

## CLINICAL REVIEW

### Clinical Review Section

#### Cisplatin Exposure in JMCH

In the pre-NDA meeting Briefing Document (scheduled for the January 30, 2002), the proposed Indication for malignant pleural mesothelioma stipulated: "

Also, the proposed Dosage and Administration section of the package insert outlined three regimens: The draft Protocol for treatment, JMFE (submitted April 3, 2002, serial #399), initially contained these regimens. The rationale for the inclusion of the was based on patients who could not tolerate cisplatin. FDA disagreed with the inclusion of two of the three regimens in the label and in the expanded access program. This was because the combination of alimta + cisplatin was reported to increase survival in JMCH and there was no data that showed an increase in survival with alimta alone or the combination of Thus, the FDA did not believe it was appropriate to offer expanded access to alimta alone or the combination of

Later, in an amendment to JMFE (submitted 12/16/2002;), it was stipulated that patients would receive alimta + cisplatin who have been previously treated with cisplatin-based regimen and responded for six months, and who did not have medical contra-indications to receiving more cisplatin, i.e., renal insufficiency, significant neuropathy, ototoxicity and very low left ventricular ejection fraction. Again, all of these reasons did not appear appropriate to exclude cisplatin. First, patients, who have renal insufficiency and cannot have more cisplatin, cannot receive alimta--a drug excreted renally. Second, patients who have a very low left ventricular ejection fraction, which contra-indicated cisplatin, may not tolerate three days of potent corticosteroids--a part of the alimta regimen. Third, patients who have a non-response to prior cisplatin can have cisplatin + alimta in view of the claimed synergy between cisplatin and alimta in an *in vitro model*.

However, the promotion of may have been derived from safety concerns or investigator preferences in JMCH. Review of the dose-intensity tables provided by Lilly in the JMCH study report suggested that overall planned cisplatin dose-intensity was the same as planned alimta dose-intensity (table below). Based on this analysis, it did not appear that alimta was given without cisplatin to a significant extent.

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**Table JMCH.12.4. Dose Intensity (DI)  
RT Population  
H3E-MC-JMCH**

Statistics	LY/cis		Cisplatin
	LY231514	Cisplatin	Cisplatin
Number of Patients	226	226	222
Planned Mean / Patient (mg/m <sup>2</sup> /week)	166.7	25	25
Delivered Mean / Patient	153.4	23.2	24.1
Percent of planned DI (delivered/planned)	92.0%	92.8%	96.4%

**Table JMCH.12.5. Dose Intensity (DI)  
RT Population by Supplementation Status  
H3E-MC-JMCH**

Statistics	LY/cis				Cisplatin	
	LY231514		Cisplatin		Cisplatin	
	FS	PS+NS	FS	PS+NS	FS	PS+NS
Number of Patients	168	58	168	58	163	59
Planned Mean / Patient (mg/m <sup>2</sup> /week)	166.7	166.7	25	25	25	25
Delivered Mean / Patient	154.6	149.7	23.4	22.6	24.1	24.2
Percent of planned DI (delivered/planned)	92.7%	89.8%	93.6%	90.4%	96.4%	96.8%

In Appendix 16.1.10, **Listing of Patients Receiving Test Drug(s) or Investigational Product(s) by Lot or Batch Number (p. 1763-1874)**, of the JMCH study report, it appeared that there were several patients who did not have cisplatin lot or batch numbers recorded at baseline and/or at some time during the study. Non-recording of the cisplatin lot number may have been because the site did not record it or the cisplatin lot number was not recorded because cisplatin was not given to the patient. Below is the portion of the CRF where the information was to be recorded.

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*Lilly*

Clinical Report Form  
 A Single-blind Randomized Phase 3 Trial of MTA plus  
 Cisplatin versus Cisplatin in Patients with Malignant  
 Pleural Mesothelioma  
 H3E-MC-JMCH

All variables from CTLOT No. Dataset

Normal Saline & Cisplatin Cycle (Visit) 1  
 Study Drug Packet

Initials  
 Date Verified  
 Initials  
 d

**STUDY DRUG CT NUMBER : CISPLATIN** DRUG

If two or more vials with the same Lot number are used for the infusion, record the Lot number only once. If there are only one, two, or three Lot numbers to record, leave other spaces blank.

Lot Number	Lot Number	Lot Number	Lot Number

CISPLATIN

Below is a table of patients on the alimta + cisplatin arm, who the cisplatin lot number was not reported at baseline and throughout the treatment.

INVESTIGATOR SITE	PATIENT #	# OF CYCLES	dose delayed or reduced cycle#-reason for dose delay or reduced
107	1072	4	No
107	1073	6	No
107	1074	1	No
109	1092	1	No
124	1201	2	No
130	1261	6	2,3,6-cisplatin & alimta delayed, creatinine clearance; 5-cisplatin & alimta delayed, neutrophil; 5-alimta reduced, stomatitis
131	1272	4	4-cisplatin & alimta delayed, creatinine clearance
131	1277	6	No
142	1475	2	No

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INVESTIGATOR SITE	PATIENT #	# OF CYCLES	dose delayed or reduced cycle#-reason for dose delay or reduced
510	5100	2	2-cisplatin & alimta delayed, anemia
802	8020	2	No
804	8040	1	No

A sample from Appendix 16.1.10 is patient #130-1261 (also, included is patient #130-1196 who had the cisplatin lot numbers recorded).

```

130  1196  M2A/C18p  1  14062  M2A
                               2  110928  CISPLATIN
                               3  14062  M2A
                               4  110928  CISPLATIN
                               5  14062  M2A
                               6  110928  CISPLATIN
                               7  14062  M2A
                               8  110928  CISPLATIN
                               9  14062  M2A
                              10  110928  CISPLATIN
                              11  14062  M2A
                              12  110928  CISPLATIN

130  1261  M2A/C18p  1  14062  M2A
                               2  14062  M2A
                               3  14062  M2A
                               4  14062  M2A
                               5  14062  M2A
                               6  14062  M2A
    
```

Below is a table of patients on the alimta + cisplatin arm, who the cisplatin lot number was not reported at baseline and the cisplatin lot number was reported in later cycle(s).

INVESTIGATOR SITE	PATIENT #	# OF CYCLES CISPLATIN LOT NUMBER NOT REPORTED	TOTAL # CYCLES	dose delayed or reduced cycle#-reason for dose delay or reduced
130	1266	1st 2 cycles, 6th cycle	6	no
131	1044	1st 2 cycles, 6th cycle	10	no
136	1631	1st 3 cycles, 5th-12th cycle; only 4th cycle with cisplatin	12	4-cisplatin reduced, deafness; 5-12-cisplatin omitted, deafness; 9-alimta delayed, URI
140	1450	1st cycle	2	2-cisplatin & alimta reduced, nausea
251	2550	1st 2 cycles	3	2-cisplatin & alimta reduced, platelet count reduced
510	5103	1st cycle	6	5-cisplatin & alimta reduced, dehydration
554	5516	1st cycle	3	3-cisplatin & alimta

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INVESTIGATOR SITE	PATIENT #	# OF CYCLES CISPLATIN LOT NUMBER NOT REPORTED	TOTAL # CYCLES	dose delayed or reduced cycle#-reason for dose delay or reduced
				delayed, creatinine clearance
805	8070	1st cycle	6	no

A sample from Appendix 16.1.10 is patient #136-1631.

```

136 1631 MTA/Cispl 1 14862 MTA
2 14862 MTA
3 14862 MTA
4 14862 MTA
5 14862 MTA
6 14862 MTA
7 14862 MTA
8 14862 MTA
9 14862 MTA
10 14862 MTA
11 14862 MTA
12 14862 MTA
13 14862 MTA
14 14862 MTA

```

Below is a table of patients on the alimta + cisplatin arm, who the cisplatin lot number was reported at baseline and the cisplatin lot number was not reported in later cycle(s).

INVESTIGATOR SITE	PATIENT #	# OF CYCLES CISPLATIN LOT NUMBER NOT REPORTED	TOTAL # CYCLES	TOTAL # OF MTA+CISPLAT PTS. @ SITE	dose delayed or reduced cycle#-reason for dose delay or reduced
104	1046	2,3,8-11	11	2	no
119	1146	3,4	6	2	no
130	1191	2,3,4	6	4	no
131	1278	2	6	10	2-cisplatin & alimta delayed, creatinine clearance; 3-cisplatin & alimta delayed, white blood count
136	1633	8,9, CYCLES 1-6 were not reported for both cisplatin +alimta.	9	2	no
142	1476	2,3,4,5	5	3	2, 4, 5-cisplatin & alimta delayed, creatinine clearance; 2-cisplatin & alimta reduced, serum creatinine increased
510	5101	2,3	6	8	4-cisplatin & alimta

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INVESTIGATOR SITE	PATIENT #	# OF CYCLES CISPLATIN LOT NUMBER NOT REPORTED	TOTAL # CYCLES	TOTAL # OF MTA+CISPLAT PTS. @ SITE	dose delayed or reduced cycle#-reason for dose delay or reduced
					reduced, neutrophil count reduced
720	7200	4	4	7	3-cisplatin & alimta delayed and reduced, vomiting; 4-cisplatin omitted, vomiting
804	8046	3,5	6	6	no

Samples from Appendix 16.1.10 are patients #136-1633 and #720-7200.

136	1633	MTA/Cispl	1	14062	MTA
				11897	CISPLATIN
				118161	CISPLATIN
			8	14062	MTA
			9	14062	MTA
720	7200	MTA/Cispl	1	98221015	MTA
			2	98221019	CISPLATIN
			3	98221019	MTA
			4	98221019	CISPLATIN
				98221019	MTA

The tables suggested that several patients might not have received cisplatin at baseline and/or at some time during the JMCH study. In response to FDA concern about this, Lilly stated that only two patients--#136-1631 and #720-7200 had cisplatin omitted (response dated 9/19/2003). For patient #136-163, Lilly acknowledged that cisplatin was omitted cycles 5 -12. Appendix 16.1.10 indicated that the cisplatin lot number was also not reported for cycles 1-3. By using this appendix, there was no way to tell the difference between cycles that cisplatin was omitted and cycles that the cisplatin lot number was not recorded. Also, Lilly stated that no patients on the alimta/cisplatin arm of study JMCH received \_\_\_\_\_ at baseline or at any time during the study and that there were no patients on the alimta/cisplatin arm of study JMCH who had alimta omitted and received only cisplatin at baseline or at any time during the study.

In their response submitted 11/6/2003, Lilly stated, "on inspection of Appendix 16.1.10 in the JMCH study report, it might appear that some patients received Alimta but not cisplatin." Additionally, Lilly stated that the cisplatin lot numbers were not collected for these patients and that only two patients had cisplatin omitted in the alimta/cisplatin arm of study JMCH.

In conclusion, the requests for inclusion of regimens of \_\_\_\_\_ in the first proposed package insert and Protocol for Treatment were not based on information generated in the pivotal trial, JMCH. Except for the two patients acknowledged by Lilly, Lilly stated that all patients on the alimta + cisplatin arm received both alimta + cisplatin while they were on the JMCH study.

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### Survival: The Primary Endpoint

No source documents were provided or reviewed. The FDA statistician used datasets submitted by Lilly on December 6, 2002. The datasets were located in the Electronic Document Room (EDR) of CDER of FDA under the Letter Date "24-OCT-2002" and "6-DEC-2002", respectively. The major data set for the efficacy analysis was "SURVLOCK" which defines the survival time and events.

### Survival Analysis of Randomized and Treated Patients

Below are the results of the FDA statistician's survival analysis of study JMCH.

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

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=168)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients dead <sup>a</sup>	145 (64)	159 (72)	95 (57)	103 (63)	50 (86)	56 (95)
<b>Survival time (months)</b>						
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)
<b>p-value<sup>b</sup></b>						
Long-rank	0.021		0.051		0.253	
Wilcoxon	0.028		0.039		0.440	
<b>Hazard Ratio<sup>c</sup></b>						
95% CI for Hazard Ratio <sup>c</sup>	0.766 (0.61, 0.96)		0.758 (0.57, 1.0)		0.798 (0.54, 1.17)	

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

<sup>a</sup> Patients were died for different reasons: study disease related, study toxicity, and other causes.

<sup>b</sup> P-value is based on the test results for the two treatment groups.

<sup>c</sup> Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

In the randomized and treated (RT) (n=448), the median survivals for alimta/cisplatin and cisplatin alone were 12.1 and 9.3 months, respectively (log-rank, p=0.021); this was a statistically significant increase in median survival of 2.8 months. In the subgroup<sup>149</sup> of the fully folic acid and vitamin B12 supplemented patients (n=331), the median survivals for alimta/cisplatin and cisplatin alone were 13.3 and 10 months, respectively (log-rank, p=0.051); this was a marginally statistically significant increase in median survival of 3.3 months. In the underpowered subgroup of partially folic acid and vitamin B12 supplemented plus never

<sup>149</sup> Lilly tested three models in the prognostic evaluation of survival the optimal parameterization was found to be Model *FS+PS versus NS*. A comparison of Model *FS versus PS+NS* (defined in the statistical analysis plan) had less prognostic power than the alternative parameterization (*FS+PS versus NS*). This finding was based on the fact that Model *FS+PS versus NS* had a smaller p-value for the 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.

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supplemented patients, the median survivals for alimta/cisplatin and cisplatin alone were 9.5 and 7.2 months, respectively (log-rank,  $p=0.253$ ); although this was a 2.3 month increase in survival, it was not statistically significant. The hazard ratios of 0.766, 0.758, and 0.798, for the respective survival analyses were consistent with regard to a survival benefit in the alimta/cisplatin arm compared to the cisplatin alone arm.

### "Intent-to-Treat" Analysis of Survival

There were 8 patients (2 alimta/cisplatin, 6 cisplatin alone) who were randomized and not included in the survival analysis. With 456 randomized patients (304 events, 152 censored), i.e., 448 + 8 patients, the results of the FDA survival analysis were:

INTENT-TO-TREAT	ALIMTA/CISPLATIN (N=153)	CISPLATIN ALONE (N=150)	p-value log-rank
Survival, median (95% CI)	12 months (10, 14.4)	9.3 months (7.8, 10.7)	0.0205

In the intent-to-treat population ( $n=456$ ), the median survivals for alimta/cisplatin and cisplatin alone were 12 and 9.3 months, respectively (log-rank,  $p=0.0205$ ); this was a statistically significant increase in median survival of 2.7 months.

The intent-to-treat analysis (with the inclusion of the 8 patients, i.e.,  $n=456$ ) was comparable to the randomized and treated analysis ( $n=448$ ) of survival.

### Confirmed Pathological Diagnosis of Mesothelioma

In the past, expert panels have been set up to review suspected malignant pleural mesothelioma cases. One editorialist wrote about the need for a panel of experts to review pathological material to guarantee the accuracy of diagnosis.<sup>150</sup> The reason for this is three-fold. First, epithelial cell type has been associated with a more favorable prognosis in most large series; the fibrosarcomatous type carries the worst prognosis, and the mixed type is intermediate. Second, it is important to differentiate mesothelioma from adenocarcinoma--tumors with histologic similarities--since it may influence the treatment and the natural history. Adenocarcinomas from primary lung, breast, ovary, stomach, kidney, or prostate cancer frequently metastasize to the pleura and can be extremely difficult to distinguish from epithelial mesothelioma cytologically or histologically. Metastatic adenocarcinoma with extensive pleural involvement may grossly resemble mesothelioma and has been called pseudomesothelioma. Third, sarcomatous mesotheliomas must be distinguished from fibrosarcoma, malignant fibrous histiocytoma, malignant schwannoma, and hemangiopericytoma. Synovial sarcoma and carcinosarcomas,

<sup>150</sup> Jett JR. Malignant pleural mesothelioma. A proposed new staging system. *Chest*. 1995;108:895-897)

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which may also have mixed sarcomatous and epithelial components, usually present as a localized mass in the lung.

In general, mesothelioma is difficult to diagnose, even by expert pathologists. Initial misdiagnosis is common.

In a FDA comment faxed to Lilly on 8/31/2000,<sup>151</sup> the importance of independent pathology review was stated:

Although all patients may not have sufficient tissue for an independent review of histopathology, the slides should be available for review by an independent pathologist. The rigor of the study, regarding confidence in the histopathological diagnosis, will be decreased without independent review of all cases. In view that only one randomized trial in mesothelioma will be accepted for this indication, the one study in mesothelioma must be strictly performed.

The following were amendments made to the JMCH protocol, regarding pathology and its independent review:

19 June 2000 (~323 out of 574 patients entered on study JMCH at this time)<sup>152</sup>:

**3.4.2.1. Inclusion Criteria** – Not all patients have sufficient tissue for an independent review, but will still be allowed in our analysis. (p. 1141 of study report JMCH)

Patients may be entered and randomized based on local pathology; however, independent centralized pathology review will be carried out on all patients if feasible. In case of a discrepancy between the assessment of the independent reviewer and the investigator, the assessment of the independent reviewer will take precedence. (p. 1145)

24 January 2001 (~518 out of 574 patients entered on study JMCH at this time):

Patients may be entered and randomized based on local pathology; however, independent centralized pathology review will be carried out on all patients if feasible. ~~In case of a discrepancy between the assessment of the independent reviewer and the investigator, the assessment of the independent reviewer will take precedence.~~<sup>153</sup> (p. 1166)

<sup>151</sup> This was in response to submission serial #242, dated 7/12/2000).

<sup>152</sup> Lilly met with the FDA on 6/21/2000, This was a follow-up to EOP2 re: mesothelioma indication. One of issues for discussion was whether FDA would accept an interim analysis of secondary endpoints from the mesothelioma trial.

<sup>153</sup> The strikeouts were part of the citation.

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The protocol submitted in the JMCH study report stated:

Histologically proven diagnosis of mesothelioma of the pleura in patients not candidates for curative surgery. Patients will be clinically staged using the IMIG TNM staging criteria (see Protocol Attachment JMCH.1). Patients may be entered and randomized based on local pathology; however, independent centralized pathology review will be carried out on all patients if feasible.<sup>154</sup>

On page 959 of the JMCH study report, it was stated that: " — will assay the blood chemistries, homocysteine, and calculated creatinine clearance (CrCl) and will manage the centralized independent pathology review and pharmacokinetic samples."

However, the ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT form<sup>155</sup> indicated that independent centralized pathology review was to be carried out on all patients.

*Lilly* WORKSHEET  
H3E-40C-JMCH

Box Entry Criteria Checklist to Janine Klopf (217-277-3236) Visit 0  
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### ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT

CONTRACEPTION is ensured through (check one):

<input type="checkbox"/> Sterilization (surgical or radiation-induced)	<input type="checkbox"/> Intra-uterine device (IUD)
<input type="checkbox"/> Post-menopausal	<input type="checkbox"/> Contraceptive implant* or Depo-Provera*
<input type="checkbox"/> Oral contraceptives*	<input type="checkbox"/> Strict abstinence
<input type="checkbox"/> Diaphragm	<input type="checkbox"/> Solitary partner who is vasectomized
<input type="checkbox"/> Sponge* or spermicide*	<input type="checkbox"/> Not sexually active
<input type="checkbox"/> Condom and spermicide*	<input type="checkbox"/> Not applicable

\*Enter description/brand name on the Concomitant Medication page (located behind a separate tab); applies to male patients or prepubertal females.

Inclusion Criteria: The answers for items 1-10 must be YES to qualify for study.

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	1. Histologically proven diagnosis of mesothelioma of the pleura in patients not candidates for curative surgery. Patients will be clinically staged using the IMIG TNM staging criteria (see Protocol Attachment JMCH.1). Patients may be entered and randomized based on local pathology; however, independent centralized pathology review will be carried out on all patients. In case of a discrepancy between the assessment of the independent reviewer and the investigator, the assessment of the independent reviewer will take precedence.

For pathological diagnosis, the case report form (CRF) provided for checking-off of the box. There was no indication on whether the pathological and subtype diagnoses were from the local site or from independent centralized pathology review.

<sup>154</sup> Page 932 of the JMCH study report

<sup>155</sup> Page 1179 of the JMCH study report

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*Lilly* Clinical Report Form  
A Single-Armed Randomized Phase III Trial of MTA  
plus Cisplatin versus Cisplatin in Patients with  
Malignant Pleural Mesothelioma  
HSE/MC/JMCH

Cycle (Visit) 0

**DIAGNOSIS: INITIAL PATHOLOGICAL DIAGNOSIS**

Basis for diagnosis →  (H) Histopathological

Pathological diagnosis code (Check one) →  0100 Sarcomatoid Pleural Mesothelioma  
 0200 Epithelial Pleural Mesothelioma  
 0300 Mixed Cell Pleural Mesothelioma  
 0400 Other Specify diagnosis  
PMD

Date of initial pathological diagnosis (Use Date Specimens Collected) → MM/DD/YYYY

Grade of histopathological diagnosis (Check one) →  G0 Undifferentiated  
 G1 Poorly Differentiated  
 G2 Moderately Differentiated  
 G3 Well Differentiated  
 U Unknown

In response to FDA query, Lilly responded with (dated 1/10/2003): "One of the entry requirements for study JMCH was to have local pathologic confirmation of malignant pleural mesothelioma. This requirement was validated by independent (independent from the site) monitors who were fluent in the local language. In addition, local pathology could be validated by the FDA during site audits."

In response to FDA query, Lilly responded with (dated 2/13/2003): "Regarding DODP's request for pathological confirmation documentation for the patients entered on JMCH, the monitors (independent from the site) verified that the diagnosis of mesothelioma on the Case Report Form (CRF's) matches the diagnosis shown on the local pathology report."

Although the published report of the JMCH study did not mention central review of pathology specimens,<sup>156</sup> the accompanying editorial stated that "Central review of all CT scans and all pathology specimens was performed. This rigorous approach to analysis lends credibility to the study results, especially in a disease for which correct pathologic diagnosis can still be difficult, and for which there has been little uniformity in measuring response to treatment."<sup>157</sup>

<sup>156</sup> Vogelzang NJ, Rusthoven JJ, Symanowski J, et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 21:2636-2644, 2003

<sup>157</sup> Rusch VW. Pemetrexed and Cisplatin for Malignant Pleural Mesothelioma: A New Standard of Care? *Journal of Clinical Oncology*, 21:2629-2630, 2003

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The information below, regarding independent central pathology review, was requested from Lilly on 9/2/2003 and the response received by FDA on 9/22/2003.

INDEPENDENT CENTRAL PATHOLOGY REVIEW CATEGORIES	RANDOMIZED AND TREATED, N=448 (%)
Independent review confirmed pathology of malignant mesothelioma	302 (67%)
Independent review suggestive/consistent of malignant mesothelioma	16 (3.6%)
Independent review did not confirm pathology of malignant mesothelioma	30 (6.7%)
Documented as tissue unsatisfactory to confirm pathology	13 (2.9%)
Not feasible to send in samples for independent pathology review	87 (19.4%)

67% of the randomized and treated patients had the diagnosis of mesothelioma confirmed by independent review; 3.6% of the randomized and treated patients' pathology was suggestive of consistent with malignant mesothelioma. 6.7% of the patients did not have the diagnosis of mesothelioma confirmed. 22.3% of the patients' either had tissue that was unsatisfactory to confirm pathology or it was not feasible to send samples for independent pathology review. In view that only one randomized trial in mesothelioma will be accepted for this indication, the JMCH study in mesothelioma was not strictly performed.

Lilly stated that "no adjudication took place in cases where there was discrepancy between local and centralized pathology reviews."<sup>158</sup>

The information provided on independent pathology review did not take into account the histological subtypes of mesothelioma, i.e., epithelial, sarcomatoid, and mixed. As stated in FDA's BACKGROUND ON MESOTHELIOMA section in this review, *the histological subtype of mesothelioma--a baseline stratification factor in study JMCH--can have impact on prognosis and an imbalance would affect the results of a survival analysis.* FDA requested this

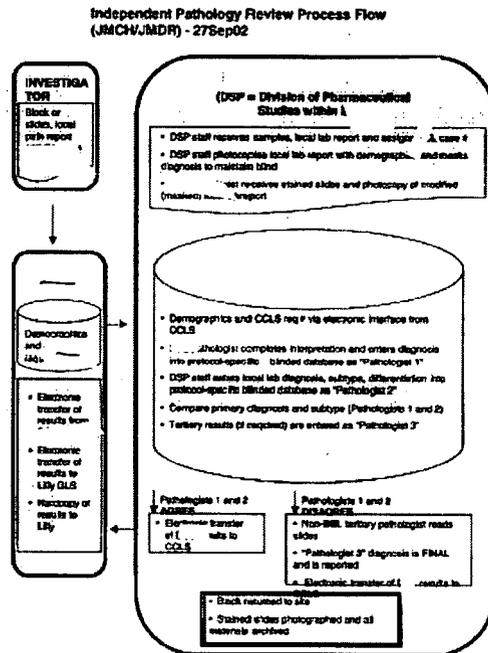
<sup>158</sup> Response received from Lilly dated 9/22/2003.

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information, as well as, the charter of the independent pathology review and what responsibilities were charged to the review.<sup>159</sup>

Lilly sent FDA a flow sheet, illustrating the Independent Pathology Review on 12/16/2003. Note the date on the sheet is "27Sep02"--about a month prior to when Rolling submission of NDA began and conflicts with prior amendments and correspondences from Lilly.



**BEST POSSIBLE COPY**

Summary of the Independent Pathology Review process:

- Local investigator site: slides or blocks, and local pathology report were sent to \_\_\_\_\_
- At \_\_\_\_\_  
 → pathologist interprets slide and enters diagnosis into a blinded database--Pathologist 1

DSP staff enters *local* diagnosis, subtype, differentiation into a blinded database--Pathologist 2

*IF* Diagnosis<sub>Pathologist1</sub> = Diagnosis<sub>Pathologist2</sub> → results entered

<sup>159</sup> From the JMCH study report (p. 77): \_\_\_\_\_  
 tissue samples for pathological determination (transported and reported via \_\_\_\_\_)

!Analysis of tumor-

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*IF* Diagnosis<sub>Pathologist1</sub> ≠ Diagnosis<sub>Pathologist2</sub> → Pathologist 3 reads slides →  
 Diagnosis<sub>Pathologist3</sub> → FINAL

In Lilly's response (dated 9/22/2003) to FDA query, a statement was made that "no adjudication took place in cases where there was discrepancy between local and centralized pathology reviews". According to the Independent Pathology Review Process Flow outlined above, it appears that the determination by Pathologist 3 was the final diagnosis if there was a discrepancy between local and Pathologist 1 (review pathologist).

Below is the analysis of mesothelioma subtype derived from independent pathology review submitted by Lilly on 12/16/2003. This analysis is on patients whose diagnosis of mesothelioma was confirmed and the mesothelioma subtype was confirmed or determined after independent review. *21% of the 302 confirmed mesothelioma patients (alimta/cisplatin: 24%, 37 out of 153 confirmed; cisplatin alone: 18%, 27 out 149 confirmed) had their subtype changed from the designation determined at the investigators' site.*

153 patients on the alimta/cisplatin arm had the diagnosis of mesothelioma confirmed by independent pathology review; 149 patients on the cisplatin alone arm had the diagnosis confirmed.

Folic acid and vitamin B12 supplement statuses were balanced on both arms in confirmed mesothelioma pathology patients (table below).

FOLIC ACID/VITAMIN B12 SUPPLEMENT STATUS	ALIMTA/CISPLATIN	CISPLATIN ALONE
FS	111	108
NS	20	27
PS	22	14
total	153	149

Stage was balanced on both arms in confirmed mesothelioma pathology patients (table below).

STAGE	ALIMTA/CISPLATIN	CISPLATIN ALONE
Ia	6	4
Ib	1	4
II	26	23
III	47	45
IV	73	72
?		1
total	153	149

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### Clinical Review Section

Gender was balanced on both arms in confirmed mesothelioma pathology patients (table below).

GENDER	ALIMTA/CISPLATIN	CISPLATIN ALONE
female	26 (17%)	25 (17%)
male	127 (83%)	124 (83%)
total	153	149

### Confirmed Pathological Diagnosis of Mesothelioma Subtypes

The table below illustrates the list of pathological diagnoses entered from the investigators' site from patients with confirmed mesothelioma. The independent review consolidated the varied mesothelioma diagnoses to subtypes of epithelial, mixed, and sarcomatoid.

PATHOLOGIC DIAGNOSIS	INVESTIGATOR'S		INDEPENDENT REVIEW	
	Alimta/cisplatin	cisplatin alone	alimta/cisplatin	Cisplatin alone
Epithelial Pleur. Meso	107	107	130	127
Mixed Cell Pleur. Meso	27	22	15	13
Sarcomatoid Pleur. Meso	10	10	8	9
Biphasical Pleur. Meso	1	2		
Meso Fibrosum Cellular		1		
Neop M, Meso	5	3		
Papillar Pleur. Meso		1		
Pleur. Meso		1		
Poorly Differentiated Carcinoma		1		
Tubulo-Papillar, Spindle Cell		1		
Meso Malignum	1			
Other	1			
Spindle and Epitheloid	1			
<b>total</b>	<b>153</b>	<b>149</b>	<b>153</b>	<b>149</b>

# CLINICAL REVIEW

## Clinical Review Section

None of the results of the independent pathology subtype review and diagnoses were recorded in the DIAGDATA database (the CRF page is below) and there was no "blank" to record the information on the CRF.

*Site* Clinical Report Form  
 A Single-Arm Randomized Phase 3 Trial of MTA plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma  
 H3E-MC-IMCH Cycle (Max) 0

**DIAGNOSIS: INITIAL PATHOLOGICAL DIAGNOSIS**

Basis for diagnosis  (H) Histopathological

Pathological diagnosis code (Check one)  1000 Sarcomatoid Pleural Mesothelioma  
 2000 Epithelial Pleural Mesothelioma  
 3000 Mixed Cell Pleural Mesothelioma  
 9999 Other Specify diagnosis OADR

Date of initial pathological diagnosis (the Date Specimens Collected)  MM/DD/YYYY  
 MM DD YYYY

Grade of histopathological diagnosis (Check one)  100 Undifferentiated  
 200 Poorly Differentiated  
 300 Moderately differentiated  
 400 Well differentiated  
 999 Unknown

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37 alimta/cisplatin patients had their mesothelioma subtype changed or determined after independent pathology review; 27 cisplatin alone had the subtype changed or determined.

The table below illustrates the pattern of change in or determination of subtype diagnoses from the investigator to the independent review for the alimta/cisplatin arm.

**CHANGE IN PATHOLOGY FROM INVESTIGATOR TO INDEPENDENT REVIEW**

investigator's pathology	independent review pathology	alimta/cisplatin
Mixed Cell Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	17
Neop M, Meso	Malign. Meso, Epithelial Type, Pleur.	5
Sarcomatoid Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	3
Spindle and Epitheloid	Malign. Meso, Epithelial Type, Pleur.	1
Other	Malign. Meso, Epithelial Type, Pleur.	1
Biphasical Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	1

## CLINICAL REVIEW

### Clinical Review Section

investigator's pathology	independent review pathology	alimta/cisplatin
Epithelial Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	3
Meso Malignum	Malign. Meso, Mixed Type, Pleur.	1
Sarcomatoid Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	2
Epithelial Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	1
Mixed Cell Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	2

The table below illustrates the pattern of change in or determination of subtype diagnoses from the investigator to the independent review for the cisplatin alone arm.

#### CHANGE IN PATHOLOGY.FROM INVESTIGATOR TO INDEPENDENT REVIEW

investigator's pathology	independent review pathology	cisplatin alone
Biphasical Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1
Mixed Cell Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	12
Neop M, Meso	Malign. Meso, Epithelial Type, Pleur.	2
Neop M, NOS	Malign. Meso, Epithelial Type, Pleur.	1
Papillar Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1
Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1
Poorly Differentiated Carcinoma	Malign. Meso, Epithelial Type, Pleur.	1
Sarcomatoid Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	2
Tubulo-Papillar, Spindle Cell	Malign. Meso, Epithelial Type, Pleur.	1
Biphasical Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	1
Epithelial Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	2
Meso Fibrosum Cellular	Malign. Meso, Mixed	1

## CLINICAL REVIEW

### Clinical Review Section

	Type, Pleur.	
Mixed Cell Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	1

In both treatment arms, independent pathology review shifted more patients to the epithelial mesothelioma subtypes or good prognosis subtype. There was a moderate decrease in the mixed subtype or intermediate prognosis subtype. There was minimal change in the sarcomatoid subtype or poor prognosis subtype.

The two tables below illustrate the effect on prognosis due to the change in mesothelioma subtype from the investigators's site diagnosis to the independent pathology review diagnosis. Although there is an overall improvement in subtype prognosis, the changes appear balanced with respect to both treatment arms.

investigator's pathology	Independent review pathology	Alimta/cisplatin	change in prognosis or prognosis determination
Mixed Cell Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	17	intermediate • good
Neop M, Meso	Malign. Meso, Epithelial Type, Pleur.	5	good
Sarcomatoid Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	3	poor • good
Spindle and Epitheloid	Malign. Meso, Epithelial Type, Pleur.	1	intermediate • good
Other	Malign. Meso, Epithelial Type, Pleur.	1	good
Biphasical Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	1	unchanged
Epithelial Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	3	good • intermediate
Meso Malignum	Malign. Meso, Mixed Type, Pleur.	1	intermediate
Sarcomatoid Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	2	poor • intermediate
Epithelial Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	1	good • poor
Mixed Cell Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	2	intermediate • poor

## CLINICAL REVIEW

### Clinical Review Section

Investigator's pathology	Independent review pathology	cisplatin	change in prognosis or prognosis determination
Biphasical Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1	intermediate • good
Mixed Cell Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	12	intermediate • good
Neop M, Meso	Malign. Meso, Epithelial Type, Pleur.	2	good
Neop M, NOS	Malign. Meso, Epithelial Type, Pleur.	1	good
Papillar Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1	unchanged
Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	1	good
Poorly Differentiated Carcinoma	Malign. Meso, Epithelial Type, Pleur.	1	good
Sarcomatoid Pleur. Meso	Malign. Meso, Epithelial Type, Pleur.	2	poor • good
Tubulo-Papillar, Spindle Cell	Malign. Meso, Epithelial Type, Pleur.	1	intermediate • good
Biphasical Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	1	unchanged
Epithelial Pleur. Meso	Malign. Meso, Mixed Type, Pleur.	2	good • intermediate
Meso Fibrosum Cellular	Malign. Meso, Mixed Type, Pleur.	1	intermediate
Mixed Cell Pleur. Meso	Malign. Meso, Sarcomatoid Type, Pleur.	1	intermediate • poor

## CLINICAL REVIEW

### Clinical Review Section

#### Survival Analyses of Confirmed Mesothelioma Pathology

On page 962 of the JMCH study report was the following statement:

"Because there may be a discrepancy between the pathological diagnosis assessment of the independent reviewer and the investigator, data analysis will also be performed on all patients whose diagnoses were confirmed by the independent reviewer."

This analysis was not in the JMCH study report. Below is that analysis:

In the 9/22/2003 Lilly response, the following directions were provided in order that a survival analysis of the mesothelioma confirmed patients who were the randomized and treated and the fully folic acid/vitamin B12 supplemented on study JMCH.

In Stage A of the Alimta mesothelioma NDA, there is a SAS data file titled, "LABRESLT.XPT". This file is located in the Stage A of the NDA as follows:

N21462

CRT

datasets

JMCH

LABRESLT.XPT

Column 13 of this data file is titled TESTCODE. The test code for the diagnosis is "P14". In the rows where the TESTCODE equals "P14", the code for the diagnosis can be found in Column 20 titled "CHLBRSLT". The table below provides descriptions for the diagnosis.

As stated above, it is noted that the CRF page for INITIAL PATHOLOGICAL DIAGNOSIS did not indicate whether or not the diagnosis was the investigator's, independent reviewer's, or confirmed. Also, the CRF page LABORATORY VALUES (this page has the same SAS data file name and data file titles as the directions, i.e., LABRESLT, TESTCODE, CHLBRSLT) did not have a "blank" for pathological diagnosis nor did it indicate whether or not the diagnosis is the investigator's, independent reviewer's, or confirmed. The pages are below.

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# CLINICAL REVIEW

## Clinical Review Section

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All variables from QASDATA Database

Clinical Report Form  
A Single-Arm Randomized Phase 3 Trial of MTA  
plus Celecoxib versus Celecoxib in Patients with  
Metastatic Pleural Mesothelioma

Cycle (Year) 0

H3E-MC-JMCH  
**DIAGNOSIS: INITIAL PATHOLOGICAL DIAGNOSIS**

Basis for diagnosis

Histopathological

Pathological diagnosis code

C000 Sarcomatoid Pleural Mesothelioma

C001 Epithelial Pleural Mesothelioma

C002 Mixed Cell Pleural Mesothelioma

C999 Other Not Reported in Literature

Specify diagnosis code

Date of initial pathological diagnosis

(Use Date Specimen or Collection)

MM DD YYYY

Grade of histopathological diagnosis

(Check one)

U00 Undifferentiated

P00 Poorly Differentiated

M00 Moderately Differentiated

W00 Well Differentiated

Unknown

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Clinical Report Form  
A Single-Arm Randomized Phase 3 Trial of MTA  
plus Celecoxib versus Celecoxib in Patients with  
Metastatic Pleural Mesothelioma

Cycle (Year) 0

**LABORATORY VALUES: HEMATOLOGY**

NOT DONE

LABORATORY Name of Laboratory

LABORATORY Collection Date

MM DD YYYY

- Patient must have adequate bone marrow reserve (absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$ , platelets  $\geq 100 \times 10^9/L$ , and hemoglobin  $\geq 8 g/dL$ ).
- If a test was NOT run, enter a "-" in the Result column and do not check any boxes in the Unit column for that test.
- If a result is clinically significant, explain on the Comments page.
- If trends are reported, add to neutrophil count.

Test Name (ONDC)	Test Code	Result	UNITS	Unit
Hemoglobin	A02		<input type="checkbox"/> g/L, g/dL, g/dL, g/dL, g/dL	
H2C	A03		<input type="checkbox"/> %	
WBC	A10		<input type="checkbox"/> 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L	
			<input type="checkbox"/> cells/L, cells/mm <sup>3</sup>	
Neutrophils	A13		<input type="checkbox"/> 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L	
			<input type="checkbox"/> cells/L, cells/mm <sup>3</sup>	
			<input type="checkbox"/> %	
Lymphocytes	A14		<input type="checkbox"/> 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L	
			<input type="checkbox"/> cells/L, cells/mm <sup>3</sup>	
			<input type="checkbox"/> %	
Monocytes	A15		<input type="checkbox"/> 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L	
			<input type="checkbox"/> cells/L, cells/mm <sup>3</sup>	
			<input type="checkbox"/> %	
Eosinophils	A16		<input type="checkbox"/> 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L	
			<input type="checkbox"/> cells/L, cells/mm <sup>3</sup>	
			<input type="checkbox"/> %	
Basophils	A17		<input type="checkbox"/> 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L	
			<input type="checkbox"/> cells/L, cells/mm <sup>3</sup>	
			<input type="checkbox"/> %	
Platelets	A20		<input type="checkbox"/> 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L, 10 <sup>9</sup> /L	
			<input type="checkbox"/> cells/L, cells/mm <sup>3</sup>	

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## CLINICAL REVIEW

### Clinical Review Section

For the randomized and treated-mesothelioma confirmed patients, the results of the FDA survival analysis were:

RT-MESOTHELIOMA CONFIRMED	ALIMTA/CISPLATIN (N=153)	CISPLATIN ALONE (N=150)	p-value log-rank Wilcoxon
Survival, median (95% CI)	13 months (10.8, 14.8)	10.2 months (8, 12)	0.066 0.101

In the randomized and treated (RT) (n=303), the median survivals for alimta/cisplatin and cisplatin alone were 13 and 10.2 months, respectively (log-rank, p=0.066); this was a marginally statistically significant increase in median survival of 2.2 months.

For the fully folic acid/vitamin B12 supplemented-mesothelioma confirmed patients, the results of the FDA survival analysis were:

FOLIC ACID/VITAMIN B12 SUPPLEMENTED-MESOTHELIOMA CONFIRMED	ALIMTA/CISPLATIN (N=111)	CISPLATIN ALONE (N=109)	p-value log-rank Wilcoxon
Survival, median (95% CI)	14.4 months (12.1, 15.7)	10.3 months (8, 12.2)	0.058 0.045

In the subgroup of the fully folic acid and vitamin B12 supplemented patients (n=220), the median survivals for alimta/cisplatin and cisplatin alone were 14.4 and 10.3 months, respectively (log-rank, p=0.058); this was a marginally statistically significant increase in median survival of 4.1 months.

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# CLINICAL REVIEW

## Clinical Review Section

### Gender Survival Analysis

Below are the results of the FDA statistician's gender survival analysis of study JMCH.

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

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=168)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Multivariate Analysis</b>						
<b>p-value<sup>a</sup></b>						
Treatment	0.011		0.008		0.995	
Gender	0.489		0.483		0.998	
Treatment * Gender	0.072		0.035		0.604	
<b>Hazard Ratio (95% CI)<sup>b</sup></b>						
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)	
<b>Male</b>						
Total number of patients	184	181	136	134	48	47
Patients with event <sup>b</sup>	124 (67)	130 (72)	82 (60)	85 (63)	42 (87)	45 (96)
<b>Survival time (months)</b>						
Median (95% CI)	11.0 (9.4, 13.3)	9.4 (7.9, 10.8)	12.8 (9.9, 14.6)	10.4 (8.7, 13.2)	9.85 (8.1, 11.0)	7.1 (6.5, 9.9)
<b>p-value<sup>c</sup></b>						
Long-rank	0.176		0.388		0.219	
Wilcoxon	0.233		0.390		0.343	
Hazard Ratio (95% CI) <sup>d</sup>	0.843 (0.66, 1.08)		0.875 (0.65, 1.18)		0.767 (0.50, 1.17)	
<b>Female</b>						
Total number of patients	42	41	32	29	10	12
Patients with event <sup>b</sup>	21 (50)	29 (71)	13 (41)	18 (62)	8 (80)	11 (92)
<b>Survival time (months)</b>						
Median (95% CI)	15.7 (10.6, 25.8)	7.5 (5.8, 11.9)	18.9 (15.3, -)	7.4 (5.5, 12.2)	8.2 (5.4, 20.6)	9.3 (5.7, 12.0)
<b>p-value<sup>c</sup></b>						
Long-rank	0.012		0.010		0.878	
Wilcoxon	0.008		0.003		0.913	
Hazard Ratio (95% CI) <sup>d</sup>	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.

<sup>a</sup> Multivariate analysis is based on a multivariate Cox regression model with treatment, covariate, interaction.

<sup>b</sup> Patients were died by different reasons: study disease related, study toxicity, and other causes.

<sup>c</sup> P-value is based on the test results for the two treatment groups.

<sup>d</sup> Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

In the multivariate analysis, there was an interaction of treatment and gender that was marginally significant in the randomized and treated population ( $p=0.072$ ); in the fully folic acid/vitamin B12 supplemented population, this interaction was statistically significant ( $p=0.035$ ); the interaction was not statistically significant for the partially supplemented/never supplemented population ( $p=0.604$ ).

## CLINICAL REVIEW

### Clinical Review Section

In the female subgroup, the analysis showed that alimta/cisplatin was favored over cisplatin alone in the randomized and treated population and the fully folic acid/vitamin B12 supplemented population (log-rank:  $p=0.012$  and  $p=0.010$ , respectively); although there was a trend in favor of the alimta/cisplatin arm, it was not significant in the partially supplemented+never supplemented population. Although the male population was four-fold greater than the female population (i.e., more power), there were trends in favor of alimta/cisplatin in all the treatment populations but none was statistically significant.

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# CLINICAL REVIEW

## Clinical Review Section

### Race Survival Analysis

Below are the results of the FDA statistician's race survival analysis of study JMCH.

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

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
<b>Multivariate Analysis</b>						
<b>p-value<sup>a</sup></b>						
Treatment	0.581		0.566		0.114	
Race	0.674		0.821		0.478	
Treatment * Race	0.901		0.238		0.173	
<b>Hazard Ratio (95% CI)<sup>d</sup></b>						
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)	
<b>Conclusion</b>						
Total number of patients	204	206	150	153	54	53
Patients with event <sup>b</sup>	132 (65)	147 (71)	84 (56)	56 (63)	48 (89)	50 (94)
<b>Survival time (months)</b>						
Median (95% CI)	12.2 (10.1, 14.4)	9.3 (7.8, 10.8)	13.3 (12.1, 13.3)	10.2 (8.5, 12.2)	9.3 (7.1, 10.8)	7.2 (6.4, 10.7)
<b>p-value<sup>c</sup></b>						
Long-rank	0.024		0.026		0.487	
Wilcoxon	0.030		0.021		0.693	
Hazard Ratio (95% CI) <sup>d</sup>	0.762 (0.60, 0.97)		0.717 (0.54, 0.96)		0.868 (0.58, 1.29)	
<b>Others</b>						
Total number of patients	22	16	18	10	4	6
Patients with event <sup>b</sup>	13 (59)	12 (75)	11 (61)	6 (60)	2 (50)	6 (100)
<b>Survival time (months)</b>						
Median (95% CI)	9.0 (6.7, 17.2)	8.4 (6.6, 12.9)	8.8 (6.2, 16.0)	9.55 (6.6, -)	17.2 (9.8, -)	8.0 (6.4, 10.7)
<b>p-value<sup>c</sup></b>						
Long-rank	0.715		0.619		0.093	
Wilcoxon	0.894		0.596		0.077	
Hazard Ratio (95% CI) <sup>d</sup>	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.

<sup>a</sup> Multivariate analysis is based on a multivariate Cox regression model with treatment, covariate, interaction.

<sup>b</sup> Patients were died by different reasons: study disease related, study toxicity, and other causes.

<sup>c</sup> P-value is based on the test results for the two treatment groups.

<sup>d</sup> Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

In multivariate analysis, there was no interaction of treatment and race that was statistically significant for the randomized and treated population, fully folic acid/vitamin B12 supplemented population, and partially supplemented+never supplemented population (p-values: 0.901, 0.238, 0.173, respectively).

In the white subgroup, the analysis showed that alimta/cisplatin was favored over cisplatin alone in the randomized and treated population and the fully folic acid/vitamin B12 supplemented population (log-rank: p=0.024 and p=0.026, respectively); although there was a trend in favor of the alimta/cisplatin arm, it was not significant in the partially supplemented+never supplemented population (p=0.487). There was a trend in favor of alimta/cisplatin in the randomized and treated populations for the non-white subgroup; in the fully supplemented group, the trend was in favor of the cisplatin alone arm; the never supplemented group was marginally statistically significant (p=0.093).

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# CLINICAL REVIEW

## Clinical Review Section

### Age Survival Analysis

Below are the results of the FDA statistician's age survival analysis of study JMCH.

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

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
<b>Multivariate Analysis</b>						
<b>p-value<sup>a</sup></b>						
Treatment	0.410		0.546		0.448	
Age (< 65 years)	0.584		0.621		0.556	
Treatment * Age	0.447		0.453		0.950	
<b>Hazard Ratio (95% CI)<sup>d</sup></b>						
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)	
<b>Age (&lt; 65 years)</b>						
Total number of patients	143	136	107	97	36	39
Patients with event <sup>b</sup>	88 (61)	95 (70)	57 (53)	58 (60)	31 (86)	37 (95)
<b>Survival time (months)</b>						
Median (95% CI)	13.3 (10.7, 15.7)	10.2 (8.4, 11.9)	14.7 (11.7, 17.6)	10.8 (8.7, 12.7)	9.4 (7.9, 14.0)	9.3 (6.6, 12.0)
<b>p-value<sup>c</sup></b>						
Long-rank	0.020		0.052		0.277	
Wilcoxon	0.076		0.079		0.643	
<b>Hazard Ratio (95% CI)<sup>d</sup></b>						
	0.704 (0.53, 0.95)		0.693 (0.48, 1.00)		0.760 (0.46, 1.25)	
<b>Age (≥ 65 years)</b>						
Total number of patients	83	86	61	66	22	20
Patients with event <sup>b</sup>	57 (69)	64 (74)	38 (62)	45 (78)	19 (86)	19 (95)
<b>Survival time (months)</b>						
Median (95% CI)	10.0 (8.3, 12.9)	7.5 (6.2, 10.4)	12.2 (7.9, 14.4)	8.7 (6.8, 14.2)	9.7 (5.1, 12.3)	6.45 (4.2, 9.3)
<b>p-value<sup>c</sup></b>						
Long-rank	0.376		0.503		0.457	
Wilcoxon	0.186		0.311		0.418	
<b>Hazard Ratio (95% CI)<sup>d</sup></b>						
	0.850 (0.59, 1.22)		0.862 (0.56, 1.33)		0.783 (0.41, 1.49)	

<sup>a</sup> Statistical reviewer's results based on the analysis data sets provided by the sponsor.  
<sup>b</sup> Multivariate analysis is based on a multivariate Cox regression model with treatment, covariates, interaction.  
<sup>c</sup> Patients were died by different reasons: study disease related, study toxicity, and other causes.  
<sup>d</sup> P-value is based on the test results for the two treatment groups.  
<sup>e</sup> Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

The comparison were for age < 65 years and age ≥ 65 years. In the multivariate analysis, there was no interaction of treatment and age that was statistically significant for the randomized and treated population, fully folic acid/vitamin B12 supplemented population, and partially supplemented+never supplemented population (p-values: 0.447, 0.453, 0.95, respectively).

In the subgroup age (< 65 years), the analysis showed that alimta/cisplatin was favored over cisplatin alone in the randomized and treated population and the fully folic acid/vitamin B12 supplemented population (log-rank: p=0.02 and p=0.052, respectively); there was no trend in favor of the alimta/cisplatin arm in the partially supplemented+never supplemented population (p=0.277). There were trends in favor of alimta/cisplatin in all the treatment populations for the subgroup of age (≥ 65 years), but none were statistically significant (p-values: 0.376, 0.503, and 0.457, respectively);

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### Summary of the FDA's Survival Analyses of Study JMCH

#### FDA SURVIVAL ANALYSES OF STUDY JMCH

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Randomized and treated (n=448)	12.1 months	9.3 months	0.021
Fully folic acid/vitamin B12 supplemented (n=331)	13.3 months	10 months	0.051
Partial supplemented + never supplemented (n=117)	9.5 months	7.2 months	0.253
Intent-to-treat (n=456)	12 months	9.3 months	0.0205
Confirmed mesothelioma pathology	13 months	10.2 months	0.066
Randomized and treated (n=303)			
Confirmed mesothelioma pathology	14.4 months	10.3 months	0.058
Fully folic acid/vitamin B12 supplemented (n=220)			
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388
Race White	12.2 months	9.3 months	0.024

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GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Randomized and treated (n=410)			
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white Fully folic acid/vitamin B12 supplemented (n=28)	8.8 months	9.55 months	0.619
Age < 65 years Randomized and treated (n=279)	13.3 months	10.2 months	0.02
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

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

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

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

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### 3.4 FDA's Assessment of Tumor Response in Study JMCH

#### Introduction

#### The Role of Lilly and \_\_\_\_\_

At Lilly's request, \_\_\_\_\_ provided medical imaging core laboratory services in support of Protocol JMCH. \_\_\_\_\_ was contracted to collect, quality control and translate Computerized Tomography (CT) scans obtained on patients enrolled in this trial. Additionally, \_\_\_\_\_ was to perform preliminary lesion quantitation, program a Computer Assisted Masked Read (CAMR) system and conduct a blinded read of trial-related images. Two readers reviewed the data and a third reader functioned as an adjudicator to review any discrepancies in the Best Overall Response. The CAMR for this study consisted of two separate sessions, each of which was designed to derive an interpretation in an unbiased fashion.

\_\_\_\_\_ was sent directly to Lilly in Indianapolis. Lilly forwarded all of the imaging data to \_\_\_\_\_. A total of 428 patients were received which included 3588 timepoints, 1659 timepoints were quantitated. All CT scans obtained on patients enrolled in Protocol JMCH were read by two readers who had no knowledge of patient identity, medical history or treatment group. If either reader disagreed a third reader (adjudicator) was used to read the patients. His decision was final. The readers were oriented to the CAMR process by \_\_\_\_\_ and Lilly personnel. The reader was responsible for reading all two CAMR sessions.

Two independent readers and an Adjudicator were selected for Protocol JMCH. The two readers \_\_\_\_\_ MD, who was a radiologist employed by \_\_\_\_\_ and \_\_\_\_\_ MD, who was a pulmonologist employed by the \_\_\_\_\_ were recommended by Lilly. \_\_\_\_\_ MD, a radiologist at the \_\_\_\_\_ was the adjudicator for this study. All reads took place in the \_\_\_\_\_ headquarters in \_\_\_\_\_ on the dates indicated below:

**JMCH Read Dates**

READ DATES	NO. PTS READ	/ READ DATES	NO. PTS READ	/ READ DATES	NO. PTS READ
30-Mar-2001	32	30-Mar-2001	13	11-Aug-2001	22
20-Apr-2001	6	16-May-2001	66	15-Dec-2001	54
07-Jun-2001	61	26-Jul-2001	84	12-May-2002	7
31-Jul-2001	Blank in report	03-Oct-2001	84		
25-Sep-2001	62	29-Nov-2001	144		
12-Nov-2001	98	25-Feb-2002	6		
13-Nov-2001					
05-Dec-2001	68				
12-Apr-2001	6				

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Exports were sent to Lilly in SAS format on the following dates:

08-Aug-2001 sample

14-Aug-2001

20-Dec-2001

18-Jan-2002

14-May-2002<sup>160</sup>

### The Role of the FDA

In consultation with of Dr. George Mills (OND/ODEVI/DTBOP), radiologist, images were reviewed from study JMCH.

— loaded the independent review database on the imaging review system in Dr. Mill's office. The system was fully functional and presented the available CT scans and the independent review findings.

Dr. Mills and the Medical Officer (FDA Imaging Reviewers) reviewed subject image files during multiple review sessions. The Medical Officer chose the cases for review from a list of subjects (Desk copy Lilly list of all responders by study site [10/22/2003]) for each CDER imaging review session. In the course of the review, the Medical Officer identified the subject case numbers and Dr. Mills selected the case by the stated number from the imaging dataset and independently interpreted the images for tumor burden and response for the various time points. These assessments were correlated with the independent reviewer assessments documented in the imaging database.

The focus of the FDA Imaging Review was on the Lilly list of alimta + cisplatin responders. The FDA believed that these were the protocol-specified responders. For quality assurance reasons, review of the cisplatin alone arm would have required review of all the images from that arm; time limitations for the review restricted the review for response to the alimta + cisplatin arm. For purposes of comparison, the cisplatin alone responders will be referred to as Listed responders and not FDA confirmed responders.

With regard to the independent reviewers' evaluation in the database, the FDA imaging review included review of the measurements of lesions recorded by the independent reviewers, cursory calculations of baseline and follow-up evaluations for response, sites of disease evaluation, cycle by cycle evaluation of response by each independent reviewer, and overall response determination. The review of the images for response included: a) focusing on evaluation timepoints that the independent reviewers scored a response, and b) confirmation of response, or progressive disease.

<sup>160</sup> The ASCO Plenary Session, where the results of JMCH were presented, was on May 20, 2002.

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The Medical Officer received from Lilly a laptop that contained the \_\_\_\_\_ of the independent reviewers' evaluations. This was not a searchable database. The information in the database was used: a) to do response calculations from the measurements recorded by the independent reviewers, b) to identify patients whose images were not contained in the database, c) to compare the Lilly list of alimta + cisplatin responders with the overall response determination by the independent reviewers of alimta + cisplatin responders, d) to identify, in all cases, the type of measurable disease evaluated by the independent reviewers, i.e., unidimensional and/or bidimensional disease, e) to identify cases who the independent reviewer(s) did not record measurements of disease, and f) to identify cases that the independent reviewer(s) evaluated metastatic disease, i.e., liver metastases. There was no verification of the time of response confirmation, i.e., the difference in the dates of response and confirmation of response were not checked.

Also, the Medical Officer supplemented the review with the following items:

- Case report forms
- Investigator lesion measurements in SITINVOL dataset
- Overall response from OVRRESP dataset

Prospectively, the review of the JMCH images was intended to validate alimta + cisplatin arm responders. Retrospectively, due to deficiencies detected, the review involved: a) review of the listed alimta + cisplatin responders, b) review of the independent review-determined alimta + cisplatin responders, c) independent reviewers' assessments of distant metastases, measurability of disease, determinations of unidimensional and bidimensional disease, d) missing patients in the independent review of images, and e) the independent review process.

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### Missing Images

456 patients were enrolled in JMCH. 448 patients were randomized and treated. According to the final report of the Computer Assisted Masked Read Methodology Report of Protocol JMCH, dated October 28, 2002, <sup>161</sup> imaging data was sent directly to Lilly. Lilly forwarded all of the imaging data to —. Imaging data on a total of 428 patients were received<sup>162</sup>. However, based on the number of patients read by Dr. —, only 397 patients had their images read (the number recorded for Dr. — was 333).

During the review of the 94 alimta + cisplatin responders on the list provided by Lilly, FDA Imaging Reviewers noted that patients #503-5052, #601-6007, and #851-8512 were absent from the imaging database. The entire database of both alimta + cisplatin and cisplatin alone patients was examined. There were 55 additional patients with whole sets of images missing from the imaging database and thus, not reviewed by the independent reviewers. The table below contains the 58 patients with whole sets of images missing from the imaging database.

PATIENT #	ARM <sup>163</sup>	US CITY OR COUNTRY	LISTED AS RESPONDER
101-1017	c	NJ	no
102-1022	c	Pittsburgh	no
104-1043	a	NY	no
107-1074	a	Baltimore	no
109-1092	a	Houston	no
111-1342	c	Turkey	no
111-1354	a	Turkey	no
111-1357	c	Turkey	no
112-1290	c	Czech Republic	no
114-1402	a	Slovakia	no
118-1133	c	Miami	no
124-1201	a	Wisconsin	no
126-1222	c	Colorado	no
136-1634	c	Los Angeles	no
141-1463	c	Louisiana	no
142-1472	c	Cleveland	no
150-1580	a	Czech Republic	no
150-1582	c	Czech Republic	no
201-2187	c	Mexico City	no

<sup>161</sup>

<sup>162</sup> There has been no audit of the completeness of the images: 1) performed at site, 2) submitted to Lilly, 3) submitted to —, and 4) reviewed by the independent reviewers.

<sup>163</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

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PATIENT #	ARM <sup>163</sup>	US CITY OR COUNTRY	LISTED AS RESPONDER
201-2191	a	Mexico City	no
201-2200	c	Mexico City	no
213-2133	c	Belgium	no
214-2148	a	Belgium	no
214-2401	c	Belgium	no
301-3159	a	France	no
301-3161	a	France	no
402-4025	a	Germany	no
402-4036	a	Germany	no
409-4164	c	Germany	no
409-4333	c	Germany	no
413-4241	a	Germany	no
413-4243	c	Germany	no
413-4244	a	Germany	no
453-4519	a	India	no
501-5007	a	Italy	no
501-5062	c	Italy	no
502-5017	c	Italy	no
502-5052	a	Italy	yes
502-5054	a	Italy	no
510-5109	a	Australia	no
510-5144	c	Australia	no
513-5121	a	Australia	no
552-5508	a	Argentina	no
558-5537	c	Chile	no
558-5538	a	Chile	no
558-5541	c	Chile	no
601-6005	a	Spain	no
601-6007	a	Spain	yes
601-6008	c	Spain	no
601-6010	c	Spain	no
601-6011	a	Spain	no
601-6014	c	Spain	no
804-8040	a	UK	no
804-8044	a	UK	no
851-8512	a	Poland	yes
412-4221	c	Germany	no
513-5125	c	Australia	no
556-5526	a	Argentina	no

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Only three of these cases were listed as responders; the FDA requested these images from Lilly. The independent reviewers did not review these alimta + cisplatin patients who were listed as responders. Patient #851-8512 was a responder by FDA review of images. Patient #502-5052, was not a responder by FDA review of images. The FDA did not review patient #601-6007 because according to a Lilly correspondence about this patient, there was either no baseline scan or baseline scans were incomplete<sup>164</sup>.

After FDA request, the scans for the following formerly missing scans (n=26) were provided by Lilly. The independent reviewers did not review these patients' images. The FDA reviewed these images for the presence of measurable disease and liver metastases. The FDA did not evaluate the images for response.

PATIENT#	ARM <sup>165</sup>	IMAGES RECEIVED AFTER REQUEST	MEASURABLE DISEASE/LIVER METS
107-1074	a	received 8/28/2003	yes/no
111-1354	a	Received 8/28/2003	yes/no
111-1357	c	Received 8/28/2003	yes/no
114-1402	a	Received 8/28/2003	yes/no
124-1201	a	received 8/28/2003	yes/no
150-1582	c	received 8/28/2003	NO/no
201-2187	c	received 8/28/2003	yes/no
201-2191	a	received 8/28/2003	yes/no
214-2148	a	received 8/28/2003	yes/no
214-2401	c	received 8/28/2003	yes/no
402-4025	a	received 8/28/2003	yes/space-occupying lesion
402-4036	a	received 8/28/2003	yes/no
409-4164	c	received 8/28/2003	yes/no
413-4241	a	received 8/28/2003	yes/no
413-4243	c	received 8/28/2003	yes/no scans of abdomen
413-4244	a	received 8/28/2003	yes/no
453-4519	a	received 8/28/2003	yes/no
501-5007	a	received 8/28/2003	yes/no
501-5062	c	received 8/28/2003	yes/no
502-5017	c	received 8/28/2003	yes/no
510-5144	c	received 8/28/2003	yes/no
513-5121	a	received 8/28/2003	yes/no
552-5508	a	received 8/28/2003	yes/no
601-6005	a	received 8/28/2003	yes/no scans of liver except for 1 cut of liver
804-8040	a	received 8/28/2003	yes/no
804-8044	a	received 8/28/2003	yes/no

Except for one patient (#150-1582), all of these patients had measurable disease at baseline. One patient did not have the protocol-specified abdominal CT scan and another patient had only one cut of the liver<sup>166</sup>. Only one patient, #402-4025, had a space-occupying lesion in the liver.

<sup>164</sup> Eligibility could not be confirmed on this patient.

<sup>165</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

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After FDA request, the following missing scans of 30 patients were not provided to the FDA. The presence of measurable disease--an eligibility criterion--could not be verified in these patients. The presence or absence of liver metastases could not be verified in these patients. The independent reviewers did not review these patients' images. No secondary review for disease measurability (and study eligibility) was performed.

PATIENT#	ARM <sup>167</sup>	SPONSOR RESPONSE TO FDA REQUEST FOR SCANS
101-1017	c	scans not available
102-1022	c	scans not available
104-1043	a	scans not available
109-1092	a	scans not available
111-1342	c	patient did not receive drug
112-1290	c	either no baseline scan or baseline scans incomplete
118-1133	c	scans not available
126-1222	c	either no baseline scan or baseline scans incomplete
136-1634	c	patient did not receive drug
141-1463	c	either no baseline scan or baseline scans incomplete
142-1472	c	patient did not receive drug
150-1580	a	either no baseline scan or baseline scans incomplete
201-2200	c	patient did not receive drug
213-2133	c	patient did not receive drug
301-3159	a	scans not available
301-3161	a	patient did not receive drug
409-4333	c	scans not available
502-5054	a	either no baseline scan or baseline scans incomplete
510-5109	a	patient did not receive drug
558-5537	c	either no baseline scan or baseline scans incomplete
558-5538	a	either no baseline scan or baseline scans incomplete
558-5541	c	either no baseline scan or baseline scans incomplete
601-6007	a	either no baseline scan or baseline scans incomplete
601-6008	c	either no baseline scan or baseline scans incomplete
601-6010	c	scans not available
601-6011	a	either no baseline scan or baseline scans incomplete
601-6014	c	patient did not receive drug
412-4221	c	Lilly received scans
513-5125	c	none of the imaging data was digitized--patient was screen failure <sup>168</sup>
556-5526	a	none of the imaging data was digitized--patient was screen failure <sup>169</sup>

<sup>166</sup> These should be protocol violations.

<sup>167</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

<sup>168</sup> Patient's lot number for cisplatin was listed on p. 1865 of the JMCH study report.

<sup>169</sup> Patient's lot numbers for alimta and cisplatin were listed on p. 1822 of the JMCH study report.

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### Clinical Review Section

Below are the numerical values for the reasons the scans were not provided to the FDA. Over 60% of these scans (19 of 30) were not done at baseline, incomplete at baseline, or not available.

REASONS FOR NOT PROVIDING THE FDA (AND INDEPENDENT REVIEWERS WITH THE SCANS)	NUMBER OF PATIENTS WITH MISSING SCANS
either no baseline scan or baseline scans incomplete	11
scans not available	8
patient did not receive drug	8
none of the imaging data was digitized--patient was screen failure	2
Lilly received scans	1

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## CLINICAL REVIEW

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#### Subjects with No Disease Measured by Both Independent Reviewers

The following is taken from the final report of the Computer Assisted Masked Read Methodology Report of Protocol JMCH, dated October 28, 2002.<sup>170</sup> The FDA Medical Reviewer inserted the *italics*.

"Another core laboratory service provided by \_\_\_\_\_ for Protocol H3E-MC-JMCH was the *pre-quantification of lesions on the CT scans*. This function was performed in order to expedite review of lesions during the blinded reads of the CT data. All measurements performed by \_\_\_\_\_ were overread by a physician as part of the blinded read sessions." (page 6)

"Uni-dimensional (rind thickness, drawn manually) and Bi-dimensional (cross product) measurement techniques were employed to measure pleural based disease. \_\_\_\_\_ was to identify up to nine index lesions for measurement. An index lesion was defined as one that met certain minimum size criteria for the rind thickness (uni) or lesion diameter (bi)." (page 7)

"The purpose of Session #1 of the JMCH Computer Assisted Masked Read (CAMR) was to provide an overall assessment of each available CT scan for a given patient. This session required an assessment of the overall technical adequacy of the images and definition and characterization of the index lesions to be followed through all other CAMR sessions." (page 9)

"Upon selection of a patient for review, the Screening CT scan was displayed. Once technical adequacy was rated, *the reader was prompted to identify the presence or absence of lesions. If the presence of lesions was indicated, the reader was then to determine the number of index lesions that were present.* The CAMR accepted the designation of up to six (6) index lesions per patient. Index lesions were to be measurable which, by definition, meant that they were to have bidimensional measurements of  $\geq 0.8 \times 0.8$  cm." (page 9)

"Session 1 also requested the identification of the number of "evaluable" lesions present, representing those that were to be visually evaluated during future sessions but did not meeting (sic) *the measurability criterion*. In determining the index lesions and the evaluable non-index lesions, the reader was required to review all \_\_\_\_\_-generated Regions of Interest (ROIs). *Any ROIs that did not meet the measurability criterion for index lesions were to be deleted by the reader.* After the identification of index and evaluable lesions, Session 1 required the reader to characterize each index lesion. This required the entry of a label, by which each lesion would be identified during subsequent CAMR sessions, and information on the location of each lesion." (page 10)

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There were 20 cases that both the independent reviewers did not record any measurable disease. *This was important because: 1) eligible patients were required to have measurable lesions with clearly defined margins by computerized tomography (CT) or MRI; 2) pleural effusions were not considered measurable; 3) patients were excluded who had disease which could not be radiologically imaged; and 4) degree of measurability of disease was a stratification factor.* For patient #302-3023, the adjudicator wrote, "Pt failed eligibility." For patient #804-8055, the baseline CT scan report from the investigator's site stated, "in the absence of any definite solid tumour I am uncertain whether the patient qualifies for the trial." The table below has the 20 cases that both the independent reviewers did not record any measurable disease.

PATIENT#	ARM <sup>171</sup>	US CITY OR COUNTRY	LISTED AS RESPONDER	ADJUDICATOR: NO MEASURABLE DISEASE	TECHNICAL COMMENT (S) FROM DATABASE
119-1141	a	NY	No	Yes	Optimal x 3 readers
130-1266	a	Chicago	Yes		Optimal x 2 readers
131-1286	c	Dallas	Yes		Not readable x 2
140-1450	a	NY	No		Not readable x 2
302-3023	a	France	No	yes: adjudicator stated "Pt failed eligibility."	Not readable by #1; optimal by other 2
409-4332	a	Germany	Yes	pleural effusion by #2	Optimal x 2 readers
453-4512	a	India	No		Not optimal @ baseline but readable by #1 then optimal; readable not optimal for all by #2
453-4513	a	India	No	#2 @ visit 2 no measurement possible	readable not optimal by both
453-4514	a	India	No	yes: adjudicator stated "no scale bar-can't measur"	not readable by #1; readable not optimal by other 2
453-4515	c	India	No		readable not optimal by both @ baseline; optimal by both @ visit 2 then readable not optimal by both at last evaluation
453-4516	a	India	No		readable not optimal by both; #2 multi-image, can't measure
502-5055	c	Italy	No	pleural effusion by #2	optimal by both
503-5024	c	Italy	No		optimal by both
510-5110	a	Australia	Yes		no measurements (0.0 by #1); optimal by #1; readable not optimal by #2; no scale bar at BL by both
512-5111	a	Australia	Yes		optimal by both
720-7203	a	Finland	No		optimal by #1; readable not optimal by #2

<sup>171</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

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PATIENT#	ARM <sup>171</sup>	US CITY OR COUNTRY	LISTED AS RESPONDER	ADJUDICATOR: NO MEASURABLE DISEASE	TECHNICAL COMMENT (S) FROM DATABASE
804-8055	a	UK	Yes	pleural effusion by both	optimal by both
851-8519	c	Poland	Yes		optimal by both
852-8521	a	Poland	No		readable not optimal by both; no measurable disease
852-8523	c	Poland	Yes		not readable #1; readable not optimal by other 2 (optimal for other 2 evaluations)

In response to FDA request for clarification, for patients #852-8521, #852-8523, and #302-3023, Lilly stated they had no scans to review.

Also, for patients #512-5111 and #804-8055, who were listed as alimta/cisplatin responders, Lilly claimed that the patients had stable and progressive disease, respectively.<sup>172</sup>

Five of these cases were listed as alimta responders. As indicated below, only one of them was a responder after FDA review of the images.

PATIENT #	ARM <sup>173</sup>	LISTED AS RESPONDER	RESPONSE BY FDA REVIEW OF IMAGES OF LISTED ALIMTA RESPONDERS
130-1266	a	yes	no
409-4332	a	yes	no; pleural effusion
510-5110	a	yes	YES
512-5111	a	yes	no; fluid
804-8055	a	yes	no; fluid

The assessment by \_\_\_\_\_ and the independent reviewers was also to serve as check for the presence or absence of measurable disease--an eligibility criterion. The eligibility of many of these patients was questionable.

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<sup>172</sup> Lilly response to FDA query dated 12/4/2003

<sup>173</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

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### Clinical Review Section

#### Subjects with No Disease Measured by One or More Independent Reviewers and the Independent Adjudicator

There were 37 cases that one or more independent reviewers and the independent adjudicator measured no disease although per protocol measurable disease was an eligibility criterion. *This was important because: 1) eligible patients were required to have measurable lesions with clearly defined margins by computerized tomography (CT) or MRI; 2) pleural effusions were not considered measurable; 3) patients were excluded who had disease which could not be radiologically imaged; and 4) degree of measurability of disease was a stratification factor.*

PATIENT#	ARM <sup>174</sup>	US CITY OR COUNTRY	LISTED AS RESPONDER	COMMENT <sup>175</sup>
103-1031	c	Chicago	no	no measurements #1; u for #2
113-1301	c	Czech Republic	yes	no measurements for #1; u for #2 and adjudicator
114-1403	c	Slovakia	yes	u by #2; no measurements for #1
119-1144	c	NY	no	u by #2; no measurements by #1
119-1147	c	NY	no	u by #2; no measurements by #1
125-1216	a	San Francisco	no	no measurements by #1 and adjudicator; u by #2
141-1461	a	Louisiana	yes	no measurements #1; b by #2
142-1475	a	Cleveland	no	no measurements #1; u by #2
301-3155	c	France	no	no measurements by #1; u by #2
301-3162	c	France	no	no measurements by #1 & adjudicator; u by #2
302-3022	C	France	no	no measurable disease #1; u by #2
302-3024	A	France	no	no measurable disease by #1; b by #2 and adjudicator
302-3025	a	France	no	no measurable disease by #1; b by #2: liver mets.
308-3180	c	France	no	no measurements by #1; b by #2: liver mets
401-4004	a	Germany	yes	no measurements by #1 & adjudicator; u by #2
401-4014	c	Germany	yes	no measurements by #1; u by #2
402-4301	c	Germany	no	u described for #2; no lesion described for #1
451-4509	a	India	yes	u by #2; no measurable disease by #1
452-4502	c	India	no	no measurements by #1 and adjudicator; u by #2; #2 called PR
501-5008	c	Italy	yes	u by #2; no measurements by #1
501-5061	a	Italy	yes	u by #2; no measurements by #1
502-5014	a	Italy	no	u by #2; no measurable disease by #1
502-5020	c	Italy	no	u by #2; no measurable disease by #1
505-5046	a	Italy	yes	no measurements by #1; u by #2
510-5143	a	Australia	yes	no measurements #1 & adjudicator; u by #2
510-5147	a	Australia	yes	no measurements #1 & adjudicator; b by #2
512-5116	c	Australia	yes	no measurements by #1 & #2; u by adjudicator
557-5531	c	Argentina	no	u by #1; no measurements by #2

<sup>174</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

<sup>175</sup> #1 refers to independent reviewer #1; #2 refers to independent reviewer #2. Key u=unidimensional disease; b=bidimensional disease

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PATIENT#	ARM <sup>174</sup>	US CITY OR COUNTRY	LISTED AS RESPONDER	COMMENT <sup>175</sup>
601-6009	a	Spain	no	no measurements #1; b by #2
601-6013	a	Spain	no	no measurements #1; u by #2
720-7200	a	Finland	no	no measurements for #1 & adjudicator; u only for #2;
720-7206	a	Finland	no	no measurements #1; b by #2
720-7212	a	Finland	yes	no measurements #1; b #2 and adjudicator
721-7225	a	Finland	yes	no measurements by #1 (not readable); u by #2
804-8047	c	UK	yes	no measurable disease by #1 & adjudicator; u by #2
850-8503	a	Poland	no	no measurements by #1; b by #2
851-8511	c	Poland	no	b #2; no measurements #1

Independent reviewer #1 recorded no measurable disease for 36 cases. Independent reviewer #2 recorded no measurable disease for 2 cases. The adjudicator recorded no measurable disease for 8 cases. There were 9 cases that 2 out of 3 independent reviewers did not record measurable disease. There were 3 cases that 2 out of 3 independent reviewers *did* record measurable disease.

In response to FDA response for clarification, for patients #119-1144, #142-1475, #301-3155, #301-3162, #302-3022, #302-3024, and #308-3180, Lilly stated they had no scans available to review.<sup>176</sup>

For patients, #141-1461, #401-4004, and #510-5143, who were listed as alimta/cisplatin responders, Lilly claimed that the patients had stable disease. Also, regarding patient # 510-5147, who was listed as an alimta/cisplatin responder, Lilly claimed that the patient had progressive disease.<sup>177</sup>

Nine of these cases were listed as alimta responders. As indicated below, only two of them were responders after FDA review of the images.

PATIENT#	ARM <sup>178</sup>	LISTED AS RESPONDER	RESPONSE BY FDA REVIEW OF IMAGES OF LISTED ALIMTA RESPONDERS
141-1461	a	yes	no
401-4004	a	yes	No; more fluid
451-4509	a	yes	YES
501-5061	a	yes	no: not impressive disease
505-5046	a	yes	no; fluid reduction, not a decrease in tumor
510-5143	a	yes	no; reduction in fluid
510-5147	a	yes	no; minimal disease
720-7212	a	yes	YES

<sup>176</sup> Lilly response to FDA query dated 12/4/2003

<sup>177</sup> Lilly response to FDA query dated 12/4/2003

<sup>178</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

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PATIENT#	ARM 178	LISTED AS RESPONDER	RESPONSE BY FDA REVIEW OF IMAGES OF LISTED ALIMTA RESPONDERS
721-7225	a	yes	no; artifact • cannot review films

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ON ORIGINAL

## CLINICAL REVIEW

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#### Subjects with Liver Metastases at Baseline by at Least One Independent Reviewer or FDA

Malignant pleural mesothelioma is a malignancy characterized by local progression with rare hematogenous spread compared to adenocarcinoma of the lung--a malignancy with common hematogenous spread. However, for malignant pleural mesothelioma, distant metastatic disease in at least 50% of all patients is an event at autopsy and at relapse in patients who have achieved local control of their disease via extrapleural pneumonectomy.<sup>179</sup>

Patients #306-3103 and #407-4125 were noted to have baseline space-occupying lesions in the liver by FDA review of the images, as well as, by independent reviewer #2. Search of the — Base laptop data files and Appendix 16.2.7 (Individual Efficacy Response Data) revealed 21 patients with space-occupying lesions in their liver (8 alimta + cisplatin arm; 13 cisplatin alone arm). Most were called liver metastases by an independent reviewer and/or by the investigator. Importantly, nine of the 21 patients were reported on the case report form as Stage II or III (6 alimta + cisplatin arm; 3 cisplatin alone arm), suggesting an inaccuracy in staging.

PATIENT#	ARM <sup>180</sup>	US CITY OR COUNTRY	SITE OF OTHER LESIONS OR METASTASES ON IMAGES	STAGE
101-1017	c	NJ	Liver	IV
102-1024	c	Pittsburgh	Liver	III
104-1045	c	NY	Liver	IV
130-1192	c	Chicago	Liver	II
130-1270	c	Chicago	Liver	III
140-1451	c	NY	Liver	IV
215-2151	c	Belgium	liver???? May be anatomic structure in left-lobe of liver	IV
302-3022	c	France	Liver	IV
302-3025	a	France	Liver	III
306-3103	a	France	Liver	III
308-3180	c	France	Liver	IV
403-4048	c	Germany	Liver	IV
407-4125	a	Germany	Liver	III
410--4182	a	Germany	Liver	III
451-4507	a	India	Liver	II
512-5113	c	Australia	Liver	IV
512-5117	c	Australia	Liver	IV
554-5517	c	Argentina	Liver	IV
601-6012	a	Spain	Liver	IV
720-7205	a	Finland	Liver	III
850-8503	a	Poland	Liver	IV

<sup>179</sup> Rusch VW. Oncology 1999;13:931-932

<sup>180</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

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For 8 patients, independent reviewer #2 called the space-occupying lesions, liver metastases; all the cases were Stage II or III; independent reviewer #1 did not indicate the presence of the space-occupying lesions in the liver for these cases. Both independent reviewers called the lesions liver metastases for two patients (#104-1045 and #403-4048); both cases were Stage IV. For five patients (#101-1017, #140-1451, #215-2151, #302-3022, and #308-3180) liver metastases were not called by the independent reviewers but were recorded by the investigator; all these cases were Stage IV.

According to the response criteria in the Protocol,

patients with bidimensionally and unidimensionally measurable disease: greater than or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of bidimensionally measurable disease (and no progression in the sum of the unidimensionally measurable lesions) *or* a 30% decrease under baseline in the sum of the greatest diameters of unidimensionally measurable lesions (and no progression in the sum of bidimensionally measurable lesions).

When both unidimensional and bidimensional measurable disease are evaluated, the declaration of a response by either unidimensional or bidimensional response may be appropriate for the same lesion but it may not be appropriate in the case of different lesions in the same organ (e.g., a unidimensional RUL lesion and a bidimensional RML lesion) or lesions in different organs (e.g., a unidimensional lung lesion and a bidimensional liver lesion). In the article that described the RECIST criteria, the interchangeability of unidimensional and bidimensional response appeared to be with the same lesion and not lesions in a different part of an organ or lesions in different organs. In the case of the same lesion evaluated by either unidimensional or bidimensional measurements, there was no difference in response by both assessments of response. Also, in view that no pleural malignant mesothelioma patients were included in the RECIST criteria study,<sup>181</sup> there was no validation of these methods, i.e., RECIST, for malignant pleural mesothelioma.

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ON ORIGINAL

<sup>181</sup> Therasse et al. J Natl Cancer Inst 2000; 92:205-16

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The table below provides additional information, such as, 1) which independent reader saw liver metastases, 2) the independent reviewer's baseline measurements of disease: lung/liver, and 3) the independent reviewer's response evaluation: lung/liver.

PATIENT #	ARM <sup>182</sup>	STAGE	WHICH INDEPENDENT READER SAW LIVER METS?	FUTHER COMMENTS	RESPONDER'S LIST	INDEPENDENT REVIEWER'S BASELINE MEASUREMENTS OF DISEASE: LUNG/LIVER	INDEPENDENT REVIEWER'S RESPONSE EVALUATION: LUNG/LIVER
101-1017	c	IV		not seen by independent reviewers; metastases seen by investigator	no: MISSING IMAGES; scans requested; Lilly response: scans not available	no measurement of lesion in liver by independent reviewers	
102-1024	c	III	2		No	14.088/2.34	
104-1045	c	IV	both	not noted by investigator	No	14.473/16.476	
130-1192	c	II	2		No	24.689/7.863	
130-1270	c	III	2; not seen by adjudicator		No	9.663/8.257	
140-1451	c	IV		not seen by independent reviewers; metastases seen by investigator; a few lesion seen by FDA imaging reviewers	No	no liver measurements	
215-2151	c	IV		not seen by independent reviewers; metastases seen by investigator; FDA imaging reviewers: questionable lesion???no clean, round lesion, anatomic structure of	No	no liver measurements	

<sup>182</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

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PATIENT #	ARM 162	STAGE	WHICH INDEPENDENT READER SAW LIVER METS?	FUTHER COMMENTS	RESPONDER'S LIST	INDEPENDENT REVIEWER'S BASELINE MEASUREMENTS OF DISEASE::LUNG/LIVER	INDEPENDENT REVIEWER'S RESPONSE EVALUATION: LUNG/LIVER
				L-lobe of liver • doubt liver mets.			
302-3022	c	IV	none seen	baseline: cuts did not go far enough at baseline to see liver but on p. 14696 liver mets at baseline; in lung no L-lung • L-pneumo-ectomy???. mediastinal shifts; viisit 2:bad liver disease (gross disease); also brain scan at visit 2	no	no liver measurements	no liver measurements by independent reviewers
302-3025	a	III	2		no	no meas/11	
306-3103	a	III	2		yes	15.744/11.346	Yes/no
308-3180	c	IV	2	noted at site in response data	no	no meas/77.825	
403-4048	c	IV	both	not noted at site; abdomen disease followed for response, not reported by investigator as liver	no	no meas/194.165	
407-4125	a	III	2		yes	4.739/163.424	Yes/no
410--4182	a	III	2		yes	24.232/4.468	Yes/no
451-4507	a	II	none	lesions in liver only seen by FDA imaging reviewers	yes	not seen by readers	yes/no???
512-5113	c	IV	2	not noted by investigator	yes	15.997/8.461	no/no; overall was SD by

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PATIENT #	ARM <sup>182</sup>	STAGE	WHICH INDEPENDENT READER SAW LIVER METS?	FUTHER COMMENTS	RESPONDER'S LIST	INDEPENDENT REVIEWER'S BASELINE MEASUREMENTS OF DISEASE::LUNG/LIVER	INDEPENDENT REVIEWER'S RESPONSE EVALUATION: LUNG/LIVER
							readers
512-5117	c	IV	2	not noted by investigator	no	13.239/49.292	
554-5517	c	IV	2		no	16.368/3.807	
601-6012	a	IV	2	not noted by investigator	no	21.427/3.109	
720-7205	a	III	2		no	5.953/1.87	
850-8503	a	IV	2	noted by investigator	no	no meas/33.615	

There were four alimta + cisplatin patients listed as responders (for one of these cases, the lesions in the liver were reported only by the FDA Imaging Reviewers [#451-4507]); there was one cisplatin alone patient listed as a responder. Independent reviewer #2 recorded and evaluated a) disease in the lung and the liver for 12 patients and b) only liver disease for three patients. Both independent reviewers recorded and evaluated only liver disease for one patient (#403-4048). The four alimta + cisplatin patients, who were listed as responders, *only* had a response in the unidimensional lung disease; there was no response recorded in the bidimensional liver disease (this includes the one case the FDA imaging reviewers evaluated).

The FDA requested source documents, i.e., CT scan reports, in order to determine if liver metastases were called by the radiologist at the investigator site. In general, the local radiologist, called the lesions hypodense lesions consistent with liver cysts or hemangiomas. Only for patient # 302-3022, did the local radiologist call the lesions liver metastases. Only three of the CT scan reports recommended additional studies to evaluate the lesions in the liver.

PATIENT#	ARM <sup>183</sup>	REVIEW OF CT SCAN REPORT FROM INVESTIGATOR SITE	BASED ON CT SCAN FROM INVESTIGATOR SITE, WERE LIVER METASTASES CALLED?
101-1017	c	CT scan report @ baseline: small left lobe hepatic hypodensity unchanged • in IMPRESSION: called small probable left hepatic lobe cyst or hemangioma	no
102-1024	c	CT scan at baseline: multiple hypodense lesions in the liver consistent with simple cysts • suggested correlation with	no

<sup>183</sup> Key a=alimta + cisplatin arm; c=cisplatin alone arm

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PATIENT#	ARM <sup>185</sup>	REVIEW OF CT SCAN REPORT FROM INVESTIGATOR SITE	BASED ON CT SCAN FROM INVESTIGATOR SITE, WERE LIVER METASTASES CALLED?
		MRI of liver; liver cysts again noted @ visit 2	
104-1045	c	CT scan @ baseline: liver is enlarged, low density mass in dome of liver, 4.3 cm, nodular peripheral enhancement on early post contrast images • hemangioma, correlate with MR; visit 2: mass in liver • suggestive of hemangioma	no
130-1192	c	CT scan @ baseline: numerous probable liver cysts (HU 8 of 8); visit 2: hypodense lesions in liver, probable cysts	no
130-1270	c	CT scan @ baseline: multiple hypodensities in liver likely representing hemangioma or cysts; visit 2: hypodense lesions in liver unchanged	no
140-1451	c	CT scan report baseline: no mention of liver but a mass seen in retrocrural region and a mass in posterior abdomen • called intraabdominal disease	no
215-2151	c	CT scan report @ baseline: mass 30 x 20 mm near left point of liver	no
302-3022	c	CT scan report @ baseline: liver mets.; multiple hypodense nodular lesions, deforming contours of liver, lesion in left liver appears to invade liver capsule	yes
302-3025	a	CT scan report at baseline: hypodense lesions in liver, unchanged with IV contrast; visit 3: nodular hypodense cystic formation; visit 4:	no