PATIENT#	ARM[183]	REVIEW OF CT SCAN REPORT FROM INVESTIGATOR SITE	BASED ON CT SCAN FROM INVESTIGATOR SITE, WERE LIVER METASTASES CALLED?
		secondary lesions or hepatic cysts? • suggested echo; noted again in subsequent studies	
306-3103	a	CT scan report at baseline & follow-up studies: liver biliary cysts; liver cysts unchanged with time	no
308-3180	c	CT scan report at baseline & follow-up: liver cysts in right liver	no
403-4048	c	CT scan report at baseline: massive destruction of liver, particularly lower lobe, unusual for pleural mesothelioma, look to peritoneum; also noted in follow-up & growing	no but reported as unusual for pleural mesothelioma and disease called destructive of liver
407-4125	a	CT scan report at baseline & follow-up studies: extended cystic hepatic lesions, 11 cm	no
410--4182	a	CT scan report at baseline: hepatic cyst? Vs. hepatic mets.?; follow-up studies: liver cysts, unchanged	no
451-4507	a	CT scan @ baseline: focal lesion in posterior of right lobe of liver, a known case of hemangioma, written on report Stage II, T2N0M0; visits 2 & 4: focal lesion in liver, known case of hemangioma	no
512-5113	c	CT scan report at baseline: multiple low attenuation lesions in liver compatible with cysts; visit 3: multiple low density lesions in liver consistent with cysts; visit 7:low attenuation areas in liver	no
512-5117	c	CT scan report @ baseline: multiple cysts visible in the	no

PATIENT#	ARM[183]	REVIEW OF CT SCAN REPORT FROM INVESTIGATOR SITE	BASED ON CT SCAN FROM INVESTIGATOR SITE, WERE LIVER METASTASES CALLED?
		liver; on follow-up report: no mention of liver cysts and no mention of any measurements or status of disease	
554-5517	c	CT scan report at baseline: hepatic single cysts: not noted at visit 2	no
601-6012	a	CT scan report visit 4: hepatic cyst	no
720-7205	a	CT scan report visit 2: liver cyst size of finger tip noted	no
850-8503	a	CT scan report at baseline: focuses in liver, right diaphragmatic lobe (5x4) and left lobe (02 cm), meta? Hemangioma? Visit 2: right lobe 5x4, left lobe 2.5x2	no

Eleven of the patients with space-occupying lesions in the liver had a confirmed pathological diagnosis of mesothelioma. For patient #302-3022, who the investigator-site radiologist called the lesions in the liver, metastases, the diagnosis of mesothelioma was not confirmed. It is unknown how this information may have influenced the investigator-site radiologist's interpretation of the space-occupying lesions in the liver.

Regarding patients with space-occupying lesions in the liver, the table below provides the results of independent pathology review or indicates patients who did not have independent pathology review.

PATIENT#	ARM[184]	WAS PATHOLOGY CONFIRMED?
101-1017	c	not feasible
102-1024	c	yes
104-1045	c	not feasible
130-1192	c	not feasible
130-1270	c	yes
140-1451	c	yes
215-2151	c	yes
302-3022	c	not feasible
302-3025	a	not feasible

[184] Key a=alimta + cisplatin arm; c=cisplatin alone arm

306-3103	a	yes
308-3180	c	yes
403-4048	c	yes
407-4125	a	yes
410--4182	a	no
451-4507	a	tissue unsatisfactory
512-5113	c	not feasible
512-5117	c	yes
554-5517	c	yes
601-6012	a	consistent with
720-7205	a	yes
850-8503	a	Consistent with

There were divergent interpretations of the space-occupying lesions in the liver between: a) the independent reviewers, b) investigators, and c) investigator-site radiologists. No responses in the liver were recorded in the JMCH study.

APPEARS THIS WAY
ON ORIGINAL

Subjects Listed as Alimta Responders but Independent Reviewers' Tumor Measurements do not Calculate as Responders

There were 19 patients listed as alimta responders whose disease measurements that were derived from the independent reviewers did not calculate to a response. In 7 of these patients, the unidimensional disease calculated to PR but the bidimensional disease--and at times larger--did not calculate to PR. In 7 patients, the calculations from the independent reviewers diverged with regard to response, i.e., in 7 patients, reviewer #1's measurements calculated to response but reviewer #2's measurements did not calculate to response and in 2 cases the reverse was the case. In one patient, both independent reviewers' measurements did not calculate to response but the adjudicator's measurements did calculate to response.

PATIENT#	US CITY OR COUNTRY	COMMENT	LILLY RESPONSE TO FDA QUERIES ABOUT CALCULATIONS	RESPONSE BY FDA REVIEW OF IMAGES
107-1072	Baltimore	unidimensional calculates OK; larger bidimensional disease does not calculate to PR.	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
111-1344	Taiwan	No; OK by reader #1; SD by numbers by reader #2; response also not confirmed on CRF (PD)	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
111-1351	Taiwan	No; PR by reader #1;no PR by reader #2's numbers; adjudicator not confirmed by numbers	CT scan reports suggest response; Lilly response dated 11/26/2003 not adequate • no mention of adjudicator and dredging for response with data	YES
136-1631	Los Angeles	unidimensional calculates OK; larger bidimensional disease does not calculate to PR.	8/21/2003: referred back to response dated 8/15/2003	no
201-2192	Mexico	no; reviewer #1: PD; reviewer #2: PR; no adjudication	Lilly response dated 11/26/2003 does not take into account reviewer #1 PD and no adjudicator	YES???
216-2164	Belgium	No; called PR but numbers do not support	Lilly response dated 11/26/2003 agrees that numbers do not calculate to PR	no
301-3170	France	No; problematic; do not meet criteria for PR #1; #2 OK not confirmed ;(no #s for 103)	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate	no

PATIENT#	US CITY OR COUNTRY	COMMENT	LILLY RESPONSE TO FDA QUERIES ABOUT CALCULATIONS	RESPONSE BY FDA REVIEW OF IMAGES
			to PR	
306-3103	France	No; reader #2: unidimensional disease & bidimensional disease; bidimensional disease does not calculate to PR	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
308-3178	France	no; calculates to SD	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	YES
402-4029	Germany	no: no for reader #1; reader #2:yes for unidimensional, no for bidimensional SD	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	YES
407-4125	Germany	no; response in unidimensional disease in lung but no effect in massive disease in liver	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
410-4182	Germany	No; response only by unidimensional disease; only #2 saw liver mets. • •SD	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
501-5001	Italy	No; #1 & #2 do not calculate to PR; only adjudicator calculates but not @ 4 & 6 only @ 101 & 192	Lilly response dated 11/26/2003 agrees that numbers do not calculate to PR	YES???
501-5061	Italy	No measurements for #1; #2 unidimensional yes, bidimensional no	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
505-5041	Italy	No; #1 & #2: PR @ visit1 but PD by #s visit 4;	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no
510-5103	Australia	no; #1 does not calculate at confirmation; #2 calculates to PR	response dated 8/15/2003 did not challenge that numbers did not calculate to PR	no
510-5141	Australia	no;#s by readers do not calculate to PR	8/15/2003 Lilly response: Lilly did not challenge that	no

PATIENT#	US CITY OR COUNTRY	COMMENT	LILLY RESPONSE TO FDA QUERIES ABOUT CALCULATIONS	RESPONSE BY FDA REVIEW OF IMAGES
			numbers do not calculate to PR	
851-8518	Poland	no; visit 6 calculates to PR but at confirmation (visit 102) #s double and calculate to PD	Lilly response dated 9/2/2003: confirms FDA's findings about the numbers but believes and implies that independent reviewers evaluated overall tumor burden • by Lilly's assessment PR	no
852-8532	Poland	no; calculates to PD at 1st evaluation	8/21/2003: referred back to response dated 8/15/2003: response did not challenge that numbers do not calculate to PR	no

In response to FDA queries, Lilly either agreed or did not challenge that the measurements of an independent reviewer or both independent reviewers did not calculate to an objective response. Five of these 19 patients had a response based on FDA review of the images.

APPEARS THIS WAY
ON ORIGINAL

Subjects Listed as Alimta Responders in the NDA But Reported as SD, PD, or UK in the Independent Imaging Review

There were 22 patients listed as alimta responders whose overall response by the independent review was stable disease (SD), progressive disease (PD), or unknown (UK). It has not been clarified why these patients were on the responders' list; according to the protocol, the assessment by the independent review would have priority.

PATIENT#	US CITY OR COUNTRY	OVERALL BEST RESPONSE SCORE BY INDEPENDEPENT READERS	INFORMATION CONFIRMED BY LILLY	RESPONSE BY FDA REVIEW OF IMAGES
3-3001	Taiwan	SD	yes	no
107-1073	Baltimore	SD	yes	no
125-1217	San Francisco	SD	yes	no
130-1191	Chicago	SD	yes	no
131-1272	Dallas	SD even though calculates to PR	yes	YES
141-1461	Louisiana	SD	yes	no
401-4011	Germany	PD	yes	no
409-4170	Germany	SD	yes	no
501-5006	Italy	SD	yes	no
503-5022	Italy	SD	yes	no
505-5042	Italy	calculates to PD but scored as SD	yes	no
509-5133	Australia	SD; reviewer #2 confirmed PR with PD x 3	yes	no
510-5143	Australia	UK; reviewer #2: 1st response does not calculate to PR but scored as SD	yes	no
510-5147	Australia	SD; reviewer #2 scored as PD	yes	no
511-5151	Australia	SD; #s do not calculate to PR although scored as PR by reviewer #2	yes	no
512-5112	Australia	SD	yes	no
554-5516	Argentina	SD	yes	no
721-7225	Finland	SD	yes	no
722-7251	Finland	SD	yes	no
804-8055	UK	PD	yes	no
805-8070	UK	SD	yes	no
851-8517	Poland	SD; numbers calculate to PR	yes	no

In response to FDA queries, Lilly either agreed that the overall response by the independent review panel was as cited above or did not challenge the assertion that the independent review

panel scored the patient as a nonresponder.. One of these 22 patients had a response based on FDA review of the images.

APPEARS THIS WAY
ON ORIGINAL

Listed Subjects as Alimta Responders in Study JMCH and FDA Agreed as Responders

Below were 47 alimta patients who were listed as responders, declared a responder by independent review, and scored a responder by FDA Imaging Review. The shaded rows were FDA responder patients who had the diagnosis of mesothelioma confirmed on independent review.

PATIENT#	ASSESSMENT BY THE NUMBERS	REVIEW OF IMAGES: ASSESSMENT	CONFIRMED RESPONSE	BIDIMENSIONAL (B) OR UNIDIMENSIONAL (U) BY INDEPENDENT REVIEWERS
111-1351	no; PR by reader #1;no PR by reader #2's numbers; adjudicator not confirmed by numbers	Yes; "knuckles of tumor to a rind"	yes; PR confirmed by imaging @ 5	u by all 3
118-1134	Yes	Yes; response confirmed by images	Yes	u
119-1146	yes	Yes	yes?	u
131-1272	yes but best overall response was SD even though calculates to PR	yes	Yes (response confirmed before 28 days)	u
131-1278	yes	yes	Yes	u
136-1633	yes	yes; remarkable response	Yes	u
141-1465	yes; little-minimal disease	yes; minimal disease	Yes	u
142-1476	yes	yes	Yes	u
201-2192	no; reviewer #1: PD; reviewer #2: PR; no adjudication	yes; remarkable response	yes but need adjudication	u
201-2202	yes	yes; remarkable response	yes; remarkable response	u
250-2500	yes	yes	yes	u
250-2502	yes	yes	yes	u
252-2565	yes	yes	yes	u
301-3150	yes	yes	yes	u
301-3151	yes; ask why images required an adjudicator because #1 PR, PR, PD, #2 PR, SD, SD, adjudicator PR, PR, PR	yes	yes	u by #1 & #2; u & b by adjudicator

PATIENT#	ASSESSMENT BY THE NUMBERS	REVIEW OF IMAGES: ASSESSMENT	CONFIRMED RESPONSE	BIDIMENSIONAL (B) OR UNIDIMENSIONAL (U) BY INDEPENDENT REVIEWERS
301-3156	yes	yes	yes	u
302-3021	yes	yes	yes	u
308-3176	yes	yes	yes	u
308-3177	yes	yes	yes	u
308-3178	no; calculates to SD	yes	yes	u
308-3181	yes	yes	yes	u & b by both
308-3182	Yes	yes	yes	u
309-3192	Yes	yes	yes	u
401-4001	yes with PR by adjudicator	yes but not a lot of disease and not impressive	yes; weak	u by all 3
401-4009	Yes	yes	yes	u
402-4029	no: no for reader #1; reader #2:yes for unidimensional, no for bidimensional SD	yes; anterior mediastinum clean with response and opening up; images #25-28	yes	u & b by reader #2 only
403-4042	Yes	yes	yes	u
406-4102	yes but readers using same #s diverged in assessment	yes	yes	u by #1 & #2; u & b by adjudicator
406-4104	Yes	yes; good response by 101		u
409-4179	Yes	yes	yes	u
413-4242	Yes	yes; maybe CR		u
451-4508	yes but at later points calling PR when PD by #s	yes; transient response	yes	u
451-4509	yes but only had #s for #2	yes	yes	u by #2; no measurable disease by #1
501-5001	no; #1 & #2 do not calculate to PR; only adjudicator calculates but not @ 4 & 6 only @ 101 & 192	yes	yes???	u by all 3
501-5004	yes; #1 calculated to PR sooner than declared	yes	yes	u
510-5101	Yes	yes	yes	u
510-5110	no; no disease measurements but reader #1 counted 9	yes	yes	no measurements (0 by #1)

PATIENT#	ASSESSMENT BY THE NUMBERS	REVIEW OF IMAGES: ASSESSMENT	CONFIRMED RESPONSE	BIDIMENSIONAL (B) OR UNIDIMENSIONAL (U) BY INDEPENDENT REVIEWERS
	index rind lesions			
512-5114	Yes	yes	yes	u
552-5509	Yes	yes	yes	u
552-5510	Yes	yes	yes	u
720-7212	Yes	yes but PR	Yes PR	no measurements #1; b #2 and adjudicator
721-7229	yes	yes	Yes	u
804-8048	yes: #1 calculates to PD in b; #2 & adjudicator calculates to PR	Yes	Yes	u & b by all 3 but may have been measuring different bidimensional disease
851-8512	Not read by independent readers because images not provided to readers or to FDA until requested	Yes: V2: PR, V3: confirmed PR; time points: baseline, V2, V3	Yes	missing images: images received & reviewed **no independent review of measurability of disease**
851-8515	yes	yes	yes	u
852-8525	yes	yes	yes	u
852-8534	yes	yes	yes	u

Except for six patients, all the patients had a response by calculation of the measurements reported by the independent reviewer(s); one patient (#851-8512) had no measurements from the independent reviewers because the independent reviewers did not review the images. Except for six patients, who also had assessment of bidimensional disease and the one patient that the independent reviewers did not review, the independent reviewers based all the patients' responses on assessment of unidimensional disease.

Alimta Responders by Independent Review in Study JMCH and FDA Agreed as Responders

Although the published report of the JMCH study did not mention independent review of the images,[185] the accompanying editorial stated that "Central review of all CT scans and all pathology specimens was performed. This rigorous approach to analysis lends credibility to the study results, especially in a disease for which correct pathologic diagnosis can still be difficult, and for which there has been little uniformity in measuring response to treatment."[186] In an earlier article about the results from a Phase II trial of alimta in malignant pleural mesothelioma, there was "an external expert panel" who "independently assessed the best response status of each patient at a later date". The article also compared Investigator-Determined Best Tumor Responses and Independent Reviewer–Determined Best Tumor Responses. The co-authors wrote that "independent review of patient responses increases confidence that the response rate is a true result for this patient population".[187]

The list of responders sent by Lilly had 94 alimta/cisplatin responders and 37 cisplatin responders.[188] There was a minor difference with the number of alimta/cisplatin responders reported in the JMCH study report, i.e., 93.

Table JMCH.11.22. Summary of Best Tumor Response (Investigator-Determined) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=225)	Cisplatin (N=222)	LY/cis (N=167)	Cisplatin (N=163)	LY/cis (N=58)	Cisplatin (N=59)
Number of responding patients	93*	37	76*	32	17*	5
Response rate (%)	41.3	16.7	45.5	19.6	29.3	8.5
95% CI for response rate	34.8 - 48.1	12.0 - 22.2	37.8 - 53.4	13.8 - 26.6	18.1 - 42.7	2.8 - 18.7
Fisher exact p-value	<0.001		<0.001		0.005	

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

[185] Vogelzang NJ, Rusthoven JJ, Symanowski J, et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636-2644, 2003

[186] Rusch VW. Pemetrexed and Cisplatin for Malignant Pleural Mesothelioma: A New Standard of Care? Journal of Clinical Oncology, 21:2629-2630, 2003

[187] Scagliotti et al. Phase II Study of Pemetrexed With and Without Folic Acid and Vitamin B12 as Front-Line Therapy in Malignant Pleural Mesothelioma. J Clin Oncol. 2003; 21:1556-1561

[188] Cover letter from Lilly dated 10/22/2002

The tables below are from the JMCH study report. In the two tables below, the alimta + cisplatin arm number of responders after independent review was not as different (i.e., alimta/cisplatin responders: 93 by the investigator vs. 86 by independent review) as one would expect in view of the FDA's review of the — database revealed 22 patients listed as alimta responders whose overall response by the independent review was stable disease (SD), progressive disease (PD), or unknown (UK), meaning the number of alimta + cisplatin responders should be 94 - 22 = 72. Since the assessment by the independent reviewers of response was to take precedence in determination of response, the FDA believed that the list of 94 alimta + cisplatin provided by Lilly to the FDA were the valid responders. Based on the information provided in the NDA, it was not apparent how the numbers for independent reviewer-determined best tumor response were derived. After further review, it appeared that the list provided to the FDA was the list of investigator-determined responders.

Table JMCH.11.23. Summary of Best Tumor Response (Independent Reviewer-Determined) As of Database Lock (13 February 2002) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=194)	Cisplatin (N=195)	LY/cis (N=145)	Cisplatin (N=143)	LY/cis (N=49)	Cisplatin (N=52)
Number of responding patients	85*	28	67*	23	18*	5
Response rate (%)	43.8	14.4	46.2	16.1	36.7	9.6
95% CI for response rate	36.7 - 51.1	9.8 - 20.1	37.9 - 54.7	10.5 - 23.2	23.4 - 51.7	3.2 - 21.0
Fisher exact p-value	<0.001		<0.001		0.002	

* Two CRs were on the LY/cis arm (1 FS patient and 1 PS+NS patient).

Table JMCH.11.24. Summary of Best Tumor Response (Independent Reviewer-Determined) As of — Update (10 June 2002) RT Population H3E-MC-JMCH

	RT Patients		FS Patients		PS+NS Patients	
	LY/cis (N=197)	Cisplatin (N=200)	LY/cis (N=148)	Cisplatin (N=148)	LY/cis (N=49)	Cisplatin (N=52)
Number of responding patients	86*	30	68*	25	18*	5
Response rate (%)	43.7	15.0	45.9	16.9	36.7	9.6
95% CI for response rate	36.6 - 50.9	10.4 - 20.7	37.7 - 54.3	11.2 - 23.9	23.4 - 51.7	3.2 - 21.0
Fisher exact p-value	<0.001		<0.001		0.002	

* Two CRs were on the LY/cis arm (1 FS patient and 1 PS+NS patient).

The inconsistency of response assessments between the NDA dataset (the Lilly list of responders) and the independent review dataset (see section, **Subjects Listed as Alimta Responders in the NDA But Reported as SD, PD, or UK in the Independent Imaging Review**) suggested that the response assessments reported in the NDA were not based on the independent review.

The FDA requested the best tumor response data from the investigator, independent reviewer #1, independent reviewer #2, and the adjudicator.

The investigator's assessments of the alimta + cisplatin arm are in the table below. The number of objective responders--CR + PR--was 3 + 91 or 94.

ALIMTA + CISPLATIN BEST OVERALL RESPONSE	NUMBER
CR	3
ND	5
PD	39
PR	91
SD	80
U	8

The investigator's assessments of the cisplatin alone arm are in the table below. The number of objective responders- PR--was 37.

CISPLATIN ALONE BEST OVERALL RESPONSE	NUMBER
ND	7
PD	78
PR	37
SD	94
U	6

There were 28 patients on the alimta + cisplatin arm that did not have their images reviewed by the independent panel. The images of patients with progressive disease were most frequently not reviewed by the independent panel.

ALIMTA + CISPLATIN BEST OVERALL RESPONSE BY THE INVESTIGATOR	NUMBER
ND	4
PD	13
PR	3
SD	4
U	4
TOTAL	28

There were 22 patients on the cisplatin alone arm who did not have their images reviewed by the independent panel. The images of patients with stable disease were most frequently not reviewed by the independent panel.

CISPLATIN ALONE BEST OVERALL RESPONSE BY THE INVESTIGATOR	NUMBER
BEST OVERALL RESPONSE	NUMBER
ND	6
PD	4
SD	7
U	5
TOTAL	22

There were 66 patients on the alimta + cisplatin arm that had the investigator's response changed with independent review. As described in the section **Subjects Listed as Alimta Responders in the NDA But Reported as SD, PD, or UK in the Independent Imaging Review** of this review, there were 22 patients who had the investigator's assessment of partial response downgraded to non-response by independent review of the images. There were 17 patients who had their response upgraded from SD to PR. The data from the 16 patients who had their assessment changed from PD to SD may have an effect on the analysis of time to progression, i.e., increase the time to progression. Although less frequent, patients who had their assessment changed from PR to PD and SD to PD may also have an effect on the analysis of time to progression.

ALIMTA + CISPLATIN CHANGE IN BEST OVERALL RESPONSE AFTER INDEPENDENT REVIEW INVESTIGATOR RESULT • INDEPENDENT RESULT	NUMBER
ND • SD	1
PD • SD	16
PD • U	2
PR • PD	2
PR • SD	19
PR • U	1
SD • PD	2
SD • PR	17
SD • U	2
U • SD	4
Total	66

The results of independent review of alimta + cisplatin arm patients are below. The final number--89--does not match the independent-reviewer determined response number in the JMCH study report, i.e., 86.

Alimta + cisplatin arm	NUMBER
Investigator responders	94
Investigator responders downgraded to non-responders	-22
Investigator non-responders upgraded to responders	+17
Total	89

There were 38 alimta + cisplatin patients who the assessment of their imaging studies required adjudication of the independent review; nine cases of investigator-determined SD were upgraded to PR by independent review plus adjudication.

The FDA reviewed the images of the 17 alimta + cisplatin patients who the investigator scored the best overall response as SD and the independent reviewers scored the best overall response as PR; 9 cases had the non-response upgraded to response by adjudication (marked as PR*). These 17 patients were not on the list of responders provided to the FDA by Lilly and thus, were not reviewed when the FDA reviewed the alimta + cisplatin responders on the list. Only 6 of the 17 patients' disease measurements calculated to a response. Six patients had a response by FDA review of the images; 5 cases had lesion measurements that calculated to a response; 1 case had lesion measurements that calculated to a non-response. Only 2 of the 9 adjudicated responders were responders on FDA review of the images. The shaded rows were FDA responder patients who had the diagnosis of mesothelioma confirmed on independent review.

PATIENT#	INVESTIGATOR RESPONSE	INDEPENDENT REVIEWERS' RESPONSE	COMMENTS BY FDA	FDA ASSESSMENT OF RESPONSE BY NUMBERS	FDA REVIEW OF IMAGES FOR RESPONSE
102-1026	SD	PR*	All reviewers evaluated different disease; adjudicator's numbers confirm response as PD	No	Visit 2 PD in ant. Mediastinum; use as example
111-1347	SD	PR	#2: numbers confirm response as PD	No	visit 2 to viisit 4: PD
111-1352	SD	PR*	#2: measured both uni- and bidimensional disease, SD on uni, bidimensional confirms to PD by numbers; adjudicator: measured both uni-	No	SD

PATIENT#	INVESTIGATOR RESPONSE	INDEPENDENT REVIEWERS' RESPONSE	COMMENTS BY FDA	FDA ASSESSMENT OF RESPONSE BY NUMBERS	FDA REVIEW OF IMAGES FOR RESPONSE
			and bidimensional disease, SD on uni, bidimensional confirms to PD by numbers		
131-1274	SD	PR	Both reviewers had numbers as PR	Yes	PR
131-1283	SD	PR	#1: numbers calculate to SD; #2 same as #1	No	SD
131-1044	SD	PR*	both uni & bidimensional disease: same numbers for all three reviewers; numbers do not calculate to PR or no numbers and next value would be PD	No	SD
214-2145	SD	PR*	#1,#2, and adjudicator: measured both uni- and bidimensional disease (unidimensional larger• anidimension al PR, bidimensional SD; only #2 called it SD	No	SD
216-2165	SD	PR	Both reviewers had numbers as PR for visit 2; 2nd visit calculates to PD with new baseline but still in range for PR with old baseline	no???	SD/PD
302-3025	SD	PR	#1: no numbers; #2 bidimensional in liver only: NR	No	SD
402-4039	SD	PR*	#1:calculates to PR visit 2 but calculates to PD visit 4 although still in range of PR of old baseline; #2:same as	No	PR

PATIENT=	INVESTIGATOR RESPONSE	INDEPENDENT REVIEWERS' RESPONSE	COMMENTS BY FDA	FDA ASSESSMENT OF RESPONSE BY NUMBERS	FDA REVIEW OF IMAGES FOR RESPONSE
			#1; adjudicator: visit 2 & visit 4 measurements about the same -->PR but response less than visit 2 for #1 and #2		
406-4101	SD	PR*	#1, #2, and adjudicator: visit 2 calculates to PR but visit #4 calculates to PD although within range of PR with old baseline;	No	PD; inadequate scan• • missing 1/2 lung at baseline
407-4121	SD	PR*	#1 does not calculate; both #2 and adjudicator calculate to PR and then 0.00	Yes	SD; low tumor burden • • minimal disease; right fluid and left fluid; check pathology (OK, confirmed mesothelioma), Stage IV
409-4162	SD	PR	Both calculate to PR	Yes	PR; more fluid response; disease on both sides
501-5010	SD	PR	Both calculate to PR	Yes	PR
502-5018	SD	PR	Both calculate to PR	Yes	PR
553-5511	SD	PR*	#2 & adjudicator calculate to PR	Yes	PR
804-8041	SD	PR*	#1 calculates to PR, #2 measured uni- & bidimensional disease: unidimensional calculates to PR, bidimensional disease calculates to SD; adjudicator only measured unidimensional disease• •PR	no???	SD; bidimensional disease not a response; unidimensional disease a response

*adjudicated

Recall from the introduction to this section that the FDA did not review images of the listed cisplatin alone responders. There were 60 patients on the cisplatin arm alone who had the investigator's response changed with independent review. There were 14 patients who had the investigator's assessment of partial response downgraded to non-response by independent review of the images. There were 6 patients who had their response upgraded from ND, PD, or SD to PR. The data from the 34 patients who had their assessment changed from PD to SD may have

an effect on the analysis of time to progression, i.e., increase the time to progression. Although less frequent, the data from patients who had their assessment changed from PD to PR and SD to PD may also have an effect on the analysis of time to progression.

CISPLATIN ALONE CHANGE IN BEST OVERALL RESPONSE AFTER INDEPENDENT REVIEW INVESTIGATOR RESULTS-->INDEPENDENT PANEL RESULTS	NUMBER
ND• •PR	1
PD• •PR	1
PD• •SD	34
PD• •U	2
PR• •SD	13
PR• •U	1
SD• •PD	3
SD• •PR	4
U• •SD	1
Total	60

The results of independent review of cisplatin alone arm patients are below. The final number--29--does not match the independent-reviewer determined response number in the JMCH study report, i.e., 30.

Cisplatin alone arm	NUMBER
Investigator responders	37
Investigator responders down-graded to non-responders	-14
Investigator non-responders up-graded to responders	+6
Total	29

There were 45 cisplatin alone patients who the assessment of their imaging studies required adjudication of the independent review; one case of investigator-determined SD was upgraded to PR by independent review plus adjudication.

Nine cases of SD were upgraded to PR.

An analysis of the results of the independent review for both treatment arms is below. A higher proportion of cisplatin alone patients had their investigator's PR downgraded than the alimta + cisplatin alone patients. Response upgrading to PR by independent review was balanced in both arms.

RESULT OF INDEPENDENT REVIEW	ALIMTA/CISPLATIN	CISPLATIN ALONE
Response downgraded	22/94 (23%)	14/37 (38%)
Response upgraded	17/94 (18%)	6/37 (16%)
Total changed	39/94 (41%)	20/37 (54%)

APPEARS THIS WAY
ON ORIGINAL

Agreed upon Alimta Responders with a Confirmed Pathology Diagnosis of Mesothelioma

The 38 FDA confirmed alimta + cisplatin with a confirmed pathology diagnosis are derived from tables in sections "**Listed Subjects as Alimta Responders in Study JMCH and FDA Agreed as Responders**" (32 patients) and "**Alimta Responders by Independent Review in Study JMCH and FDA Agreed as Responders**" (6 patients). Identification of patients with a confirmed pathological diagnosis of mesothelioma and the patients' folic acid/vitamin B12 supplementation status was derived from Lilly correspondences dated 12/16/2003 and 8/21/2003, respectively.

RESPONSE RATE IN PATIENTS WITH CONFIRMED PATHOLOGY

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

Regulatory Decision Concerning the Inclusion of Response Rate and Time to Progression in the Label

Response rate was originally the proposed primary endpoint for study JMCH. Unidimensional measurements were believed to be sufficient to provide information for response. The FDA required survival as the primary endpoint and was uncertain about the application of unidimensional disease for response assessments.

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

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

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

- There was dissociation of overall response scoring and calculation of response by independent readers, i.e., patients were scored as PR but calculations of measurements indicated NR or PD.
- FDA review of imaging studies confirmed only 47 of 94 responses listed by Lilly in the alimta/cisplatin group.

Also, according to Lilly:

- In patients with "extensive lobulated disease", it was difficult to select the appropriate lesions to follow and the tumor burden may not be accurately represented by the lesions chosen at baseline.[189]
- When the disease is "extensive and lobulated" or has "irregular contours", it makes it difficult to measure.[190]

[189] Lilly correspondence dated 11/26/2003
[190] Lilly correspondence dated 12/4/2003

4. Efficacy Conclusions

IIn the pivotal trial, A Single-blind Randomized Phase 3 Trial of MTA[191] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma, survival was the primary endpoint. The following table illustrates the survival benefit achieved in this randomized, controlled trial.

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

[191] alimta

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388
Race White Randomized and treated (n=410)	12.2 months	9.3 monts	0.024
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white Fully folic acid/vitamin B12 supplemented (n=28)	8.8 months	9.55 months	0.619
Age < 65 years Randomized and treated (n=279)	13.3 months	10.2 months	0.02
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The data supports the following indication:

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

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

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

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

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

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

VII. Integrated Review of Safety

1. Brief Statement of Conclusions

The pivotal trial was a multicenter, randomized, single-blind Phase III trial in chemo-naïve patients with malignant pleural mesothelioma (MPM) treated with Alimta in combination with cisplatin compared to patients who received cisplatin alone. Alimta was administered at a dose of 500 mg/ m^2 intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/ m^2 intravenously over approximately 2 hours on Day 1 of each 21- day cycle. In the cisplatin only arm, normal saline which did not contain Alimta was administered intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/ m^2 intravenously over approximately 2 hours on Day 1 of each 21- day cycle. Patients in both arms were pre- and post- hydrated according to local practice. Dexamethasone 4 mg, or equivalent corticosteroid was taken orally twice per day on the day before, the day of, and the day after each dose of Alimta plus cisplatin. Folic acid supplementation, 350–1000 µg or equivalent was taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of Alimta plus cisplatin and continued daily until the patient discontinued from study therapy. A vitamin B_{12} injection, 1000 µg was given intramuscularly approximately 1 to 3 weeks prior to the first dose of Alimta plus cisplatin and was repeated approximately every 9 weeks until the patient discontinued from study therapy.

The median age of patients at the time of randomization was 60 years. Although 456 patients were randomized, 8 patients did not receive the study drug; a total of 448 patients were treated and received at least one dose of study drug(s). The primary analysis of this study was performed on the population of all patients who received study drug in the treatment arm. A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy. Randomized and treated patients completed a median of 6 cycles of the Alimta/cisplatin arm and 4 cycles of the cisplatin only arm. Supplemented patients completed a median of six cycles and nonsupplemented patients completed a median of 2 cycles of Alimta/cisplatin. The planned mean dose for Alimta and cisplatin were 166.7 and 25 mg/m^2/wk respectively. The mean dose delivered was 153.4 mg/m^2/wk of Alimta and 23.2 mg/m^2/wk of cisplatin in the RT group and 154.6 mg/m^2/wk and 23.4 mg/m^2/wk in the FS group. When used alone, cisplatin was given at 24.1 mg/m^2/wk. The percent of planned dose intensity was 92/92.8% for Alimta/cisplatin in the RT group and 92.7/93.6% Alimta/cisplatin in the FS group. 96.4% of cisplatin alone could be given in both the RT and FS groups. In the RT group, 308 (28.9%) dose delays were reported in the Alimta/cisplatin arm and 171 (19.5%) in the cisplatin alone arm. Scheduling conflicts constituted the majority of dose delays. The most common clinical cause of dose delay on both arms was neutropenia. On both arms, cycle 4 was the cycle with the most delays. The common grade 3 or grade 4 laboratory toxicities in the RT group treated with Alimta/cisplatin were neutropenia (28.8%), leucopenia (18.1%), thrombocytopenia (5.8%) and anemia (6.2%). In the cisplatin only arm, neutropenia (2.3%), leucopenia (1.4%) and decreased creatinine (1%). In the FS group, the Alimta/cisplatin treated arm had neutropenia (24.4%), leucopenia (15.5%), anemia

(6%), thrombocytopenia (5.4%) while the cisplatin only arm had neutropenia (3.1%), leucopenia (0.6%) and decreased creatinine (1%). The common nonlaboratory grade 3 and grade 4 adverse events in the RT group treated with Alimta/cisplatin were fatigue (18.1%), nausea (14.6%), vomiting (13.7%), diarrhea (4.9%), dehydration (4.4%), stomatitis (4%), anorexia (3.5%) and rash (1.3%). In the cisplatin alone arm the common adverse events were fatigue (15.3%), nausea (6.3%), and vomiting (3.6%). In the FS group, the patients treated with Alimta/cisplatin had fatigue (17.3%), nausea (11.9%), vomiting (10.7%), dehydration (4.2%), diarrhea (3.6%), stomatitis (3%) and anorexia (2.4%). Those in the cisplatin alone arm had fatigue (12.9%), nausea (5.5%) and vomiting (4.3%). A comparison between the two treatment arms in the FS group showed a statistically significant difference for neutrophils and leukocytes with more neutropenia and leucopenia in the Alimta/cisplatin group. Effect of supplementation reduced many of the laboratory and non-laboratory toxicities.

Use of vitamin supplementation by patients must be emphasized. Patients treated with Alimta must be instructed to take low-dose folic acid daily so that at least 5 doses are taken during the 7-day period preceding the first dose of Alimta and continuing until 21 days after the last dose. Patients must also receive 1 injection of vitamin B_{12} during the week prior to receiving the first dose of Alimta and every 3 cycles thereafter during therapy. Subsequent vitamin B_{12} injections may be given the same day as Alimta.

Alimta with dexamethasone or equivalent reduces the incidence and severity of cutaneous reactions.

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

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

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

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

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

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

2. Description of Patient Exposure

All patients were randomly assigned to either the Alimta/ cisplatin arm or the cisplatin alone arm, defined as follows:
A. Alimta, 500 mg/ m^2, diluted in normal saline, 100 mL, administered intravenously over approximately 10 minutes, followed approximately 30 minutes later by cisplatin, 75 mg/ m^2, administered intravenously over approximately 2 hours on Day 1 of each 21- day cycle.
B. Normal saline, 100 mL, that did not contain Alimta administered intravenously over approximately 10 minutes, followed approximately 30 minutes later by cisplatin, 75 mg/ m2, administered intravenously over approximately 2 hours on Day 1 of each 21- day cycle.
Both arms were treated as follows: Patients were pre- and post hydrated according to local practice. Patients were instructed to take dexamethasone 4 mg, or equivalent corticosteroid, orally twice per day on the day before, the day of, and the day after each dose of assigned treatment. Patients were instructed to take folic acid supplementation, 350 to 1000 µg or equivalent, orally each day beginning approximately 1 to 3 weeks before the first dose of treatment arm and continued daily until the patient discontinued from study therapy. A vitamin B_{12} injection, 1000 µg, was given intramuscularly approximately 1 to 3 weeks before the first dose of treatment and was repeated approximately every 9 weeks until the patient discontinued from study therapy. The primary analysis of this study was performed on the population of all patients who received study drug in the treatment arm. A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy.

The decision to add folic acid and vitamin B_{12} was made after the start of the study. At the time of the decision, approximately 117 patients had been accrued to the pivotal study. All patients still on study therapy (in both treatment arms) were given folic acid (350 to 1000 µg oral daily) and vitamin B_{12} (1000 µg intramuscular every 9 weeks). In addition, the same doses and schedules of these vitamins were routinely given to all subsequent new patients enrolled into the study.

2.1 Extent of Exposure

Drug Administration

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

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

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

The Table below summarizes the number of cycles of therapy administered by treatment arm by supplementation status. Within the Alimta/ cisplatin arm, FS patients received a median of six cycles compared with two cycles in the never-supplemented (NS) patients (p=< 0.001). For the cisplatin alone arm, there was also a difference favoring a larger number of cycles in the FS group (p= 0.049).

Table 7.1. Summary of Cycles Given RT Population FS and NS

	LY/cis		Cisplatin	
Completed Cycles	FS (N=168)	NS (N=32)	FS (N=163)	NS (N=38)
Mean	4.9	3.2	4.0	3.2
Median	6.0	2.0	4.0	2.0
Standard Deviation	2.2	1.8	2.1	1.8
Minimum				
Maximum				

Source: Section 12.1.7. Applicant's Table JMCH 12.13

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

The following tables show the duration of exposure, doses and dose intensity in all the treatment groups. The FDA exposure analysis is consistent with that submitted by the applicant.

Alimta exposure was for a median of 18 weeks. The median doses of Alimta and cisplatin were higher in those fully supplemented. Patients in both arms received > 90% of the planned dose

intensity. Patients receiving Alimta in the RT group received a relative dose intensity of 92% of the protocol specified Alimta dose intensity and patients treated with cisplatin in the same group received 92.3% of the projected dose intensity with Alimta compared to 96.5% cisplatin alone. Similarly, after supplementation, 92.7% Alimta, 93% cisplatin when given with Alimta and 96.4% cisplatin when given alone were the relative dose intensities.

Table 7.2. Treatment Duration (weeks) (Reviewers Table)

	Randomized and treated patients			**Fully Supplemented Patients**		
	Alimta/cisplatin N=226		**Cisplatin** N=222	**Alimta/cisplatin** N=168		**Cisplatin** N=163
	Alimta	cisplatin	cisplatin	Alimta	cisplatin	cisplatin
Median duration	18	18	12	18	18	12
Mean duration	15	15	12	16	16	13
Max duration	39	39	27	39	39	27
Min duration	3	3	3	3	3	3

Table 7.3. Total Dose of Treatment Received (Reviewers Table)

	Randomized and treated patients			**Fully supplemented patients**		
	Alimta/cisplatin N=226		**Cisplatin** N=222	**Alimta/cisplatin** N=168		**Cisplatin** N=163
	Alimta Mg/m^2	Cisplatin Mg/m^2	Cisplatin Mg/m^2	Alimta Mg/m^2	Cisplatin Mg/m^2	Cisplatin Mg/m^2
Median dose	2614.5	399.4	300	2942	445	300
Mean dose	2289.7	343.6	295.3	2392.3	358.4	298.1
Max dose	6008	902	666	6008	902	666
Min dose	497	74	68	497	74	68

Table 7.4. Dose Intensity (DI) Per Week ($mg/m^{2)}$ (Reviewers Table)

	Randomized and treated patients			Fully supplemented patients		
	Alimta/cisplatin N=226		**Cisplatin** N=222	**Alimta/cisplatin** N=168		**Cisplatin** N=163
	Alimta	Cisplatin	Cisplatin	Alimta	Cisplatin	Cisplatin
Median DI	160.3	24.1	24.8	162	24.3	24.8
Mean DI	153.3	23.1	24.1	154.5	23.3	24.1
Max DI						
Min DI						
Relative dose intensity (%)*	91.9	92.3	96.5	92.7	93.1	96.4

*Dose delivered(mean)/dose planned

Reviewers Comment:
The median duration of treatment was the same in the RT and FS groups. The median doses for Alimta and cisplatin were higher in those fully supplemented. The planned dose for Alimta was 166 mg/m²/week, and the mean dose delivered was 153 mg/m²/week for a relative dose intensity of 92%. Relative dose intensity of cisplatin given alone was higher than that of cisplatin when given with Alimta. However, the relative dose intensity for both Alimta and cisplatin in the Alimta/cisplatin arm with and without supplementation was greater than 90%. Folate and vitamin B_{12} supplementation allowed the administration of more cycles of chemotherapy.

Dose Delays

In the RT population, 308 (28.9%) dose delays were reported for the patients treated on the Alimta/ cisplatin arm, and 171 (19.5%) were reported for patients treated with cisplatin alone. Scheduling conflicts constituted the majority of the dosing delays with a total of 172 (55.8%) delays on the Alimta/cisplatin arm and131 (76.6%) delays on the cisplatin alone arm. The most common clinical cause of delay on both arms was neutropenia, followed by reduced creatinine clearance, leukopenia, anemia, stomatitis and infection. On both treatment arms, Cycle 4 was the cycle of therapy with the most clinical delays.

In the FS arm, there were 231 dose delays in the Alimta/cisplatin arm and 124 reported in patients treated with cisplatin alone. As in the RT population, scheduling conflicts caused the majority of dose delays and the reasons for the delays were similar.

Table 7.5. Most Common Clinical Reasons for Dose Delay-All Cycles (Reviewers Table)

Reason	Randomized and treated patients		Fully supplemented patients	
	Alimta/cisplatin N (%)	Cisplatin N (%)	Alimta/cisplatin N (%)	Cisplatin N (%)
Scheduling conflict	172 (55.8)	131 (76.6)	134 (58.0)	91 (73.4)
Neutropenia	68 (22.1)	11 (6.4)	50 (21.6)	7 (5.6)
CrCl decreased	20 (6.5)	12 (7.0)	13 (5.6)	12 (9.7)
Anemia	11 (3.6)	1 (0.6)	5 (2.2)	1 (0.8)
Leukopenia	9 (2.9)	3 (1.8)	8 (3.5)	3 (2.4)
Stomatitis	3 (1.0)	0	3 (1.3)	0
Infection	1 (0.3)	2 (1.2)	1 (0.4)	1 (0.8)
Fatigue	2 (0.6)	0	1 (0.4)	0
Rash	2 (0.6)	0	1 (0.4)	0
Diarrhea	1 (0.3)	1 (0.6)	0	1 (0.8)
Dyspnea	1 (0.3)	1 (0.6)	1 (0.4)	1 (0.8)
URI	1 (0.3)	1 (0.6)	1 (0.4)	1 (0.8)
Vomiting	1 (0.3)	1 (0.6)	0	0

CrCl: creatinine clearance; URI: upper respiratory infection

Reviewers Comment:
There were more dose delays in patients treated with the Alimta and cisplatin combination. Scheduling conflict caused the most dose delays. Of the drug related toxicity neutropenia caused the most dose delays.

Dose Reductions/Omissions

Dose reductions on the Alimta/cisplatin arm were reported in 27 (2.5%) for Alimta and cisplatin, 9 (0.8%) for Alimta alone and 1 (0.1%) for cisplatin alone in the randomized and treated population. The most frequent reason for dose reduction was neutropenia, followed by diarrhea, thrombocytopenia, and stomatitis. On the cisplatin alone arm, 3 (0.3%) dose reductions were reported. On both arms, dose reductions occurred most frequently in Cycle 2. In the fully supplemented patients on the Alimta/ cisplatin arm, the most frequent reasons for Alimta dose reductions were diarrhea, neutropenia, and stomatitis (each 17.4%). The most frequent reasons for cisplatin dose reductions were attributed to neutropenia (4 [23.5%]), diarrhea (3 [17.6%]) and thrombocytopenia (3 [17.6%]). The Tables below summarize these findings.
Two patients (Patients #136- 1631 and #720- 7200) omitted cisplatin at some time during therapy. One patient received the last eight cycles of therapy with cisplatin omitted because of deafness; another patient omitted cisplatin in the last cycle because of vomiting. Both were on the Alimta/cisplatin arm.

Table 7.6. Reasons for Dose Reduction – All Doses Delivered RT Population

	LY/cis		Cisplatin
Reason	LY231514	Cisplatin	Cisplatin
Total Reductions	36	28	3
Neutropenia	9 (25.0%)	9 (32.1%)	1 (33.3%)
Thrombocytopenia	5 (13.9)	5 (17.9)	0
Diarrhea	5 (13.9)	4 (14.3)	0
Stomatitis	6 (16.7)	1 (3.6)	0
Blood cr increased	1 (2.8)	1 (3.6)	0
CrCl decreased	1 (2.8)	1 (3.6)	0
Nausea	2 (5.6)	2 (7.1)	0
Fatigue	2 (5.6)	1 (3.6)	0
Vomiting	2 (5.6)	1 (3.6)	0
Dehydration	1 (2.8)	1 (3.6)	0
GGT increased	1 (2.8)	1 (3.6)	0
Rash	1 (2.8)	0	0
Deafness	0	1 (3.6)	0
Hyponatremia	0	0	1 (33.3)
Neurotoxicity	0	0	1 (33.3)

Source: Section 12.1.3 Applicant Table JMCH.12.8.

Table 7.7. Reasons for Dose Reduction – All Doses Delivered RT Population by Supplementation Status

	LY/cis				Cisplatin	
Drug Associated	LY231514		Cisplatin		Cisplatin	
Reason	FS	PS+NS	FS	PS+NS	FS	PS+NS
Total Reductions	23	13	17	11	2	1
Neutropenia	4 (17.4%)	5 (38.5%)	4 (23.5%)	5 (45.5%)	1 (50.0%)	0
Thrombocytopenia	3 (13.0)	2 (15.4)	3 (17.6)	2 (18.2)	0	0
Diarrhea	4 (17.4)	1 (7.7)	3 (17.6)	1 (9.1)	0	0
Stomatitis	4 (17.4)	2 (15.4)	0	1 (9.1)	0	0
Blood cr increased	1 (4.3)	0	1 (5.9)	0	0	0
CrCl decreased	1 (4.3)	0	1 (5.9)	0	0	0
Nausea	2 (8.7)	0	2 (11.8)	0	0	0
Fatigue	2 (8.7)	0	1 (5.9)	0	0	0
Vomiting	1 (4.3)	1 (7.7)	0	1 (9.1)	0	0
Dehydration	0	1 (7.7)	0	1 (9.1)	0	0
GGT increased	1 (4.3)	0	1 (5.9)	0	0	0
Rash	0	1 (7.7)	0	0	0	0
Deafness	0	0	1 (5.9)	0	0	0
Hyponatremia	0	0	0	0	1 (50.0)	0
Neurotoxicity	0	0	0	0	0	1 (100%)

Source: Section 12.1.3, Applicant Table JMCH.12.9

While dose escalations were not permitted according to protocol, 2 patients were given dose escalations in violation of the protocol. On the Alimta/ cisplatin arm, a single dose escalation (Patient # 403- 4047) occurred in which the Alimta dose was escalated in error from 250 mg/ m^2 to 500 mg/ m^2 in Cycle 5. On the cisplatin alone arm, 1 patient (Patient #502- 5014) received a reduced cisplatin dose in Cycle 2 which was subsequently escalated to the full dose (75 mg/ m^2) in Cycle 3 and all remaining cycles.

3. Methods and Specific Findings of Safety Review

The definition of the safety population was any patient who received at least one dose of the drug. A clinical trial adverse event was defined as any undesirable experience that occurred after the patient had received the first dose of study drug without regard to the possibility of a causal relationship, and without regard to treatment group assignment. The occurrence or nature of adverse events were acquired by study site personnel and recorded on the patient's case report forms (CRF). Unless otherwise indicated, all AE rates are reported on a per patient basis.

The safety review was conducted using the electronic datasets from the randomized controlled trial comparing Alimta in combination with cisplatin and cisplatin alone for treatment of patients with MPM. All adverse events after the patient had received the first dose of study drug without regard to the possibility of a causal relationship were considered. Study datasets were constructed by deriving datasets from the raw datasets provided. The study used the Medical Dictionary for Regulatory Activities (MedDRA Version 3.0) translation dictionary for the reporting of the adverse event data. MedRA was used to code the investigators adverse event terms to actual term or CTC text. Adverse events were graded using the NCI Common Toxicity Criteria.

3.1 Summary of Adverse Events

A total of 226 patients on the Alimta/cisplatin arm and 222 patients on the cisplatin alone arm qualified for safety analysis. On the Alimta/cisplatin arm, 223 (98.7%) patients reported at least one adverse event (AE). On the cisplatin alone arm, a total of 218 (98.2%) patients reported at least one AE.

Tables 7.8 and 7.9 summarize the adverse events (≥5%) reported for all patients who received study drug, regardless of drug causality.

On both treatment arms in both populations nausea, fatigue and dyspnea were the most commonly reported AEs of all grades.

In the RT population, in the Alimta/cisplatin arm, neutropenia, fatigue and leucopenia were the most commonly reported grade 3/4 AEs. In the cisplatin alone arm, hypertension, fatigue and

dyspnea were the most commonly reported grade 3/4 AEs. The incidence of grade 3/4 neutropenia was much higher (28.8%) when Alimta and cisplatin were used in combination than when cisplatin was used alone (2.3 %). The incidence of leucopenia (18 vs. 1.4 %), nausea (14.6 vs. 6.3%), vomiting (13.7 vs. 3.6%), anemia (6.2 vs. 0.5%), thrombocytopenia (5.8 vs. 0%), and anorexia (3.2 vs. 0.5%) were also higher in the Alimta/cisplatin arm. In the cisplatin alone arm, the incidence of hypertension was higher (16.2%) than in the Alimta/cisplatin arm (9.3%). Other AEs higher in the cisplatin alone arm were dyspnea, tumor pain, pleuritic pain, edema, depression and insomnia. In the Alimta/cisplatin arm, grade 3/4 neutropenia, leucopenia, nausea and vomiting occurred in 15% or more of the patients.

In the FS population, neutropenia, fatigue and leucopenia were the most commonly reported grade 3/4 AEs in the Alimta/cisplatin arm while hypertension, fatigue and dyspnea were most common in the cisplatin alone arm. The incidence of grade 3/4 neutropenia in the Alimta/cisplatin arm (24.4%) was higher than the cisplatin alone arm (3.1%). The incidence of fatigue (17.3 vs. 12.9%), leucopenia (15.5% vs. 0.6%), nausea (11.9 vs. 5.5%), dyspnea (11.3 vs. 9.2%), vomiting (10.7 vs. 4.3%), chest pain (8.3 vs. 6.7%), anemia (6.0 vs. 0.6%), thrombocytopenia (5.4 vs. 0.0 %), and anorexia (2.4 vs. 0.6%) were also higher in the Alimta/cisplatin arm. In the cisplatin alone arm, the incidence of hypertension was higher (17.8%) than in the Alimta/cisplatin arm (11.3%). Other AEs more common in the cisplatin alone arm are pain, decreased creatinine and hearing loss. In the Alimta/cisplatin arm, grade 3/4 neutropenia, leucopenia and fatigue occurred in more than 15% of the patients.

Table 7.10 shows the incidence of grade 3/4 toxicities in patients who were fully supplemented with folic acid and vitamin B_{12} from the time of enrollment in the study and patients who never received vitamin supplementation during the study in the Alimta/cisplatin arm. Compared to patients never supplemented, grade 3/4 hypertension, thrombosis/embolism and chest pain were more frequent among those supplemented.

As expected, there were more AEs experienced by patients on the Alimta/ cisplatin arm than on the cisplatin alone arm in both treatment populations. Overall, even after vitamin supplementation, there were more AEs with the Alimta/cisplatin combination although both populations have a reduced incidence of adverse events on supplementation. Severe toxicities reported on the Alimta/ cisplatin arm were less frequent among FS patients.

Myelosuppression was the most common toxicity of Alimta. Myelosuppression was manifested predominantly as neutropenia. In the fully supplemented Alimta/cisplatin arm, the initial incidence of grades 3/4 neutropenia was 24.4%. The incidence of febrile neutropenia and neutropenic sepsis were relatively infrequent. The incidences of grade 3/4 anemia and thrombocytopenia were 6% and 5.4% respectively.

Figures 7.1-7.3 shows the percentage of the ten commonest grade 3/4 adverse events in the RT population, FS population and the group never supplemented.

There were 2 hospitalizations for febrile neutropenia (Patient # 111-1347 and #804-8040), one of whom died while on-study (#804-840). The death of one patient (patient #510-5100) was

attributed to febrile neutropenia. The death of another patient with febrile neutropenia (patient #214-2148) could be study-drug related.

Table 7.8. Adverse Events Summary (≥5% Incidence) in RT Population (Reviewers Table)

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

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Other endocrine	18	8.0	3	1.3	18	8.1	0	0.0
Rash/desquamation	61	27.0	3	1.3	26	11.7	0	0.0
Abdominal pain or cramping	21	9.3	2	0.9	16	7.2	1	0.5
Edema	34	15.0	2	0.9	33	14.9	5	2.3
Fever	36	15.9	2	0.9	18	8.1	0	0.0
Infection/Febrile Neutropenia-Other	5	2.2	2	0.9	4	1.8	0	0.0
Inner ear/hearing	21	9.3	2	0.9	30	13.5	2	0.9
Mood alteration-depression	28	12.4	2	0.9	21	9.5	3	1.4
Other auditory/hearing	15	6.6	2	0.9	11	5.0	0	0.0
Other musculoskeletal	18	8.0	2	0.9	18	8.1	2	0.9
Alopecia	31	13.7	1	0.4	15	6.8	0	0.0
Cough	90	39.8	1	0.4	82	36.9	2	0.9
Creatinine	39	17.3	1	0.4	26	11.7	2	0.9
Dizziness/lightheadedness	20	8.8	1	0.4	19	8.6	0	0.0
Dyspepsia/heartburn	26	11.5	1	0.4	10	4.5	0	0.0
Headache	29	12.8	1	0.4	24	10.8	1	0.5
Hypercholesterolemia	10	4.4	1	0.4	20	9.0	1	0.5
Other metabolic/laboratory	7	3.1	1	0.4	14	6.3	0	0.0
Other neurology	18	8.0	1	0.4	13	5.9	1	0.5
SGPT(ALT)	17	7.5	1	0.4	20	9.0	1	0.5
Sweating	29	12.8	1	0.4	27	12.2	0	0.0
Tearing	15	6.6	1	0.4	1	0.5	0	0.0
Weight loss	42	18.6	1	0.4	31	14.0	2	0.9
Insomnia	36	15.9	0	0.0	40	18.0	3	1.4
Neuropathy-sensory	36	15.9	0	0.0	30	13.5	1	0.5
SGOT(AST)	18	8.0	0	0.0	12	5.4	1	0.5
Allergic rhinitis	20	8.8	0	0.0	8	3.6	0	0.0
Conjunctivitis	21	9.3	0	0.0	1	0.5	0	0.0
Other Dermatology/Skin	16	7.1	0	0.0	15	6.8	0	0.0
Other ocular/visual	12	5.3	0	0.0	6	2.7	0	0.0
Taste disturbance	21	9.3	0	0.0	15	6.8	0	0.0
Urinary frequency/urgency	16	7.1	0	0.0	9	4.1	0	0.0

Table 7.9. Adverse Events Summary (≥ 5% Incidence) in RT Fully Supplemented Population (Reviewers Table)

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	96	57.1	41	24.4	22	13.5	5	3.1
Fatigue	137	81.5	29	17.3	120	73.6	21	12.9
Leukocytes	92	54.8	26	15.5	30	18.4	1	0.6
Nausea	142	84.5	20	11.9	128	78.5	9	5.5
Dyspnea	110	65.5	19	11.3	103	63.2	15	9.2
Hypertension	44	26.2	19	11.3	56	34.4	29	17.8
Vomiting	99	58.9	18	10.7	83	50.9	7	4.3
Chest pain	68	40.5	14	8.3	50	30.7	11	6.7
Hemoglobin	57	33.9	10	6.0	24	14.7	1	0.6
Thrombosis/embolism	12	7.1	10	6.0	6	3.7	6	3.7
Platelets	44	26.2	9	5.4	15	9.2	0	0.0
Tumor pain	31	18.5	8	4.8	24	14.7	7	4.3
Dehydration	12	7.1	7	4.2	2	1.2	2	1.2
Constipation	78	46.4	6	3.6	66	40.5	1	0.6
Diarrhea without colostomy	43	25.6	6	3.6	25	15.3	1	0.6
Other pain	26	15.5	5	3.0	42	25.8	7	4.3
Pulmonary-Other	34	20.2	5	3.0	31	19.0	4	2.5
Renal/Genitourinary-Other	52	31.0	5	3.0	50	30.7	4	2.5
Stomatitis/pharyngitis	47	28.0	5	3.0	13	8.0	0	0.0
Anorexia	59	35.1	4	2.4	44	27.0	1	0.6
Constitutional Symptoms-Other	18	10.7	4	2.4	14	8.6	2	1.2
Infection without Neutropenia	21	12.5	4	2.4	7	4.3	0	0.0
Other Gastrointestinal	33	19.6	3	1.8	26	16.0	1	0.6
Pleuritic pain	29	17.3	3	1.8	31	19.0	8	4.9
Dysphagia, esophagitis, odynophagia	10	6.0	2	1.2	9	5.5	0	0.0
Edema	24	14.3	2	1.2	25	15.3	4	2.5
Hyperglycemia	8	4.8	2	1.2	11	6.7	6	3.7
Infection/Febrile Neutropenia-Other	5	3.0	2	1.2	3	1.8	0	0.0
Mood alteration-depression	23	13.7	2	1.2	15	9.2	2	1.2
Other	19	11.3	2	1.2	19	11.7	3	1.8

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
cardiovascular/general								
Other musculoskeletal	14	8.3	2	1.2	13	8.0	2	1.2
Cough	64	38.1	1	0.6	61	37.4	2	1.2
Creatinine	26	15.5	1	0.6	18	11.0	2	1.2
Dizziness/lightheadedness	16	9.5	1	0.6	16	9.8	0	0.0
Dyspepsia/heartburn	20	11.9	1	0.6	6	3.7	0	0.0
Headache	21	12.5	1	0.6	18	11.0	1	0.6
Hypercholesterolemia	7	4.2	1	0.6	19	11.7	1	0.6
Infection with grade 3 or 4 Neutropenia	10	6.0	1	0.6	6	3.7	0	0.0
Mood alteration-anxiety agitation	22	13.1	1	0.6	14	8.6	0	0.0
Other auditory/hearing	11	6.5	1	0.6	8	4.9	0	0.0
Other endocrine	12	7.1	1	0.6	16	9.8	0	0.0
Other metabolic/laboratory	7	4.2	1	0.6	11	6.7	0	0.0
Rash/desquamation	37	22.0	1	0.6	16	9.8	0	0.0
Sweating	24	14.3	1	0.6	17	10.4	0	0.0
Abdominal pain or cramping	13	7.7	0	0.0	13	8.0	1	0.6
Cardiac-ischemia/infarction	7	4.2	0	0.0	10	6.1	4	2.5
Inner ear/hearing	13	7.7	0	0.0	21	12.9	2	1.2
Insomnia	28	16.7	0	0.0	31	19.0	1	0.6
Neuropathy-sensory	29	17.3	0	0.0	24	14.7	1	0.6
Other neurology	14	8.3	0	0.0	11	6.7	1	0.6
SGOT(AST)	14	8.3	0	0.0	10	6.1	1	0.6
SGPT(ALT)	10	6.0	0	0.0	17	10.4	1	0.6
Weight loss	32	19.0	0	0.0	18	11.0	1	0.6

Table 7.10. Grade 3/4 Adverse Events in Fully Supplemented versus Never Supplemented Patients treated with Alimta/Cisplatin (Reviewers Table)

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

Figure 7.1. Alimta/Cisplatin: % of Ten Commonest Grade 3/4 Adverse Events RT Population (Reviewers Chart)

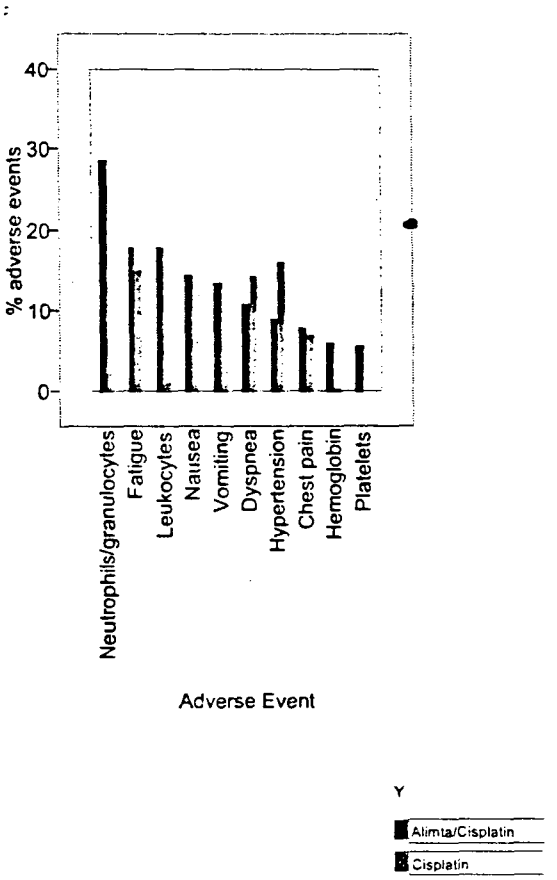


Figure 7.2. Alimta/Cisplatin: % of Ten Commonest Grade 3/4 Adverse Events RT Fully Supplemented Population (Reviewers Chart)

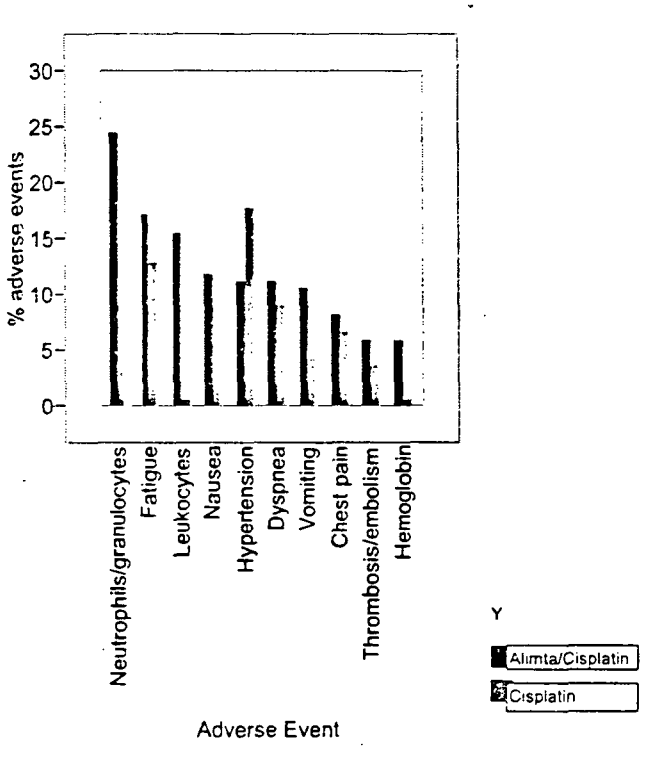
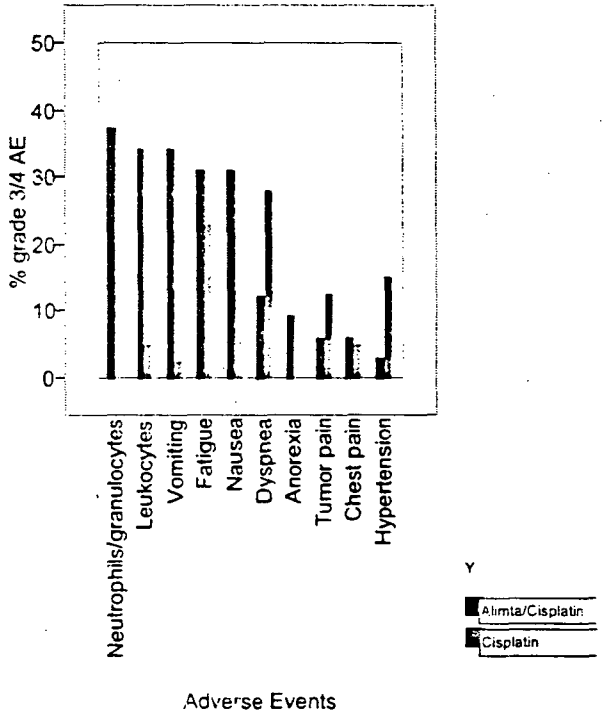


Figure 7.3. Alimta/Cisplatin: % of Ten Commonest Grade 3/4 Adverse Events RT Never-Supplemented Group (Reviewers Chart)



The following adverse events were selected to be discussed individually.

1. Neutropenia

There were 1066 cycles of Alimta delivered to the 226 patients in the Alimta/cisplatin arm. For these patients, the median nadir ANC was 1,928 cells/mm^3.
Twenty-three of these patients had nadir ANC below 500 in a total of 31 cycles (threshold for dose adjustment), with the median nadir count of 274 cells/mm^3. For these 23 patients, the median duration of neutropenia to recovery above 500 cells/mm^3 was 7 days.

There were 877 cycles of cisplatin delivered to the 222 patients in the cisplatin arm. For these patients, the median nadir ANC was 3,443 cells/mm^3. Only 1 patient had nadir ANC below 500 and this occurred in only 1 cycle, (440 cells/mm^3).

Five patients had febrile neutropenia, 4 in the Alimta/cisplatin arm, of which one was in the supplemented group. One death was attributed to febrile neutropenia (Patient # 510-5100). Two other deaths while on-study therapy also had febrile neutropenia (Patient # 804-8040 and # 150-1580). There were no deaths in the supplemented group. Two patients were hospitalized for febrile neutropenia (Patient # 111-1347 and # 804-8040).

Granulocyte colony-stimulating factors (CSFs) were given to 5 patients, all for the purpose of treating established severe neutropenia. Of the 4 patients on the Alimta/ cisplatin arm, 3 patients were in the PS+ NS subgroup. The patient on the cisplatin alone arm was also in that subgroup.

Table 7.12 shows the patients with febrile neutropenia and infection with and without neutropenia.

Table 7.11. Incidence and Severity of Neutropenia (Reviewers Table)

Neutropenia grade	RT patients				Fully Supplemented patients			
	Alimta/cisplati n N	%	Cisplatin N	%	Alimta/cisplati n N	%	Cisplatin N	%
1	31	13.7	15	6.8	23	13.7	9	5.5
2	43	19.0	13	5.9	32	19.0	8	4.9
3	47	20.8	4	1.8	32	19.0	4	2.5
4	18	8.0	1	0.5	9	5.4	1	0.6

Table 7.12. Safety: Neutropenia/Infection (Reviewers Table)

Event	Randomized and treated patients				Fully supplemented patients			
	Alimta/cisplati n N	%	Cisplatin N	%	Alimta/cisplati n N	%	Cisplatin N	%
Febrile neutropenia	4	1.8	1	0.5	1	0.6	0	0
Infection with G3/4 neutropenia	3	1.3	1	0.5	0	0	0	0
Infection without neutropenia	1	0.4	0	0	1	0.6	0	0

2. Anemia

There were no protocol restrictions to the use of erythrocyte CSFs. Of the 24 patients who received erythrocyte CSFs, 17 patients were treated for anemia. A total of 7 patients received erythrocyte CSFs prophylactically, 5 patients on the Alimta/ cisplatin fully supplemented arm and 2 patients on the cisplatin alone partially or nonsupplemented arm.
There were no patients who were transfused due to bleeding.

Table 7.13. Incidence and Severity of Anemia (Reviewers Table)

Anemia grade	RT population				Fully Supplemented			
	Alimta/cisplatin N	%	Cisplatin N	%	Alimta/cisplatin N	%	Cisplatin N	%
1	51	22.6	28	12.6	39	23.2	21	12.9
2	52	23.0	19	8.6	41	24.4	14	8.6
3	14	6.2	1	0.5	10	6.0	1	0.6
4	1	0.4	0	0.0	1	0.6	0	0.0

3. Fatigue

Grade 3 fatigue was high and not lessened by supplementation in the Alimta/cisplatin arm. Fatigue together with co-existing nausea or mild vomiting leads to decreased quality of life and may not allow most patients to maintain relatively normal function while receiving treatment.

Table 7.14. Incidence and Severity of Fatigue (Reviewers Table)

Fatigue grade	RT population				Fully Supplemented			
	Alimta/cisplatin N	%	Cisplatin N	%	Alimta/cisplatin N	%	Cisplatin N	%
1	75	33.2	71	43.6	57	33.9	50	30.7
2	71	31.4	62	38.0	51	30.4	49	30.1
3	39	17.3	33	20.2	29	17.3	20	12.3
4	2	0.9	1	0.6	0	0.0	1	0.6

5. Nausea

Both treatment arms were treated with 5-HT3 antagonists and many received additional treatments. Both treatment arms also received dexamethasone.
In the Alimta/cisplatin arm, the most frequently reported serious adverse event was nausea (8.4%) and vomiting (8.4%).

In the Alimta/cisplatin arm the median time to start of nausea after chemotherapy was one day (range of 0 to 22 days) and the median duration of nausea was 6 days. Excluding episodes of nausea recorded as intermittent, the maximum duration of nausea was 37 days.

For the cisplatin alone arm, the median time to start of nausea after chemotherapy was one day (range of 0 to 31 days), and the median duration of nausea was 5 days. Excluding episodes of nausea recorded as intermittent, the maximum duration of nausea was 58 days.

Table 7.15. Incidence and Severity of Nausea (Reviewers Table)

Nausea grade	RT population				Fully Supplemented			
	Alimta/cisplatin		Cisplatin		Alimta/cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
1	69	30.5	86	38.7	50	29.8	64	39.3
2	93	41.2	77	34.7	72	42.9	55	33.7
3	31	13.7	14	6.3	19	11.3	9	5.5
4	2	0.9	0	0.0	1	0.6	0	0.0

6. Vomiting

Vomiting was the most frequently reported serious adverse event reported in both the Alimta/cisplatin arm (8.4%) and the cisplatin alone arm (2.3%). It was also one of the main reasons for discontinuation.

Table 7.16. Incidence and Severity of Vomiting (Reviewers Table)

Vomiting grade	RT population				Fully Supplemented			
	Alimta/cisplatin		Cisplatin		Alimta/cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
1	49	21.7	57	25.7	37	22.0	43	26.4
2	65	28.8	52	23.4	44	26.2	33	20.2
3	29	12.8	7	3.2	17	10.1	6	3.7
4	2	0.9	1	0.5	1	0.6	1	0.6

7. Renal

Table 7.17 shows the incidence of renal-related adverse events. The incidence of renal-related events are higher in the Alimta/cisplatin combination arm compared to the cisplatin alone arm in both the RT and FS populations. The incidence of increased creatinine and decreased creatinine clearance are higher in the Alimta/cisplatin arm. There is a slight decrease with supplementation.

Table 7.17. Incidence of Renal Events (Reviewers Table)

Renal AE	RT patients				Fully Supplemented patients			
	Alimta/cisplatin N=248		Cisplatin N=222		Alimta/cisplatin N=168		Cisplatin N=163	
	N	%	N	%	N	%	N	%
Creatinine renal clearance decreased	61	27.0	49	22.1	40	23.8	36	22.1
Blood creatinine increased	39	17.3	26	11.7	26	15.5	18	11.0
Nocturia	1	0.4	0	0.0	1	0.6	0	0.0
Hydronephrosis	1	0.4	1	0.5	1	0.6	1	0.6
Polyuria	1	0.4	0	0.0	1	0.6	0	0.0
Blood urea increased	2	0.9	3	1.4	2	1.2	3	1.8
Renal impairment NOS	2	0.9	1	0.5	1	0.6	1	0.6
Renal failure NOS	0	0.0	1	0.5	0	0.0	1	0.6
Acute pre-renal failure	1	0.4	0	0.0	0	0.0	0	0.0

Reviewer's Comments:
All adverse events are discussed without regard to the possibility of a causal relationship. All safety reviewers' results are based on the analysis data sets provided by the sponsor.
The Alimta and cisplatin combination is more toxic than cisplatin alone.
The data suggest that Alimta has a relatively high emetogenic potential in this treatment setting, given the similarity in the frequency of 5- HT3 administration across both treatment arms. Of note is that both treatment arms also received dexamethasone.
The most frequent toxicity of Alimta, myelosuppression, was reduced by folate and vitamin B_{12} supplementation.

Supplementation resulted in overall less toxicity including grade 3/4 toxicity in the Alimta/cisplatin arm. Patients receiving cisplatin alone also seemed to benefit from vitamin

supplementation, although to a lesser degree. Despite supplementation, however, the combination of Alimta and cisplatin produces a high degree of toxicity.

Serious Adverse Events

Serious adverse events (SAE) were defined as any event that resulted in death, initial or prolonged hospitalization, severe or permanent injury, congenital anomaly, was life-threatening or significant for any other reason. Table 7.18 summarizes the serious adverse events for patients enrolled into the study, regardless of drug causality. There were 36.7% SAE on the Alimta/cisplatin arm and 21.6 % on the cisplatin arm alone.

Table 7.18. Summary of Serious Adverse Events (> 2% Incidence) Regardless of Drug Causality RT Population

Event Classification	LY231514/CISPLATIN (N=226) n (%)	CISPLATIN (N=222) n (%)	TOTAL (N=448) n (%)	p-value
PATIENT WITH >= 1 EVENT	83 (36.7)	48 (21.6)	131 (29.2)	<.001
Vomiting NOS	19 (8.4)	5 (2.3)	24 (5.4)	0.005
Nausea	19 (8.4)	3 (1.4)	22 (4.9)	0.001
Dehydration	14 (6.2)	1 (0.5)	15 (3.3)	0.001
Dyspnoea NOS	9 (4.0)	6 (2.7)	15 (3.3)	0.601
Fatigue	9 (4.0)	3 (1.4)	12 (2.7)	0.141
Diarrhoea NOS	8 (3.5)	1 (0.5)	9 (2.0)	0.037
Neutrophil count decreased	9 (4.0)	0 (0.0)	9 (2.0)	0.004
Stomatitis	8 (3.5)	0 (0.0)	8 (1.8)	0.007
Anaemia NOS	7 (3.1)	0 (0.0)	7 (1.6)	0.015
Anorexia	5 (2.2)	0 (0.0)	5 (1.1)	0.061
White blood cell count decreased	5 (2.2)	0 (0.0)	5 (1.1)	0.061

Frequencies analyzed using a Fisher's Exact test

Source: Applicant Table JMCH.12.23.

The most frequently reported SAEs in the Alimta/ cisplatin arm were nausea (8.4%), vomiting (8.4%), and dehydration (6.2%). The most frequently reported SAEs in the cisplatin alone arm were dyspnea (2.7%) and vomiting (2.3%).

3.2 Discontinuations

Table 7.19 summarizes the reasons for discontinuations due to SAEs. A total of 15 (6.6%) patients on the Alimta/ cisplatin arm and 5 (2.3%) patients on the cisplatin alone arm discontinued from the study because of a SAE in the RT population. In the Alimta/ cisplatin arm, 4% patients discontinued because of possibly drug-related serious adverse events and, except for diarrhea that occurred twice, these were all single types of events.