

CLINICAL REVIEW

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

Rationale for Surgical Management

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

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

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

¹²⁴ Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
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There are no real guidelines preoperatively that one can use to assure the patient which operation will accomplish tumor removal. The presence of irregular, bulky disease that on the CT infiltrates into the fissures probably dictates the necessity for EPP; a large effusion with minimal bulk disease may call for pleurectomy decortication. Moreover, the philosophy of the surgeon regarding the operation may affect his or her choice, because some surgeons reserve EPP for those patients with bulk disease that presents simple pleurectomy, whereas others believe that the greatest chance for complete gross excision is via EPP performed in the patient with minimal disease. This important factor, preoperative quantitative bulk of disease, may not only influence the choice of resection, but may be an important preoperative prognostic factor in any patient with malignant pleural mesothelioma.¹²⁵

Indications for Surgical Management

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

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

¹²⁶ Antman KH, Pass HI, Schiff PB. Management of Mesothelioma. P. 1943
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Chemotherapy

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

Patients Who Had Prior Chemotherapy

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

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

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

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

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

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

Agent	First Author/Year	No. of Patients	Responders		95% Confidence Interval* (%)
			No.	%	
Doxorubicin	Lerner ⁷ /1983	51	7	14	7-26
Doxorubicin	Sorenson ⁸ /1985	15	0	0	0-20
Detorubicin	Colbert ¹¹ /1985	35	9	26	14-42
Pirarubicin	Koukel ¹² /1987	35	8	22	11-38
Epirubicin	Magri ¹³ /1991	21	1	5	1-23
Epirubicin	Mattson ¹⁴ /1992	48	7	15	6-28
Mitoxantrone	Eisenhauer ¹⁷ /1986	28	2	7	2-22
Mitoxantrone	van Breukelen ¹⁸ /1991	34	1	3	0-27
Cisplatin	Mintzer ¹⁹ /1985	24	3	13	4-31
Cisplatin	Zidar ²⁰ /1988	35	5	14	6-29
Carboplatin	Mbicke ²² /1986	17	2	12	0-27
Carboplatin	Raghavan ²⁴ /1990	31	5	16	5-34
Carboplatin	Vogelzang ²⁵ /1990	40	3	7	2-21
Vindesine	Kelsen ²⁶ /1983	17	1	6	0-17
Vindesine	Boutin ²⁷ /1987	21	0	0	0-15
Vincristine	Martensson ²⁸ /1989	23	0	0	0-14
Vinblastine	Cowan ²⁹ /1988	20	0	0	0-16
Paclitaxel	Vogelzang ³⁰ /1994	15	2	13	4-38
Cyclophosphamide	Sorenson ⁸ /1985	16	0	0	0-19
Ifosfamide	Alberts ³² /1988	17	4	24	10-48
Ifosfamide	Zidar ²⁴ /1992	26	2	8	1-25
Ifosfamide	Falkson ³⁵ /1992	40	1	3	1-14
Mitomycin	Bajorin ³⁶ /1987	19	4	21	8-43
Methotrexate	Solheim ³⁷ /1992	60	22	37	26-50
Trimetrexate	Vogelzang ³⁰ /1994	51	6	12	2-33
Edatrexate	Belani ⁴¹ /1994	20	5	25	9-49
Edatrexate + leucovorin	Belani ⁴² /1995	17	3	18	6-41
CB3717	Cantwell ⁴³ /1986	18	1	6	0-27
5-FU	Harvey ⁹ /1984	20	1	5	1-24
DHAC	Harmon ⁴⁴ /1991	42	7	17	9-31
Amsacrine	Falkson ⁴² /1980	19	1	5	1-24
Diaziquone	Eagan ⁴⁶ /1986	20	0	0	0-17
BCG	Webster ⁴⁹ /1982	30	NA	NA	NA
Acicvin	Alberts ³⁰ /1988	19	0	0	0-17
Interferon alfa-2a	Christmas ⁵¹ /1993	25	3	12	4-30
Interleukin-2†	Eggermont ⁵² /1991	17	4	24	10-48
Interferon gamma†	Boutin ²⁷ /1991	22	5	23	10-44

NOTE. Modified and reprinted with permission.⁷⁹

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

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

†Intrapleural therapy for early-stage disease.

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

Agent	First Author/Year	No. of Patients	Responders		95% Confidence Interval (%)
			No.	%	
Doxorubicin + cyclophosphamide	Samson ³⁷ /1987	36	4	11	6-21
Doxorubicin + DTIC + cyclophosphamide	Samson ³⁷ /1987	40	5	13	6-21
Doxorubicin + cyclophosphamide + DTIC	Dhingra ³⁸ /1983	20	5	25	11-47
Doxorubicin + ifosfamide	Carmichael ³⁹ /1989	16	2	12.5	1-38
Doxorubicin + cisplatin	Ardizzoni ⁴⁰ /1991	24	6	25	10-47
Doxorubicin + cisplatin	Chahinian ⁴¹ /1993	35	5	14	5-30
Mitomycin + cisplatin	Chahinian ⁴¹ /1983	35	9	26	12-43
Doxorubicin + cisplatin + cyclophosphamide	Shin ⁴¹ /1993	23	6	26	12-46
Epirubicin + ifosfamide	Magni ⁴⁴ /1992	17	1	6	1-27
Rubidazole + DTIC	Zidar ⁴⁵ /1983	23	0	0	0-14
DHAC + cisplatin	Samuels ⁴⁶ /1994	30	4	13	5-29
Mitomycin + bleomycin + cisplatin + doxorubicin	Breau ⁴⁷ /1991	25	11	44	27-63
Cisplatin + etoposide	Eisenhauer ⁴⁸ /1988	26	3	12	4-30
Fluorouracil + cisplatin	Koschel ⁴⁹ /1991	39	6	15	7-29
Doxorubicin + 5-azacytidine	Chahinian ⁴⁴ /1982	36	8	22	12-38
Doxorubicin + interferon alfa	Upham ⁵² /1993	25	4	16	6-35
Mitomycin + cisplatin + interferon alfa	Tanson ⁵⁴ /1994	20	2	11	3-30
Cisplatin + interferon alfa	Trondafir ⁵³ /1994				
	Low-dose interferon	22	8	36	19-57
	High-dose interferon	15	3 + 1 CR	27	11-52

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

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

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V. Clinical Review Methods

1. How the Review was Conducted

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

Protocol H3E-MC-JMCH(g): A Single-blind Randomized Phase 3 Trial of MTA¹²⁸ plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma (Pivotal trial; reviewed by FDA)

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

The safety review included analyses from the studies listed below.

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

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

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

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

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

c Data from supplemented patients in studies JMBT, JMAM, JMDR, and JMDS.

d Data from nonsupplemented patients in studies JMAC, JMAD, JMAG, JMAH, JMAI, JMAJ, JMAK, JMAL, JMBA, JMBM, JMBP, JMBQ, JMBO, JMBR, JMBT, JMAM, and JMDR.

e Supplementation regimen: 5 mg folic acid daily for 5 days beginning 2 days before each cycle; no vitamin B₁₂ was given.

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

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

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

2. Overview of Materials Consulted in Review

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

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

DSI was consulted to audit four sites from study JMCH.

Sites for DSI Audit

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

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

The DSI consult reported no deviations from ethical standards.

5. Evaluation of Financial Disclosure

5.1 Financial Disclosure Review

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

Study ID	Count	Investigator Name	Role	Date	Rating	Financial Disclosure Status
7/133	2	Dr. David R Gandara	PI	5/21/01	A	None
			SI	8/23/01	A	None
			SI	12/18/01	D	None
			SI	9/19/01	A	None
			SI	10/15/01	D	None
			SI	10/3/01	A	None
			SI	10/17/01	A	None
			SI	8/8/01	A	None
			SI	7/12/01	A	None
			SI	10/15/01	D	None
			SI	7/11/01	A	None
			SI	10/15/01	D	None
			SI	7/12/01	A	None
			SI	10/4/01	A	None
			SI	10/15/01	D	None
			8/107	4	Dr David S. Ettinger	PI
SI						None
12/128	1	Dr. Karen Kellu	PI	6/12/01	A	None
			SI	6/8/01	A	None
15/129	1	Dr. Harvey I Pass	PI	6/7/01	A	None
			SI	6/5/01	A	None
18/130	16	Dr. Nick J Vogelzang	PI	8/5/01	A	None
			SI	6/8/01	A	None
			SI	11/18/01	D	None
			SI	6/7/01	A	None
			SI	6/8/01	A	None
			SI	6/8/01	A	None
			SI	11/18/01	D	None
			SI	11/18/01	D	None
			SI	6/8/01	A	None
			SI	11/15/01	D	None
			SI	6/8/01	A	None
			SI	6/27/01	A	None

Below is the key for the above table.

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¹In some cases, patients were consented but not enrolled in the trial
²PI = Primary Investigator; SI = Subinvestigator; CI = Co-Investigator
³A = Nothing to disclose; B = Disclosure provided; C = Refused to disclose;
⁴D = Disclosure not obtained, due diligence performed; E = Did not participate in study (Submitted on Form FDA 1572 to Regulatory, did not enroll patients)
⁵Family member name listed if information disclosed
⁶Incomplete documentation on financial disclosure: A note to the reviewer will be included in the submission indicating what is missing and stating the information will be available upon request. The ALJMTA Team will obtain the missing information or document due diligence in attempting to obtain the missing information.
⁷Disclosure not available at the time of submission. A note to the reviewer will be included in the submission indicating what is missing and stating the information will be available upon request. The ALJMTA Team will obtain the missing information or document due diligence in attempting to obtain the missing information.

HSE-MC-JMCH-Form 3464 attachment.doc
 Date: 9/24/03

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

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

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

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CO-AUTHOR INVESTIGATOR U.S CITY OR COUNTRY		LILLY RESPONSE TO FDA DEFICIENCIES DATED 12/4/2003	¹²⁹ DATE SIGNED FINANCIAL DISCLOSURE DATE LAST PATIENT @ SITE RANDOMIZED TO STUDY
			cisplatin alone
Kaukel Germany	Nothing to disclose		2/19/2001 2/5/2001 cisplatin alone
Ruffie France	Nothing to disclose		11/6/2001 3/1/2001 cisplatin alone
Boyer Australia	Nothing to disclose		8/23/2001 2/20/2001 alimta/cisplatin
Emri Turkey	Nothing to disclose		Not dated; fax date 9/1/2001 3/22/2001 cisplatin alone

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

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

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

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

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

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

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

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

Financial disclosure for JMCH submitted 3/24/2003:

H3E-MC-JMCH						
Country/Inv Number/Site Number	Number of Patients Consented per Site ¹	Study Investigators	Title ²	Response Received ³	Disclosure ³	Family Member Name ^{3,4}
UNITED STATES 8/107	4	David S. Eisinger	PI	11/18/01	B	None

Disclosure of Financial Information (USD)

H3E-MC-JMCH						
Country/Inv Number/Site Number	Number of Patients Consented per Site ¹	Study Investigators	Title ²	Response Received ³	Disclosure ³	Family Member Name ^{3,4}
CANADA 3/252	2	Dr. C A Buils	PI	12/18/01	B	None

Disclosure of Financial Information

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

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H3E-MC-JMCH

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

Disclosure of Financial Information

H3E-MC-JMCH

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

Disclosure of Financial Information

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

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

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

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

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

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

5.2 Summary Statements About Financial Disclosure

Preliminary review: 3/24/2003 submission

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

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

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

In response to FDA queries:

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

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

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

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

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VI. Integrated Review of Efficacy

1. Brief Statement of Conclusions

1.1 Lilly's Summary of Efficacy--Study JMCH

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

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

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

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

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

1.2 FDA's Summary of Efficacy--Study JMCH

Survival

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

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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.

Tumor Response

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

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.

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

Also, according to Lilly:

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

Patient Benefit Response

[

]

Pulmonary Function Tests

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

¹³¹ Lilly correspondence dated 11/26/2003

¹³² Lilly correspondence dated 12/4/2003

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

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

Protocol H3E-MC-JMCH(g): A Single-blind Randomized Phase 3 Trial of MTA¹³³ plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma (Pivotal trial; reviewed by FDA)

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

**APPEARS THIS WAY
ON ORIGINAL**

¹³³ alimta

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

Additional secondary objectives of this study were:

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

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

Entry Procedures

An informed consent was to be obtained from each patient after the nature of the study was explained. The investigator was responsible to see that informed consent was obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug. As used in this protocol, the term "informed consent" included all consent and/or assent given by subjects, patients, or their legal representatives.

Criteria for Enrollment

Enter The act of obtaining informed consent for participation in a clinical study from individuals deemed potentially eligible to participate in the clinical study. Individuals *entered* into a study were those for whom informed consent documents for the study have been signed by the potential study participants or their legal representatives.

Enroll The act of assigning an individual to a treatment group. Individuals who were *enrolled* in the study were those who have been assigned to a treatment group.

A person who has been *entered* into the study was potentially eligible to be *enrolled* in the study, but must meet *all* criteria for enrollment specified in the protocol before being *enrolled* (assigned to a treatment group). Individuals who were *entered* into the study but fail to meet the criteria for enrollment were *not* eligible to participate in the study and would not be *enrolled*.

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

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

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

Violation of Criteria for Enrollment

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

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

International Mesothelioma Interest Group Staging Criteria for Mesothelioma

Primary Tumor (T):

T1

T1a Tumor limited to the ipsilateral parietal including mediastinal and diaphragmatic pleura, no involvement of the visceral pleura mediastinal and diaphragmatic pleura, scattered foci of tumor also involving the visceral pleura

T2

Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: involvement of diaphragmatic muscle; confluent visceral pleural tumor (including the fissures), or extension of tumor from visceral pleura into the underlying pulmonary parenchyma

T3

Describes locally advanced but potentially resectable tumor: tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: involvement of the endothoracic fascia; extension into the mediastinal fat; solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall; on-transmural involvement of the pericardium

T4

Describes locally advanced technically unresectable tumor: tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features: diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction; direct transdiaphragmatic extension of tumor to the peritoneum; direct extension of tumor to the contralateral pleura; direct extension of tumor to one or more mediastinal organs; direct extension of tumor into the spine; tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

Lymph Nodes (N):

NX

Regional Lymph nodes cannot be assessed

N0

No regional lymph node metastases

N1

Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes

N2

Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary nodes

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N3

Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

Metastases (M):

MX

Presence of distant metastases cannot be assessed

M0

No distant metastasis

M1

Distant Metastasis present

Staging:

Stage Ia T1aN0M0

Stage Ib T1bN0M0

Stage II T2N0M0

Stage III Any T3M0, AnyN1M0, AnyN2M0

Stage IV Any T4, AnyN3, AnyM1

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

Inclusion Criteria

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

- Histologically proven diagnosis of mesothelioma of the pleura in patients not candidates for curative surgery. Patients were to be clinically staged using the IMIG TNM staging criteria (see above). Patients were to be entered and randomized based on local pathology; however, independent centralized pathology review was to be carried out on all patients if feasible.
- Disease status was to be that of unidimensionally and/or bidimensionally measurable disease defined as:
Measurable disease. Bidimensionally and unidimensionally measurable lesions with clearly defined margins by computerized tomography (CT) or MRI. Examples of measurable disease would include a mediastinal or hilar node, or a discrete pleural mass. A CT scan was also required for any palpable masses. For metastatic disease, this would include a clearly defined mass on CT.
NOTE: Neither pleural effusions nor positive bone scans are considered measurable.
- Patients who have undergone pleurodesis. If pleurodesis was performed, there must be at least a 2-week delay before MTA or cisplatin is administered. If the original CT scan

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

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

- Performance status of 70 or higher on the Karnofsky Scale (after any palliative measures including pleural drainage have occurred).
- Estimated life expectancy of at least 12 weeks.
- Patient compliance and geographic proximity that allow adequate follow-up.
- Adequate organ function including the following:
 - Adequate bone marrow reserve: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, and hemoglobin ≥ 9 g/dL.
 - Hepatic: bilirubin ≤ 1.5 times the upper limit of normal, alkaline phosphatase, aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times upper limit of normal (alkaline phosphatase, AST, ALT ≤ 5 times upper limit of normal is acceptable if liver has tumor involvement).
- Albumin ≥ 2.5 g/dL.
- Renal: calculated creatinine clearance (CrCl) ≥ 45 mL/min using the lean body mass formula only (see Protocol Attachment JMCH.3). If both local and central lab CrCl are ≥ 45 mL/min investigators could have chosen which value to follow for the duration of the study. If investigators had chosen to follow the local CrCl, the serum creatinine must be assayed at the same local lab each time for that patient. If the local CrCl was < 45 mL/min and the — CrCl was ≥ 45 mL/min the patient could be enrolled based on the — result. If the patient was enrolled based on the — result, — CrCl was to be used for all future dosing decisions. If the local CrCl was ≥ 45 mL/min and the — CrCl was < 45 mL/min, the Lilly physician responsible for the study was to be contacted before the patient is enrolled.
- Signed informed consent from patient.
- Males or females at least 18 years of age.
- Male and female patients with reproductive potential were to use an approved contraceptive method if appropriate (eg, intrauterine device [IUD], birth control pills, or barrier device) during and for 3 months after the study.

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Exclusion Criteria

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

- Prior systemic chemotherapy. Prior intracavitary cytotoxic drugs or immunomodulators were not permitted, unless given for the purpose of pleurodesis.
- Prior radiation therapy to the target lesion, unless the lesion was clearly progressing and the interval between the most recent radiation therapy and enrollment was at least 4 weeks.
- Active infection (at the discretion of the investigator). Patients previously treated with a nephrotoxic antibiotic were at risk of further toxicity due to cisplatin and should be very carefully monitored.
- Pregnancy or breast feeding.
- Serious concomitant systemic disorders (including oncologic emergencies) incompatible with the study (at the discretion of the investigator).
- Second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or other malignancy treated at least 5 years previously with no evidence of recurrence).
- Use of any investigational agent within 4 weeks before enrollment into the study.
- Inability to interrupt aspirin or other nonsteroidal anti-inflammatory agents 2 days before, the day of, and 2 days after the dose of MTA plus cisplatin or cisplatin alone. If a patient is taking a NSAID (Cox-2 inhibitors included) or salicylate with a long half-life (eg, naproxen, piroxicam, diflunisal, nabumetone, rofecoxib, or celecoxib) it should not be taken 5 days before the dose of MTA, the day of, and 2 days after the dose of MTA plus cisplatin or cisplatin alone.
- Disease which cannot be radiologically imaged.
- Known or suspected brain metastases.
- Any patient who was obviously malnourished or who has experienced a greater than 10% weight loss in the preceding 6 weeks.
- Inability to take folic acid or vitamin B12 administration.

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The Randomized Treatments:

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

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

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

Drugs other than MTA

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

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

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

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

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

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

Dose Adjustments or Delays for Subsequent Cycles

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

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

PLATELETS ($\times 10^9/l$) NADIR		ANC ($\times 10^9/l$) NADIR	PERCENT OF PREVIOUS Dose (both drugs)
≥ 50	and	≥ 0.5	100%
≥ 50	and	< 0.5	75%

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

Table. Dose Modifications for Mucositis

CTC GRADE	DOSE FOR NEXT CYCLE	Cisplatin
	MTA or normal saline without MTA	
Grade 0-2	100% of previous dose	100% of previous dose
Grade 3-4	50% of previous dose	100% of previous dose
Recurrence of Grade 3 or 4 after treatment at 2 dose Reductions	Discontinue patient from study	Discontinue patient from study

Diarrhea or Other Non-Hematologic Toxicity

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

Table. Neurosensory Toxicity

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

Tinnitus or Significant Clinical Hearing Loss

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

Creatinine Clearance

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

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

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

Treatment Delays Due to Insufficient Folic Acid or Vitamin B12 Supplementation

There were four situations in which treatment might be delayed due to insufficient folic acid or vitamin B12 supplementation. These were represented in the following table.

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

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Concomitant Therapy

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

Colony Stimulating Factors

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

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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

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

Leucovorin

Leucovorin rescue was allowed for CTC Grade 4 neutropenia lasting ≥ 5 days, CTC Grade 4 thrombocytopenia, and mucositis \geq Grade 3. If given for myelosuppression as described above, leucovorin was to be started on the fifth day of the Grade 4 myelosuppressive event. Leucovorin was to be started immediately if a patient developed CTC Grade 3 or 4 mucositis. The following doses and schedules were recommended:

Leucovorin 100 mg/m² intravenously times one; then Leucovorin 50 mg/m² intravenously every 6 hours for 8 days.

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

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of TS inhibition as a rescue agent, namely thymidine. Thymidine was proposed as a reversal agent for severe toxicity from either 5-fluorouracil (5-FU) or methotrexate, but overall the clinical experience was limited. Thymidine was been reported to reverse the severe toxicity associated with 5-FU in a patient with dihydropyrimidine dehydrogenase deficiency. Reversal of methotrexate toxicity has also been reported in patients with normal as well as impaired renal function. One patient treated with MTA has received thymidine after developing severe toxicity. This patient developed severe myelosuppression as well as somnolence on Day 5 following MTA. Myelosuppression was an expected toxicity of MTA, but severe neurotoxicity was not a common toxicity. Leucovorin was administered for 24 hours, beginning on Day 6. Since the leucovorin did not appear to resolve the toxic effects, thymidine was administered for 3 days by continuous infusion at a dose of 8 g/m²/day. Partial resolution of the neurotoxicity was noted after the first day of infusion and by the third day the patient had fully recovered.

Statistical Design

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

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

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

According to data examined in a multivariate analysis across a variety of MTA studies (n = 267 patients), elevated baseline homocysteine levels ($\geq 12 \cdot \text{mol/L}$) strongly correlated with severe hematologic and nonhematologic toxicities following treatment with MTA. Because of these correlations, this study was to provide for balancing the numbers of patients with baseline homocysteine levels $< 12 \cdot \text{mol/L}$ or $\geq 12 \cdot \text{mol/L}$ equally across all treatment groups. Additional prognostic factors to be balanced for between the two treatment arms included performance status, histological subtype, white blood cell count, and gender¹³⁵. Because both unidimensionally and bidimensionally measurable disease were to be permitted, treatment arms were also to be balanced for degree of measurability of disease.

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

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MEDICAL OFFICER COMMENT:

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

"The informed consent document will be used to explain in simple terms, before the patient is entered into the study, the risks and benefits to the patient. The informed consent document must contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time.

The investigator is responsible to see that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug."

From the informed consent:

"In this study you will either receive LY231514 given with a widely used drug called cisplatin or you will receive a salt water solution and the widely used drug. Your participation in this study will last until your disease gets worse, you don't want to continue the study anymore, the drug(s) make you sick, or your doctor and/or the Sponsor feels that it is in your best interest to stop taking the drug. There is no maximum time you can take this drug. At least 430 patients will be participating in this study. (p. 1733)"

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

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

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The 280 qualified patients receiving vitamin supplementation during every cycle of their study therapy were to be equally randomized between the treatment arms (ie, 140 patients per arm). A treatment was to be judged superior if it is associated with a 33% reduction in the hazard ratio of the two treatments by median survival time period of the least efficacious therapy. Assuming an exponential survival, 15 month patient accrual, and an additional minimum 9 month follow-up for all patients and a censoring rate of 30% or less after the 24 month accrual and follow-up period, the procedure described above gives at least an 81% chance (power) to detect a 33% shift in hazard ratio as reflected by a 63% survival probability on the best treatment arm by the time only 50% of patients are still alive (median time) on the least efficacious treatment arm. These calculations used a twosided logrank test with a 0.05 chance of rejecting the null hypothesis H_0 of no difference in survival between the two treatment arms when H_0 was actually true.

Patient Assignment

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

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

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

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

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

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

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patient scale.

- Analgesic consumption at entry was to have two strata:
 - Low: baseline score <60 mg morphine equivalents per day, only NSAIDS, or no analgesic consumption.
 - High: baseline score \geq 60 mg morphine equivalents per day.
- Dyspnea at entry was to have two strata:
 - Low: Baseline score <20 mm on the VAS of Question 4 in the LCSS patient scale.
 - High: Baseline score \geq 20 mm on the VAS of Question 4 in the LCSS patient scale.
- Baseline homocysteine (pre-folic acid supplementation) was to have two strata:
 - High: Baseline homocysteine \geq 12 • mol/L
 - Low: Baseline homocysteine <12 • mol/L
- Each gender was to be a stratum.
- Each country was to be a stratum.
- Each treatment center was to be a stratum.

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

Blinding

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

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

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Clinical Benefit Response

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

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

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

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

Pain intensity:

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

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

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

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

Dyspnea:

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

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

Analgesic consumption:

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

- A positive change in analgesic consumption was to be defined as a decrease in analgesic consumption in milligrams of morphine equivalents per day per week of at least 50%. (Average over at least one treatment cycle.)
- A negative change in analgesic consumption was to be defined as an increase in analgesic consumption in milligrams of morphine equivalents per day per week or at least 50%. (Average over at least one treatment cycle.)
- No change in analgesic consumption (stable analgesic consumption) was to be defined as an increase or decrease in analgesic consumption of less than 50%. (Over at least one treatment cycle.)

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Karnofsky Performance Status:

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

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

Lung Cancer Symptom Scales (LCSS):

Included in the protocol as an attachment.

Pulmonary Function Tests:

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

Tumor Response

Assessment Intervals

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

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

Within 2 weeks of study enrollment the disease status of each patient will be assessed with the following procedures:

- Medical history and physical examination, including measurements of height and weight
- Collection of information on habits
- Evaluation of performance status (Karnofsky scale)
- Measurement of pulmonary function using the following tests:
Forced vital capacity (FVC).

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Slow vital capacity (SVC).

Forced expiratory volume in one second (FEV₁).

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

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

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

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

- Complete the LCSS patient scale.

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

- Weekly (Days 8 (± 1 day), 15 (± 1 day), and 19 of each cycle):
Complete the LCSS patient scale.
- Prior to each cycle of treatment:
Weight measurements.
Performance status evaluation (should be done by an independent observer).
Limited medical history and physical examination.
LCSS observer scale administered prior to consultation with physician and other procedures (should be done by an independent observer).
- Prior to every other treatment cycle:
Pulmonary function tests.
Lung density measurements (patients on JMCH(a)-(d) only).
CT scan for tumor measurement. After first documentation of response, the studies must be repeated 4 weeks later to confirm the response.

Post Study Follow-Up

For the purposes of follow-up for tumor response and time to event variables, the following assessments were to take place at the stated intervals:

- Approximately 4 weeks after a patient has received his or her last dose of MTA or cisplatin:
CT scan for the purposes of response confirmation (for those patients who have experienced a partial or complete response which has been documented by lesion measurements).

LCSS patient and observer scales completed, unless the patient has received post study chemotherapy, radiotherapy, or surgical intervention for cancer.
- Approximately every 6 weeks after a patient without demonstrated progressive disease has received their last CT scan:
 - CT scan for the purpose of evaluating disease status. If patients had progressive disease during this time or had not progressed after 6 months off study, CT scans only were to be done if there was clinical suspicion of progression.

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- Clinical assessment to evaluate disease status. If patients had progressive disease during this time or had not progressed after 6 months off study, these clinical assessments were to be changed in frequency to every 12 weeks.
- Approximately every 3 months after the patient has received their last dose of MTA or cisplatin:
 - Information were to be collected regarding date of death, and any poststudy chemotherapy, radiotherapy, or surgical intervention.
 - LCSS patient and observer scales were to be completed, unless the patient has received post-study chemotherapy, radiotherapy, or surgical intervention for cancer.

Efficacy Criteria for Tumor Response

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

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

The measurability of a tumor was defined as follows:

Disease Status

- Measurable disease: Bidimensionally measurable lesions with clearly defined margins by 1) plain x-ray, with at least one diameter 0.5 cm or greater (bone lesions not included) or 2) CT, MRI, or other imaging scan, with both diameters greater than or equal to 1.0 cm and at least one image with both diameters greater than or equal to 1.5 cm or 3) palpation, with both diameters 2 cm or greater. Unidimensionally measurable lesions with clearly defined margins by 1) plain x-ray measuring at least 0.5 cm or greater (bone lesions not included); or 2) CT or MRI with the length greater than or equal to 1.0 cm and at least one image with the length greater than or equal to 1.5 cm.
- Evaluable disease: Lesions measured by x-ray with both diameter(s) less than 0.5 cm, lesions on scan with either diameter(s) smaller than 1.0 cm, palpable lesions with either diameter less than 2 cm, or bone disease.
- Nonevaluable disease: Pleural effusions, ascites, disease documented by indirect evidence only (e.g., by lab values). Scan only bone disease.

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

Lesion Measurement

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

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

CT scan measurement of tumor response:

Within 4 weeks of study enrollment each patient was to have been assessed by computerized tomography of the chest and upper abdomen. Contrast medium was to be used consistently throughout the study unless clinically contraindicated. The sections (cuts) should be 10 mm and should include the apex through the base of the lung. This method was to be used consistently for tumor assessment and was to be repeated every 6 weeks (prior to every other cycle) and every 6 weeks off study until documentation of progressive disease. For each patient, every CT image was to be compared to the corresponding image from the previous examination. To ensure identical localization of CT images, anatomical landmarks in vertebrae, ribs or the central bronchial tree was to be used during the CT scanning procedure. The thickness of the tumorous parietal, visceral, diaphragmatic, and mediastinal pleura was to be measured together with any enlarged lymph nodes in the mediastinum, retrocaval space, or axillae.

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

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

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

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

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

Included in the evaluations were the following standard criteria:

Objective status (to be recorded at each evaluation)

- Complete response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No disease-related symptoms. No evidence of nonevaluable disease, including normalization of markers and other abnormal lab values. All measurable, evaluable, and nonevaluable lesions and sites were to be assessed using the same technique as baseline.

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

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

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

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unidimensional RUL lesion and a bidimensional RML lesion) or lesions in different organs (e.g., a unidimensional lung lesion and a bidimensional liver lesion). From the RECIST criteria article, the 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.¹³⁷

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

Notes

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

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

Best Response

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

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

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

Definition of Efficacy Measures

A responder was defined as any patient who exhibited a CR or PR. The duration of a CR or PR was defined as the time from first objective status assessment of CR or PR to the first time of progression or death due to any cause. Time-to-treatment failure was defined as the time from study enrollment to the first observation of disease progression, death due to any cause, or early discontinuation of treatment. **Survival was defined as the time from study enrollment to time of death due to any cause.**

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

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efficacy evaluation throughout the study.

Clinical Laboratory Tests and Procedures

Prestudy

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

Approximately 1 to 3 weeks prior to study enrollment:

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

Within 2 weeks of study enrollment:

- Vital signs (blood pressure, pulse rate, and temperature).
- Concomitant medication notation.

Within 7 days of study enrollment:

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

During the Study

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

- Measurement of vital signs were to be repeated as clinically indicated.
- Concomitant medication (including any non-study vitamin supplementation) notation at every cycle.
- Number of units required for transfusions at every cycle.
- Hematology weekly (± 3 days) and up to 4 days prior to each cycle.

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- Blood chemistries on Day 8 (± 3 days) and up to 4 days prior to each cycle
- Calculated creatinine clearance up to 4 days prior to each cycle.
- Vitamin metabolites (assayed by _____ up to 4 days prior to each cycle beginning with Cycle 2.
- Toxicity rating using the NCI CTC scale prior to each cycle (see the CTC Investigator Guide, Version 1.0, supplied with the clinical report form)
- Pharmacokinetic sampling from patients at selected centers during Cycles 1 and 3.

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

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

Schedule of Events

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

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

- * Cycles 4-6 are the same as cycles 1-3.
- a - Obtain prior to infusion.
- b - Repeat prior to every other cycle; after documentation of tumor response; confirm tumor response with studies 4 weeks later.
- c - LCSS patient scale scheduled for Day 19 should be completed before dexamethasone administration begins for the following cycle.
- d - Will be documented daily by each patient.
- e - Repeat as clinically indicated.
- f - Collect up to 7 days prior to enrollment. The second homocysteine sample must not be drawn until the patient has taken folic acid for at least 5 days.
- g - Obtain +/- 1 days of the designated day
- h - 60 patients per arm at selected centers (Protocol Attachment JMCH.9.)
- i - Collect +/- 3 days of the designated day and up to 4 days prior to each cycle.
- j - Forced vital capacity, slow vital capacity, and forced expiratory volume.
- k - See Section 3.9.1.1 for an explanation of baseline measurement of pain and dyspnea.
- l - every 6 weeks until progressive disease
- m - Approximately 1 - 3 weeks prior to enrollment.
- n - Daily beginning approximately 1 - 3 weeks prior to enrollment and continuing daily while patient remains on study. To be documented via patient diary and medical interview as entered into the patient chart until the first dose of MTA plus cisplatin or cisplatin alone.
- o - Given as an intramuscular injection approximately 1 - 3 weeks prior to enrollment and repeated approximately every 9 weeks while patient remains on study.
- p - Patients enrolled on JMCH(a)-(d) only
- q - First done at entry (informed consent) by the investigator. Next two done prior to randomization or chemotherapy. Done by the investigator and used for randomization and done by an independent observer.
- r - Within 4 weeks of enrollment.

Follow-Up

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

Appropriateness and Consistency of Measurements