is statistically significantly improved in new treatment arm as compared to control arm for the randomized and treated (RT) population (p-value=0.021). The secondary endpoints, time to progressive disease, time to treatment failure, and response rate, are also demonstrated statistically significant improvement in new treatment group compared to the control group. In the fully supplemented (FS) subgroup, efficacy results are similar to those findings in the RT population. The hazard ratios for both RT and FS populations showed the consistency of the magnitude of survival benefit.

1.2 Brief Overview of Clinical Studies

This application consists of report of results from the Study H3E-MC-JMCH (referred as Study JMCH here and after) in the patients with Malignant Pleural Mesothelioma (MPM).

The registration Study JMCH was a multi-national, multi-center, single-blind, and parallel-arm Phase III trial with MPM patients randomized to LY231514 plus Cisplatin (LY/cis) and Cisplatin alone treatment arms. A total of 574 patients were entered into the study (that is, signed the Informed Consent Document); 456 of these patients were randomized to a treatment arm; 448 of these patients were treated and constitute the randomized and treated (RT) population.

LY/cis: Total: 226, Male: 184, Female: 42. Fully Supplemented (FS): 168, Partially Supplemented (PS) or Never Supplemented (NS): 58.

Cisplatin alone: Total 222, Male: 181, Female: 41. Fully Supplemented: 163, Partially Supplemented or Never Supplemented: 59.

LY/cis treatment: LY231514 was administrated at the dose of 500 mg/m^2 as a 10-minute intravenous infusion, diluted in approximately 100 mL normal saline. Approximately 30 minutes after the administration of LY231514, Cisplatin was administered at the dose of 75 mg/m^2 over 2 hours. Both drugs were administered on Day 1 of a 21-day period. This 21-day period defined one cycle of therapy.

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

Both treatment arms: (1) Dexamethasone, 4mg (or an equivalent corticosteriod), was to be taken by all enrolled patients orally twice a day (BID) 1 day before, on the day of, and 1 day after each dose of LY231514, for primary prophylaxis against rash. (2) Folic acid and vitamin B_{12} for supplementation were a standard component of therapy for all patients participating in the study. Folic acid, 350 µg to 1000 µg, was to be taken orally daily, beginning approximately 1 to 3 weeks before the first dose of therapy and continued daily for 1 to 3 weeks after the patient discontinued treatment. A vitamin B_{12} injection, 1000 µg, was to be administered intramuscularly approximately 1 to 3 weeks before the first dose of therapy and should have been the first dose of therapy and should have been repeated approximately every 9 weeks until the patient discontinued study therapy. (3) Pre- and post-hydration for Cisplatin was administered according to institutional guidelines.

The primary objective of Study JMCH was to compare survival in chemonaive patients with MPM when treated with LY231514 plus Cisplatin combination therapy to survival in the same patient population when treated with Cisplatin alone. The primary efficacy endpoint was the overall survival time.

1.3 Statistical Issues and Findings

Statistical Issues:

- 456 patients were randomized to treatment arms out of which 8 of these patients were died from study disease before any dosing. The sponsor did not follow the statistical reviewer's comments of IND 40061/SN298 that the primary survival analysis should be based on all patients as randomized. The sponsor did primary efficacy analysis based on the randomized and treated population which did not include those 8 patients.
- The sponsor' efficacy claim was based on the RT population and stated that in clinically, folic acid and vitamin B_{12} would improve the clinical outcome regardless of the treatment arm. The results of the FS subgroup also support the efficacy claim.
- There was a heterogeneous distribution for gender in the two treatment arms (male and female with 81.4% vs. 18.6% and 81.5% vs. 18.5% in LY/cis and Cisplatin groups, respectively). The multivariate analysis for the treatment and gender showed that the interaction between treatment and gender had a small p-value (p-value=0.072) for the RT population and was statistically

significant for the FS population (p-value=0.035). Therefore, the influences of treatment were depended on the subgroups of gender.

- The subgroup analysis of gender showed that the new treatment was significant for the RT population and FS population in female patients (p-value=0.012 and 0.010, respectively) and was not significant for PS+NS population (p-value=0.878). The analyses within the subgroup of male showed that the new treatment group was not statistically significant for the RT, FS, and PS+NS populations (p-value=0.176, 0.388, 0.219, respectively).
- The hazard ratios showed the consistency of the magnitude of survival benefit in both the RT population and subgroup alike. The efficacy analyses of secondary endpoints, TTPD, TTTF and response rate, showed the consistency to primary endpoint.

Findings:

Table 1 gives the summary of efficacy results of primary endpoint, survival time (months), for the RT population. A total of 226 patients on the LY/cis arm and 222 patients on the Cisplatin alone arm were included in the survival analysis. The median survival time for patients treated with LY/cis was longer than for patients treated with Cisplatin alone: 12.1 versus 9.3 months. There was a statistically significant difference (p=0.021) between the two treatment groups.

Table 1. Primary Endpoint: Survival for RT Population (FDA Analysis)

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

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients were died for different reasons: study disease related, study toxicity, and other causes.

[b] P-value is based on the test results for the two treatment groups.

[c] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

Among the 448 patients of RT population, 331 were FS and 117 were PS+NS. The analysis of the FS subgroup indicated that the median survival for patients treated with LY/cis was 13.3 months vs. 10.0 months, a difference with small p-

value (0.051). The analysis of the PS+NS subgroup indicated that the median survival time for patients treated with LY/cis was 9.5 months vs. 7.2 months, but this difference did not reach the overall significance level (p-value=0.253). The hazard ratio for the RT population and for the FS and PS+NS subgroups were 0.766, 0.758, and 0.798, respectively, indicating the consistency of the magnitude of the survival benefit in both the RT population and subgroup alike.

Reviewer's Comments:

1) The sponsor' efficacy claim was based on RT population which was by not including 8 patients randomized but died before any dosing. The sponsor also used the efficacy results of the FS subgroup to support to their efficacy claim.
2) The median survival times for the RT population and for the FS and PS+NS subgroups show the consistency of the pattern of the survival difference in both the RT population and subgroups alike.
3) The hazard ratios for the RT population and for the FS and PS+NS subgroups show the consistency of the magnitude of the survival benefit in both the RT population and subgroups alike.

2 Introduction

2.1 Overview

The beneficial effect of LY231514 is a novel antifolate that can inhibit multiple tumor targets involved in both purine and pyrimidine pathways of DNA synthesis. LY231514 exhibits highly cytotoxic in vitro activity against the CCRF-CEM human leukemia cell line. LY231514 has also shown significant antitumor activity against thymidine- and hypoxanthine-deficient murine tumor cell lines as well as two human colon xenografts resistant to methotrexate. Phase 1 studies were conducted exploring three treatment schedules: once daily times 5 every 3 weeks (Study H3E-BP-001); once weekly times 4 every 6 weeks (Study H3E-MC-JMAB); and once every 3 weeks (Study H3E-MC-JMAA). In Study JMAA, LY231514 was administered to 37 patients as a 10-minute infusion once every 3 weeks at doses ranging from 50 to 700 mg/m^2 (Rinaldi et al. 1995). Based on this study, the recommended dose for Phase 2 studies was 600 mg/m^2.

2.1.1 Background

Malignant mesothelioma is a rare, seldom curable, tumor of the pleura or the peritoneum whose origin has generally been linked to asbestos exposure. The most common sites of origin are the pleura, accounting for 80% of cases, followed by peritoneum, pericardium, and tunica vaginalis testes (Sterman et al. 1999). Survival of untreated patients is poor, with a median survival of usually 6

to 8 months, though the range may be much wider, depending on the characteristics and selection of the population of mesothelioma patients (Antman et al. 1997). Most studies in published literature have involved MPM, including those characterizing the disease and its treatment. A number of factors including histologic subtype, performance status, disease extent at baseline, presence of chest pain, gender, and white blood cell count, among others, have been suggested as predictors of outcome, including survival (Curran et al. 1998; Herndon et al. 1998).

MPM is a difficult tumor to treat. In general, neither surgery nor radiotherapy results in increased survival (Antman et al. 1997). A wide variety of chemotherapeutic agents have shown modest activity in single-agent or combination Phase 2 trials, including gemcitabine (GEMZAR®), doxorubicin, cisplatin, ifosfamide, methotrexate, edatrexate, mitoxantrone, epirubicin, etoposide, and paclitaxel. Response rates have seldom exceeded 20% in single-agent Phase 2 trials (van Breukelen et al. 1991; Mattson et al. 1992; Solheim et al. 1992; Belani et al. 1994; van Meerbeeck et al. 1996; Millard et al. 1997; Sahmoud et al. 1997).

The registration Study JMCH was a multi-nation, multi-center, single-blind, and parallel-arm Phase III trial with MPM patients randomized to LY231514 plus Cisplatin and Cisplatin alone treatment arms. A total of 574 patients were entered into the study; 456 of these patients were randomized to a treatment arm; 448 of these patients were treated and constitute the randomized and treated (RT) population. The study period was from April 1999 to February 2002.

2.1.2 Major Statistical Issues

The major statistical issues can be found in Section 1.3.

2.2 Data Sources

Data used for review is from the electronic submission received on October 24, 2002. The efficacy analysis data were submitted by the sponsor on December 6, 2002. All data sets analyzed are electronic documents and are located in the Electronic Document Room (EDR) of CDER of FDA under the Letter Date "24-OCT-2002" and "6-DEC-2002", respectively. The major data set for the efficacy analysis is "SURVLOCK" which defines the survival time and events.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The registration Study JMCH was used for efficacy evaluation. The primary analyses of the study were performed on an RT basis. The RT population was defined as all patients randomly assigned to a treatment arm, who received study drug (LY/cis or Cisplatin). Of the 456 patients randomly assigned to a treatment arm, 448 (98.2%) received LY/cis or Cisplatin monotherapy. These patients constituted the RT population for this study. Among the 448 patients in the RT population, sub-populations defined by supplementation status (FS, PS, and NS) were considered in key additional analyses and presented in this review.

3.1.1 Study JMCH

3.1.1.1 Introduction

Study JMCH was a multi-nation, multi-center, single-blind, and parallel-arm Phase III trial with MPM patients randomized to LY/cis and Cisplatin alone treatment arms. A total of 574 patients were entered into the study (that is, signed the Informed Consent Document); 456 of these patients were randomized to a treatment arm; 448 of these patients were treated and constituted the RT population.

3.1.1.2 Statistical Issues

The major statistical issues can be found in Section 1.3.

As we stated in the first bullet of statistical issues in the section 1.3, there were 456 patients randomized to treatment arms and 8 of these patients died from study disease before any dosing. Table 2 gives the detailed list for those died patients. The sponsor's primary efficacy analysis was based on the RT population which did not include those 8 patients.

Table 2. List of Randomized Patients before Dosing (FDA Analysis)

Patient ID	Enroll Date	End Date	Treatment	Primary Reason Discontinue
1342	1999/09/06	1999-09-09	Cisplatin	Protocol entry criteria not met
1472	2000-11-01	2000-11-02	Cisplatin	Personal conflict or other patient decision
1634	2001-03-26	2001-03-27	Cisplatin	Personal conflict or other patient decision
2133	2000-05-09	2000-05-25	Cisplatin	Protocol entry criteria not met
2200	2000-09-12	2000-09-13	Cisplatin	Personal conflict or other patient decision
3161	2000-02-03	2000-02-04	LY/Cis	Adverse event
5109	2000-06-06	2000-06-12	LY/cis	Death from study disease
6014	2000-12-01	2000-12-07	Cisplatin	Personal conflict or other patient decision

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

3.1.1.3 Study Objectives

The primary objective of this study was to compare survival in patients with MPM when treated with LY231514 plus Cisplatin combination therapy to survival in the same patients population when treated with Cisplatin alone.

The secondary objectives of this study were to compare the follows between the two treatment arms:

- time-to-event efficacy measures:
  - duration of response for responding patients
  - time to progressive disease
  - time to treatment failure
- tumor response rate
- clinical benefit response rate (pain intensity, analgesic consumption, dyspnea, performance status)
- Lung Cancer Symptom Scale (LCSS) patient and observer scores
- pulmonary function test scores (forced vital capacity, vital capacity, forced expiratory volume)
- lung density determinations in approximately 170 patients
- relative toxicities.

Additional secondary objectives of this study were:

- to assess toxicity experienced in cycles in which patients did receive folic acid and vitamin B_{12} supplementation and toxicity experienced in cycles in which patients did not receive folic acid and vitamin B_{12} supplementation
- to assess PK effects
- to collect information regarding vitamin deficiency markers status in this patient population.

3.1.1.4 Efficacy Endpoints

The primary efficacy endpoint was survival. Survival was defined as the time from study enrollment (randomization) to time of death from any cause.

The key secondary efficacy endpoints were time to progressive disease, time to treatment failure, tumor response rate, and duration of tumor response.

Time to progressive disease (TTPD) was defined as the time from randomization to the first observation of disease progression or death because of any cause.

Tumor response rate was defined as the ratio of responders over the total number of patients qualified for tumor response assessment times 100 to quote the rate as a percentage. A responder was defined as any patient who had a complete response (CR) or a partial response (PR). All responses were documented by

using appropriate diagnostic tests that were repeated approximately every 6 weeks to continue evaluation.

The duration of a CR or PR was defined as the time from first objective status assessment of CR or PR to the first time of disease progression or death because of any cause.

Time to treatment failure (TTTF) was defined as the time from study enrollment (randomization) to the first observation of disease progression, death because of any cause, or discontinuation because of any other reason.

3.1.1.5 Sample Size Considerations

The primary objective of this study was to compare survival of patients with MPM receiving LY/cis combination therapy versus those receiving Cisplatin monotherapy. The sponsor described the sample size considerations as follows.

During the conduct of this study, a programmatic change was made by the sponsor in the clinical development of LY231514 whereby every patient treated with LY231514 must be supplemented with folic acid and vitamin B_{12} to improve patient safety. Initiation of supplementation in this study was done in both treatment arms and at the same time point to preserve study blinding at the patient level. This programmatic change was implemented in this study beginning with Protocol Amendment (C). The decision to extend enrollment so that a planned 280 FS patients would be randomized to this trial is documented in Protocol Amendment (E). The following describes the statistical properties associated with this sample size.

A planned 280 qualified patients receiving vitamin supplementation during every cycle of their study therapy were to be randomized to this trial. A treatment was judged superior if it is associated with a 33% reduction in the hazard ratio of the two treatments by median survival time. Assuming an exponential survival, 15-month patient accrual, and an additional minimum 9-month follow-up for all patients and a censoring rate of 30% or less after the 24 month accrual and follow-up period, the procedure described above gives at least an 81% chance (power) to detect a 33% shift in hazard ratio as reflected by a 63% survival probability on the best treatment arm by the time only 50% of patients are still alive (median time) on the least efficacious treatment arm. In terms of event rate, a total of 197 deaths in the FS sub-population would yield approximately 80% power to detect a hazard ratio of 67%. These calculations use a two-sided log rank test with a 0.05 chance of rejecting the null hypothesis H_0 of no difference in survival between the two treatment arms when H_0 is actually true.

After the conduct of the planned interim analysis and before the final database lock, the sponsor and the agency confirmed that the primary survival analysis would be conducted on the entire patient population (RT population) as stated in Protocol Amendment (C).

3.1.1.6 Stratification

The study was stratified by some prognostic factors which the sponsor chose as potential confounders to survival and other study outcomes as suggested by the literature. The statistical reviewer's comments about the stratification is in Section 3.1.1.9.1.

3.1.1.7 Interim Analysis

A planned interim analysis was conducted and presented to the Data Safety Monitoring Board for resulting in a decision to continue the trial to planned completion.

3.1.1.8 Efficacy Analysis Methods

The primary analysis was comparison of survival time between the two treatment arms in the RT population. Differences were assessed using a two-sided log-rank test. Because an interim analysis was conducted, the comparison of survival was tested at the α=0.0476 level. Comparison of survival was also tested using the Wilcoxon test.

Key secondary analyses were conducted to assess the impact of supplementation on survival in the LY/cis arm. The Kaplan-Meier subgroup analyses of survival were conducted on FS and on PS+NS patients. Also, survival time was analyzed with a Cox proportional hazards model including treatment arm, supplementation group, and the treatment-by-supplementation interaction. The interaction term was evaluated to assess the impact of supplementation on the survival benefit associated with LY/cis.

Other time-to-event measures were analyzed by using the same method as described for survival time. Comparisons of the tumor response rates between the two treatment arms (in the RT, FS, and PS+NS populations) were made by using the Fisher's Exact test with 95% CI calculated using the method of Leemis and Trivedi. Tumor response was also analyzed with a logistic regression model including treatment arm, supplementation group, and the treatment-by-supplementation interaction. The interaction term was evaluated to assess the impact of supplementation on the survival benefit associated with LY/cis. Time-to-event and tumor response measures were also analyzed to assess the effect of potential prognostic factors. Subgroup analyses were conducted on statistically

significant factors ($p<0.05$). Repeated measures analyses were conducted on LCSS patient scale and PFT parameters by using linear mixed models. Clinical benefit response was analyzed by using the Fisher's Exact test. LCSS observer scale data were analyzed by the Mantel-Haenszel chi-square test and also assessed by using simple analysis of variance (ANOVA) techniques. Simple summary statistics by treatment arm and by cycle were calculated for lung density measurements. Analyses of LCSS, PFTs, and CB data were conducted in the RT, FS, and PS+NS populations.

3.1.1.9 Sponsor's Results and Statistical Reviewer's Findings/Comments

This section will summarize the results of intent to treat analysis for Study JMCH. In this study a total of 456 patients were randomized to a treatment arm; 448 of these patients were treated and constitute the randomized and treated (RT) population, where 226 patients were enrolled into the LY/cis arm and 222 patients were enrolled into the Cisplatin arm.

3.1.1.9.1 Baseline Characteristics

Table 3 shows key baseline demographic characteristics for the RT population by treatment arm and further by supplementation status. All characteristics showed balance between the two treatment arms.

Table 3. Baseline Characteristics of RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Age[a]						
< 65 years	143 (63)	136 (61)	107 (64)	97 (60)	36 (62)	39 (66)
≥ 65 years	83 (37)	86 (39)	61 (36)	66 (40)	22 (38)	20 (34)
Sex						
Male	184 (81)	181 (82)	136 (81)	134 (82)	48 (83)	47 (80)
Female	42 (19)	41 (18)	32 (19)	29 (18)	10 (17)	12 (20)
Origin						
Caucasian	204 (90)	206 (93)	150 (89)	153 (94)	54 (93)	53 (90)
Hispanic	11 (5)	12 (5)	10 (6)	7 (4)	1 (2)	5 (9)
Asian[b]	10 (4)	4 (2)	7 (4)	3 (2)	3 (5)	1 (0.7)
African	1 (0.4)	0	1 (0.6)	0	0	0

[a] Statistical reviewer's results.
[b] Western and East/Southeast Asian have been combined.

Table 4 and 5 summarize stratification factors and baseline disease characteristics for the RT population, respectively.

Table 4. Baseline Stratification Factors Used for Randomization of RT Population (Sponsor Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
KPS						
Low (≤ 80)	109 (48)	97 (44)	83 (49)	69 (42)	26 (45)	28 (47)
High (≥ 90)	117 (52)	125 (56)	85 (51)	94 (58)	32 (55)	31 (53)
Degree of Meaurability[a]						
Unidimensional	73 (32)	73 (33)	61 (36)	62 (38)	12 (21)	11 (19)
Bidimensional	152 (68)	149 (67)	106 (64)	101 (62)	46 (79)	48 (81)
Histologic Subtype						
Epithelial	154 (68)	152 (69)	117 (70)	113 (69)	37 (64)	39 (66)
Mixed	18 (8)	25 (11)	25 (15)	25 (15)	12 (21)	11 (19)
Sarcomatoid	37 (16)	36 (16)	14 (8)	17 (10)	4 (7)	8 (14)
Other	17 (8)	9 (4)	12 (7)	8 (5)	5 (9)	1 (2)
WBC						
Low (< 8.3 Gl/L)	97 (43)	91 (41)	72 (43)	68 (42)	25 (43)	23 (39)
High (≥ 8.3 Gl/L)	129 (57)	131 (59)	96 (57)	95 (58)	33 (57)	36 (61)
Pain Intensity[b]						
Low (< 20 mm)	112 (50)	113 (51)	82 (49)	80 (49)	30 (52)	33 (56)
High (≥ 20 mm)	112 (50)	109 (49)	84 (51)	83 (51)	28 (48)	26 (44)
Analgesic Consumption						
Low (< 60 mg morp eq/day)	173 (77)	170 (77)	129 (77)	124 (76)	44 (76)	46 (78)
High (≥ 60 mg morp eq/day)	53 (23)	52 (23)	39 (23)	39 (24)	14 (24)	13 (22)
Dyspnea[b]						
Low (< 20 mm)	91 (41)	92 (41)	66 (40)	68 (42)	25 (43)	24 (41)
High(≥ 20 mm)	133 (59)	130 (59)	100 (60)	95 (58)	33 (57)	35 (59)
Homocysteine						
Low (< 12 umol/L)	155 (69)	156 (70)	119 (71)	118 (72)	36 (62)	38 (64)
High (≥12 umol/L)	71 (31)	66 (30)	49 (29)	45 (28)	22 (38)	21 (36)
Sex						
Male	184 (81)	181 (82)	136 (81)	134 (82)	48 (83)	47 (80)
Female	42 (19)	41 (18)	32 (19)	29 (18)	10 (17)	12 (20)

Sponsor's results confirmed by this statistical reviewer.

[a] A single patient was missing their evaluable disease measurement at baseline.

[b] 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.

The sponsor chose these strata as potential confounders to survival. Histologic diagnosis and stage III/IV disease are known prognostic factors for survival in MPM patients. All factors and characteristics showed balance between treatment arms. The majority of patients had the epithelial subtype (68% in the LY/cis arm and 68% in the Ciaplatin alone arm).

Table 5. Baseline Disease Characteristics for RT Population (Sponsor Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Diagnosis / Histology						
Epithelial	154 (68)	152 (68)	117 (70)	113 (69)	37 (64)	39 (66)
Mixed	37 (16)	36 (16)	25 (15)	25 (15)	12 (21)	11 (19)
Sarcomatoid	18 (8)	25 (11)	14 (8)	17 (10)	4 (7)	8 (14)
Other	17 (8)	9 (4)	12 (7)	8 (5)	5 (9)	1 (2)
Stage at Entry						
Ia	9 (4)	8 (4)	8 (5)	7 (4)	1 (2)	1 (2)
Ib	7 (3)	6 (3)	7 (4)	5 (3)	0	1 (2)
II	35 (16)	33 (15)	27 (16)	27 (17)	8 (14)	6 (10)
III	73 (32)	68 (31)	51 (30)	49 (30)	22 (38)	19 (32)
IV	101 (45)	105 (48)	74 (44)	73 (45)	27 (47)	32 (54)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1)	0	0
Performance Status						
70	37 (16)	31 (14)	25 (15)	22 (13)	12 (21)	9 (15)
80	72 (32)	66 (30)	58 (34)	47 (29)	14 (24)	19 (32)
90	93 (41)	94 (42)	67 (40)	69 (42)	26 (45)	25 (42)
100	24 (11)	31 (14)	18 (11)	25 (15)	6 (10)	6 (10)

Sponsor's results confirmed by this statistical reviewer.

3.1.1.9.2 Primary Efficacy Analyses

Table 6 gives the summary of primary endpoint, survival time (months), for the RT population. A total of 226 patients on the LY/cis arm and 222 patients on the Cisplatin alone arm were included in the survival analysis. The median survival time for patients treated with LY/cis was longer than for patients treated with Cisplatin alone: 12.1 versus 9.3 months. There was a statistically significant difference (p=0.021) between the two treatment groups.

Among the 448 patients of RT population, 331 were FS and 117 were PS+NS. The analysis of the FS subgroup indicated that the median survival for patients treated with LY/cis was 13.3 months vs. 10.0 months, a difference with small p-value (0.051). The analysis of the PS+NS subgroup indicated that the median

survival time for patients treated with LY/cis was 9.5 months vs. 7.2 months, but this difference did not reach the overall significance level (p-value=0.253). The hazard ratio for the RT population and for the FS and PS+NS subgroups were 0.766, 0.758, and 0.798, respectively, indicating the consistency that the magnitude of the survival benefit in both the RT population and subgroups FS & PS+NS are similar.

Table 6. Primary Endpoint: Survival for RT Population (FDA Analysis)

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

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients were died by different reasons: study disease related, study toxicity, and other causes.

[b] P-value is based on the test results for the two treatment groups.

[c] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

Figure 1a . K-M Curve of Survival Time for LY/cis and Cisplatin alone, RT population
Population = All

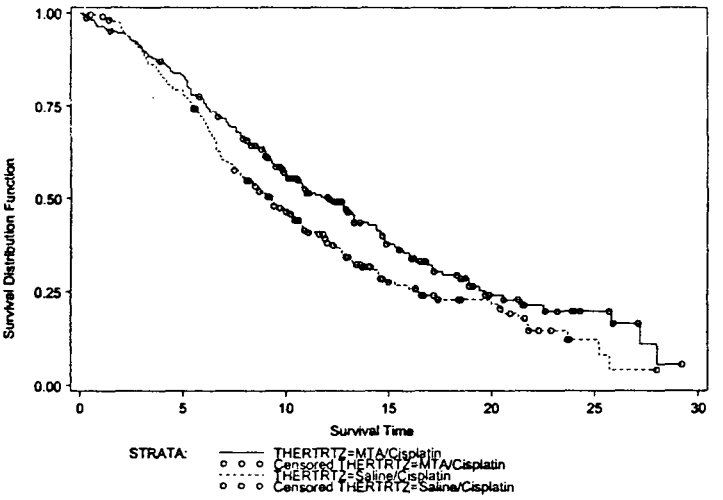


Figure 1b . K-M Curve of Survival Time for LY/cis and Cisplatin alone, RT population
Population = FS Supplemented

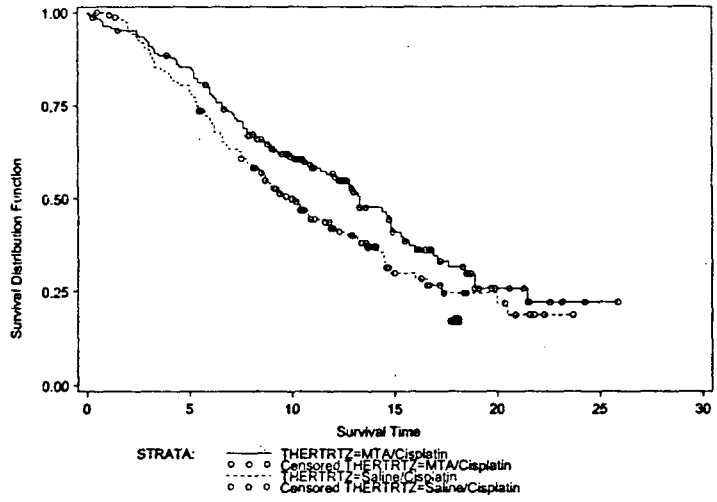
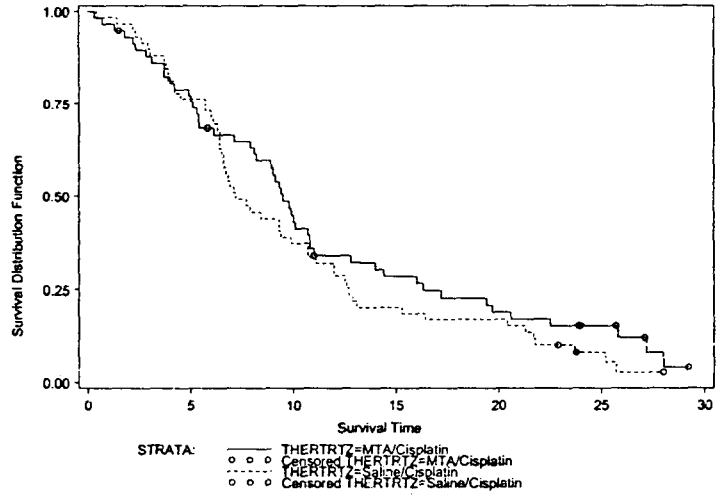


Figure 1c . K-M Curve of Survival Time for LY/cis and Cisplatin alone, RT population
Population = PS+NS Supplemented



3.1.1.9.3 Secondary Efficacy Analyses

Table 7 to Table 9 summarize the secondary efficacy analyses of the four key secondary endpoints: time to progressive disease, tumor response rate, and time to treatment failure.

The time to progressive disease (TTPD) 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 a classification of progressive disease, the date of last follow-up was used as the date of progressive

disease, and the TTPD was considered to be right-censored for purposes of these analyses.

Results from the K-M analyses are shown in Table 7. The median TTPD for patients treated with LY/cis was longer than for patients receiving Cisplatin alone; 5.7 months versus 3.9 months, a highly significant difference (p=0.001) as well as a clinically important improvement.

Table 7. Secondary Endpoint: TTPD for RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Patients with event[a]	209 (83)	202 (80)	153 (91)	143 (88)	56 (97)	59 (100)
Survival time (months)						
Median	5.7	3.9	6.1	3.9	4.6	2.8
(95% CI)	(4.9, 6.5)	(2.8, 4.4)	(5.3, 7.0)	(2.8, 4.5)	(3.7, 6.6)	(1.5, 4.6)
p-value[b]						
Long-rank	0.001		0.007		0.026	
Wilcoxon	< .0001		< .0001		0.022	
Hazard Ratio[c]	0.715		0.730		0.656	
95% CI for Hazard Ratio[c]	(0.59, 0.87)		(0.58, 0.92)		(0.45, 0.95)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients with the first observation of disease progression or death because of any cause.

[b] P-value is based on the test results for the two treatment groups.

[c] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

The sponsor analyzed the tumor response rate for investigator determined tumor response, independent reviewer determined tumor response as database lock on February 13, 200, and independent reviewer determined tumor response as database lock on June 10, 200. Table 8 summarizes the results. There were highly significant differences (p-value < 0.002) in the three populations between the two treatments.

Table 8. Secondary Endpoint: Best Tumor Response for RT Population (Sponsor Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=94) n (%)	Cisplatin (N=37) n (%)	LY/cis (N=77) n (%)	Cisplatin (N=32) n (%)	LY/cis (N=17) n (%)	Cisplatin (N=5) n (%)
Investigator Determined						
No. of patients in analysis	225	222	167	163	58	59
No. of responding patients	93[a]	37	76[a]	32	17[a]	5

Response rate (%)	41.3	16.7	45.5	19.6	29.3	8.5
95% CI for response rate	35 - 48	12 - 22	38 – 53	14 - 27	18 – 43	3 – 19
Fisher's exact p-value	< .001		< .001		< .001	
Independent Reviewer Determined by 02-13-02						
No. of patients in analysis	194	195	145	143	49	52
No. of responding patients	85[b]	28	67[b]	23	18[b]	5
Response rate (%)	43.8	14.4	46.2	16.1	36.7	9.6
95% CI for response rate	38 – 51	10 - 20	38 - 55	11 – 23	23 – 52	3 – 21
Fisher's exact p-value	< .001		< .001		0.002	
Independent Reviewer Determined by 06-10-02						
No. of patients in analysis	197	200	148	148	49	52
No. of responding patients	86[c]	30	68[c]	25	18[c]	5
Response rate (%)	43.7	15.0	45.9	16.9	36.7	9.6
95% CI for response rate	37 – 51	10 - 21	38 – 54	11 - 24	23 – 52	3 – 21
Fisher's exact p-value	< .001		< .001		0.002	

Sponsor's results confirmed by this statistical reviewer.

[a] Three CRs were on the LY/cis arm (2 FS patients and 1 PS+NS patient).

[b] Two CRs were on the LY/cis arm (1 FS patients and 1 PS+NS patient).

[c] Two CRs were on the LY/cis arm (1 FS patients and 1 PS+NS patient).

The time to treatment failure (TTTF) was defined as the time from study enrollment until the time of death or discontinuation for any reason. Results from the Kaplan-Meier analyses are shown in Table 9. The median TTTF for patients treated with LY/cis was significantly longer than for those receiving Cisplatin alone for both the RT population and FS subgroup (p=0.0004 and 0.001, respectively). By contrast, only a numerical trend favoring the LY/cis arm was seen in the PS+NS subgroup.

Table 9. Secondary Endpoint: TTTF for RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Patients with event[a]	217 (96)	214 (96)	159 (95)	155 (95)	58 (100)	59 (100)
Survival time (months)						
Median	4.45	2.7	4.7	2.7	3.65	2.6
(95% CI)	(3.9, 4.9)	(2.1, 2.9)	(4.3, 5.6)	(2.2, 3.1)	(2.8, 4.6)	(1.4, 3.0)

p-value[b]			
Long-rank	0.0004	0.001	0.195
Wilcoxon	< .0001	< .0001	0.101
Hazard Ratio[c]	0.711	0.682	0.785
95% CI for Hazard Ratio[c]	(0.59, 0.86)	(0.55, 0.85)	(0.55, 1.13)

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Patients with the first observation of disease progression, death because of any cause, or discontinuation because of any other reason.

[b] P-value is based on the test results for the two treatment groups.

[c] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

3.1.1.10 Sponsor's Conclusions and Reviewer's Conclusions/Comments

The sponsor concluded the following efficacy conclusions.

The primary analysis of the RT population demonstrated greater efficacy of the LY/cis combination compared to Cisplatin alone for multiple outcomes. Survival, the primary outcome of this study, was significantly improved in the LY/cis arm as compared to the control arm. Similarly, TTPD, TTTF, and tumor response rate (from both investigator-determined and independent reviewer-determined patient responses) all showed statistically significant improvements in the LY/cis patients compared to those in the control arm.

In the FS subgroup, results tended to parallel those seen in the RT population for all outcomes when comparisons were made across treatment arms. In the FS subgroup, survival, TTPD, TTTF, and tumor response rate were clinically significantly longer in the LY/cis arm as compared to the Cisplatin alone arm. Most importantly, the hazard ratios and odds ratios were consistent for all time-to-event and tumor response outcomes, respectively, for both RT and the FS subgroup comparisons across treatment arms. These findings testify to the consistency of the treatment effect favoring LY/cis therapy within the RT population as a whole as well as within the FS subgroup.

Within the LY/cis arm, there was no evidence of inferior results in any of the outcomes for the FS subgroup compared to the PS+NS subgroup. On the contrary, there was evidence that FS patients were associated with the delivery of more treatment cycles and a higher proportion of full doses as well as improved outcomes compared to the PS+NS subgroup. Survival, TTPD, TTTF, and tumor response rate were all numerically superior in the FS subgroup compared to the PS+NS subgroup.

In summary:

1) Treatment with LY/cis 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 clinical superiority of LY/cis over Cisplatin monotherapy was maintained even when clinically relevant prognostic factors were taken into account.
3) The clinical superiority of LY/cis 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.

Reviewer's Conclusion and Comments:

This statistical reviewer agrees with the sponsor's conclusions. The detailed reviewer's conclusion can be found in the section 1.1 or 5.2. The reviewer has the following comments.

1) The median survival times for the RT population and for the FS and PS+NS subgroups showed the consistency of the pattern of the survival difference in both the RT population and subgroup alike.
2) The hazard ratios for the RT population and for the FS and PS+NS subgroups showed the consistency of the magnitude of the survival benefit in both the RT population and subgroup alike.
3) Wilcoxon tests were used to show robustness of efficacy analyses.

3.2 Evaluation of Safety

No safety evaluation is included in this NDA statistical review.

4 Findings in Special/Subgroup Populations

The sponsor conducted subgroup analyses for the prognostic factors to explore the consistency of the efficacy benefit of LY/cis over Cisplatin alone across the various sub-populations. These analyses provided the number of patients, median of survival time, percent of censored subjects, hazard ratio, and Kaplan-Meier estimate for each subgroup. But the sponsor did not perform the statistical inference for those prognostic factors and did not conduct subgroup analyses for the demographic variables.

In this section, this reviewer conducted subgroup analyses on the primary endpoint for the demographic variables: gender, race and age. The Cox regression model was used for the multivariate analyses. The log-rank test and Wilcoxon test were used for statistical comparisons of treatments within each subgroup.

4.1 Gender

Table 10 summaries the subgroup analysis of gender for survival. Multivariate analysis showed that the interaction of treatment and gender had a small p-value for the RT population (p-value=0.072) and was statistically significant for the FS population (p-value=0.035). The interaction was not statistically significant for the PS+NS population (p-value=0.604).

The analysis in the female subgroup showed that the two treatment groups were significant for the RT population and FS population (log-rank p-values=0.012 and 0.010, respectively) and was not significant for PS+NS population. It was consistent with the analysis for all patients. The analysis within the subgroup of male showed that the two treatment groups were not statistically significant for the RT population, FS population, and PS+NS population.

Table 10. Primary Endpoint: Survival Time for Subgroup Analyses in RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Multivariate Analysis						
p-value[a]						
Treatment	0.011		0.008		0.995	
Gender	0.489		0.483		0.998	
Treatment * Gender	0.072		0.035		0.604	
Hazard Ratio (95% CI)[a]						
Treatment	0.480 (0.27, 0.84)		0.381 (0.19, 0.78)		1.003 (0.40, 2.51)	
Gender	0.867 (0.58 1.30)		0.833 (0.50, 1.39)		0.999 (0.52, 1.94)	
Treatment * Gender	1.759 (0.95, 3.25)		2.305 (1.06, 5.01)		0.766 (0.28, 2.10)	
Male						
Total number of patients	184	181	136	134	48	47
Patients with event[b]	124 (67)	130 (72)	82 (60)	85 (63)	42 (87)	45 (96)
Survival time (months)						
Median	11.0	9.4	12.8	10.4	9.85	7.1
(95% CI)	(9.4, 13.3)	(7.9, 10.8)	(9.9, 14.6)	(8.7, 13.2)	(8.1, 11.0)	(6.5, 9.9)
p-value[c]						
Long-rank	0.176		0.388		0.219	
Wilcoxon	0.233		0.390		0.343	
Hazard Ratio (95% CI)[d]	0.843 (0.66, 1.08)		0.875 (0.65, 1.18)		0.767 (0.50, 1.17)	
Female						

Total number of patients	42	41	32	29	10	12
Patients with event[b]	21 (50)	29 (71)	13 (41)	18 (62)	8 (80)	11 (92)
Survival time (months)						
Median	15.7	7.5	18.9	7.4	8.2	9.3
(95% CI)	(10.6,25.8)	(5.8, 11.9)	(15.3, -)	(5.5, 12.2)	(5.4, 20.6)	(5.7, 12.0)
p-value[c]						
Long-rank	0.012		0.010		0.878	
Wilcoxon	0.008		0.003		0.913	
Hazard Ratio (95% CI)[d]	0.479 (0.27, 0.85)		0.381 (0.18, 0.79)		0.927 (0.36, 2.42)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Multivariate analysis is based on a multivariate Cox regression model with treatment, covariate, interaction.

[b] Patients were died by different reasons: study disease related, study toxicity, and other causes.

[c] P-value is based on the test results for the two treatment groups.

[d] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

Reviewer's Comments:

1) Multivariate (Cox model) analysis showed that the interaction of treatment and gender had a small p-value for the RT population (p-value=0.072) and was statistically significant for the FS population (p-value=0.035). Therefore, the impact of gender on treatment effect should be considered.
2) The subgroup analyses showed that the median of survival between the two treatments were not statistically significant within male group (p-value=0.176, 0.388, and 0.219 for RT, FS, and PS+NS populations, respectively) even the hazard ratios showed a trend for the survival benefit in RT, FS, and PS+NS populations. These results were not consistent with the analyses for the whole population.
3) Within female population, the subgroup analyses showed that the median of survival between the two treatment arms were statistically significant for RT and FS populations (p-value=0.012 and 0.010, respectively) and was not significant for PS+NS population (p-value=0.878). The hazard ratios also showed a trend for the survival benefit in RT, FS, and PS+NS populations. Those results were consistent with the analyses for the all patients.
4) There was a heterogeneous distribution for the two subgroups. The male population had a very large proportion in the two treatment groups over the female population. The percentages were 81.4% vs. 18.6% and 81.5% vs. 18.5% in LY/cis and Cisplatin groups, respectively.

4.2 Race

Table 11 summaries the results of subgroup analyses of race for survival time in which the Caucasian subgroup was compared with all other origins. Multivariate analysis showed that the interaction of treatment and race was not statistically significant for the RT population, FS population, and PS+NS population.

The analysis of the subgroup Caucasian showed that the two treatment arms were significant for the RT population and FS population (log-rank p-values=0.024 and 0.026, respectively) and was not significant for PS+NS population. It was consistent with the analysis for all patients. The analysis within the subgroup of non-Caucasian showed that the two treatment groups were not statistically significant for the RT population, FS population, and PS+NS population.

Table 11. Primary Endpoint: Survival Time for Subgroup Analyses in RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Multivariate Analysis						
p-value[a]						
Treatment	0.581		0.566		0.114	
Race	0.674		0.821		0.478	
Treatment * Race	0.901		0.238		0.173	
Hazard Ratio (95% CI)[a]						
Treatment	0.802 (0.37, 1.76)		1.339 (0.49, 3.63)		0.274 (0.06, 1.37)	
Race	0.881 (0.49, 1.59)		1.100 (0.48, 2.51)		0.734 (0.31, 1.72)	
Treatment * Race	0.949 (0.42, 2.16)		0.535 (0.19, 1.51)		3.158 (0.60, 16.52)	
Caucasian						
Total number of patients	204	206	150	153	54	53
Patients with event[b]	132 (65)	147 (71)	84 (56)	56 (63)	48 (89)	50 (94)
Survival time (months)						
Median	12.2	9.3	13.3	10.2	9.3	7.2
(95% CI)	(10.1,14.4)	(7.8, 10.8)	(12.1,15.3)	(8.5, 12.2)	(7.1, 10.8)	(6.4, 10.7)
p-value[c]						
Long-rank	0.024		0.026		0.487	
Wilcoxon	0.030		0.021		0.693	
Hazard Ratio (95% CI)[d]	0.762 (0.60, 0.97)		0.717 (0.54, 0.96)		0.868 (0.58, 1.29)	
Others						
Total number of patients	22	16	18	10	4	6
Patients with event[b]	13 (59)	12 (75)	11 (61)	6 (60)	2 (50)	6 (100)
Survival time (months)						
Median	9.0	8.4	8.8	9.55	17.2	8.0
(95% CI)	(6.7, 17.2)	(6.6, 12.9)	(6.2, 16.0)	(6.6, -)	(9.8, -)	(6.4, 10.7)
p-value[c]						
Long-rank	0.715		0.619		0.093	
Wilcoxon	0.894		0.596		0.077	
Hazard Ratio (95% CI)[d]	0.863 (0.39, 1.90)		1.291 (0.47, 3.53)		0.159 (0.02, 1.36)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Multivariate analysis is based on a multivariate Cox regression model with treatment, covariate, interaction.

[b] Patients were died by different reasons: study disease related, study toxicity, and other causes.

[c] P-value is based on the test results for the two treatment groups.

[d] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

4.3 Age

Table 12 summaries the results of subgroup analyses of age for survival time in which age (< 65 years) was compared with age (≥65 years). Multivariate analysis showed that the interaction of treatment and age was not statistically significant for the RT population, FS population, and PS+NS population.

Table 12. Primary Endpoint: Survival Time for Subgroup Analyses in RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Multivariate Analysis						
p-value[a]						
Treatment	0.410		0.546		0.448	
Age (< 65 years)	0.584		0.621		0.556	
Treatment * Age	0.447		0.453		0.950	
Hazard Ratio (95% CI)[a]						
Treatment	0.860 (0.60, 1.23)		0.875 (0.57, 1.35)		0.781 (0.41, 1.48)	
Age (< 65 years)	0.915 (0.67, 1.26)		0.906 (0.61, 1.34)		0.845 (0.48, 1.48)	
Treatment * Age	0.836 (0.52, 1.33)		0.804 (0.46, 1.42)		1.026 (0.46, 2.30)	
Age (< 65 years)						
Total number of patients	143	136	107	97	36	39
Patients with event[b]	88 (61)	95 (70)	57 (53)	58 (60)	31 (86)	37 (95)
Survival time (months)						
Median	13.3	10.2	14.7	10.8	9.4	9.3
(95% CI)	(10.7,15.7)	(8.4, 11.9)	(11.7,17.6)	(8.7, 12.7)	(7.9, 14.0)	(6.6, 12.0)
p-value[c]						
Long-rank	0.020		0.052		0.277	
Wilcoxon	0.076		0.079		0.643	
Hazard Ratio (95% CI)[d]	0.704 (0.53, 0.95)		0.693 (0.48, 1.00)		0.760 (0.46, 1.25)	
Age (≥ 65 years)						
Total number of patients	83	86	61	66	22	20
Patients with event[b]	57 (69)	64 (74)	38 (62)	45 (78)	19 (86)	19 (95)
Survival time (months)						
Median	10.0	7.5	12.2	8.7	9.7	6.45
(95% CI)	(8.3, 12.9)	(6.5, 10.4)	(7.9, 14.4)	(6.8, 14.2)	(5.1, 12.8)	(4.2, 9.3)
p-value[c]						
Long-rank	0.376		0.503		0.457	
Wilcoxon	0.186		0.311		0.418	
Hazard Ratio (95% CI)[d]	0.850 (0.59, 1.22)		0.862 (0.56, 1.33)		0.783 (0.41, 1.49)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.

[a] Multivariate analysis is based on a multivariate Cox regression model with treatment, covariate, interaction.

[b] Patients were died by different reasons: study disease related, study toxicity, and other causes.

[c] P-value is based on the test results for the two treatment groups.

[d] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

The analysis of the subgroup age (< 65 years) showed that two treatments were significant for the RT population and FS population (log-rank p-values=0.020 and 0.052, respectively) and was not significant for PS+NS population. It was consistent with the analysis for all patients. The analysis within the subgroup of age (≥65 years) showed that the two treatment groups were not statistically significant for the RT population, FS population, and PS+NS population.

4.4 Other Special/Subgroup Populations

There was no other special/subgroup analysis in this review.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Statistical Issues:

- 456 patients were randomized to treatment arms where 8 of these patients were died from study disease before any dosing. The sponsor did not follow the statistical reviewer's comments of IND 40061/SN298 that the primary survival analysis should be based on all patients as randomized. The sponsor did primary efficacy analysis based on the randomized and treated population which did not include those 8 patients.
- The sponsor' efficacy claim was based on the RT population and stated that in clinically, folic acid and vitamin B_{12} would improve the clinical outcome regardless of the treatment arm. The results of the FS subgroup also support the efficacy claim.
- There was a heterogeneous distribution for gender in the two treatment arms (male and female with 81.4% vs. 18.6% and 81.5% vs. 18.5% in LY/cis and Cisplatin groups, respectively). The multivariate analysis for the treatment and gender showed that the interaction between treatment and gender had a small p-value (p-value=0.072) for the RT population and was statistically significant for the FS population (p-value=0.035). Therefore, the influences of treatment were depended on the subgroups of gender.
- The subgroup analysis of gender showed that the new treatment was significant for the RT population and FS population in female patients (p-value=0.012 and 0.010, respectively) and was not significant for PS+NS population (p-value=0.878). The analyses within the subgroup of male showed that the new treatment group was not statistically significant for the RT, FS, and PS+NS populations (p-value=0.176, 0.388, 0.219, respectively).
- The hazard ratios showed the consistency of the magnitude of survival benefit in both the RT population and subgroup alike. The efficacy analyses of

secondary endpoints, TTPD, TTTF and response rate, showed the consistency to primary endpoint.

Collective Evidence:

We have the following collective evidences from the subgroup analyses.

1) The primary efficacy analysis showed that the median survival time for patients treated with LY/cis was longer than for patients treated with Cisplatin alone: 12.2 versus 9.3 months. There was a statistically significant difference (p=0.021) between the two treatment groups. The analysis of the FS subgroup indicated that the median survival for patients treated with LY/cis was 13.3 months vs. 10.0 months, a difference with small p-value (0.051). The analysis of the PS+NS subgroup indicated that the median survival time for patients treated with LY/cis was 9.5 months vs. 7.2 months, but this difference did not reach the overall significance level (p-value=0.253). The hazard ratio for the RT population and for the FS and PS+NS subgroups were 0.766, 0.758, and 0.798, respectively, indicating the consistency of the magnitude of the survival benefit in both the RT population and subgroup alike.
2) The efficacy analyses of secondary endpoints showed that TTPD, TTTF, and response rate were consistent with the primary endpoint. But the difference in the median duration between two treatment arms did not reach statistical significance though the medians duration were longer in the LY/cis arm compared to the control arm.
3) The interactions of treatment and race, treatment and age were not statistically significant. The interaction of treatment and gender had a small p-value for the RT population and was statistically significant for the FS population. Therefore, the influences of treatment were depended on the two subgroups of gender.
4) The efficacy results of subgroup analyses showed that the treatment effects within female subgroup were consistent with the whole population. The treatment effects within male subgroup were not consistent with the whole population.

5.2 Conclusions and Recommendations

Based on the collective evidences and findings, in this statistical reviewer's opinion the data and results of the Phase III Study H3E-MC-JMCH support the sponsor's efficacy claim of ALIMTA® (pemetrexed, LY231514) 500 mg Vials with respect to the survival endpoint for the patients with Malignant Pleural Mesothelioma. The data and results of the study show that the primary endpoint, survival, is statistically significantly improved in new treatment arm to the control arm for the randomized and treated (RT) population (p-value=0.021). The secondary endpoints, time to progressive disease, time to treatment failure, and

response rate, are also demonstrated statistically significant improvement in new treatment group compared to the control group. In the fully supplemented (FS) subgroup, efficacy results are similar to those findings in the RT population. The hazard ratios for both RT and FS populations showed the consistency of the magnitude of survival benefit.

/S/

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6 APPENDICES

No appendix is included in this review.

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