

## Report from the Food and Drug Administration

# Pemetrexed in Malignant Pleural Mesothelioma

Maitreyee Hazarika, Robert M. White, Jr.,  
Brian P. Booth, Yong-Cheng Wang,  
Doo Y. Lee Ham, Cheng Yi Liang, Atiqur Rahman,  
Jogarao V.S. Gobburu, Ning Li,  
Rajeshwari Sridhara, David E. Morse,  
Richard Lostritto, Patricia Garvey,  
John R. Johnson, and Richard Pazdur

Division of Oncology Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Maryland

### ABSTRACT

**Purpose:** This report describes the data and analysis leading to the approval of pemetrexed (LY 231514, MTA, Alimta, Eli Lilly and Co., Indianapolis, IN) by the U.S. Food and Drug Administration (FDA) of a New Drug Application for the treatment of malignant pleural mesothelioma (MPM).

**Experimental Design:** The FDA review of the efficacy and safety of pemetrexed assessed in a randomized clinical trial of 448 patients with unresectable MPM comparing pemetrexed plus cisplatin with cisplatin alone, as well as preclinical pharmacology and chemistry data, are described. The basis for marketing approval is discussed.

**Results:** In one randomized, single-blind, multicenter international trial, 226 patients were randomized to the pemetrexed and cisplatin arm and 222 patients were randomized to cisplatin alone. Median survival times were 12.1 months for pemetrexed and cisplatin and 9.3 months for cisplatin ( $P = 0.021$ ; hazard ratio, 0.766; 95% confidence interval, 0.61-0.96). Myelosuppression, predominantly neutropenia, was the most common toxicity of pemetrexed plus cisplatin. Other common adverse events were fatigue, leucopenia, nausea, dyspnea, vomiting, chest pain, anemia, thrombocytopenia, and anorexia.

**Conclusions:** Pemetrexed in combination with cisplatin was approved by the FDA on February 4, 2004 for the treatment of patients with MPM whose disease is either unresectable or who are otherwise not candidates for curative surgery. The recommended dose of pemetrexed is 500 mg/m<sup>2</sup> intra venous infusion over 10 minutes on day 1 of each 21-day cycle in combination with 75 mg/m<sup>2</sup> cisplatin

infused over 2 hours beginning 30 minutes after the pemetrexed infusion. Patients must receive oral folic acid and vitamin B<sub>12</sub> injections before the start and during therapy to reduce severe toxicities. Patients should also receive corticosteroids with the chemotherapy to decrease the incidence of skin rash. Approval was based on a demonstration of survival improvement in a single randomized trial. Response rates and time to tumor progression were not included in product labeling because of inconsistencies in assessments among the investigators, independent radiologic reviewers, and the FDA, reflecting the difficulty of radiographic assessments in malignant mesothelioma. Complete prescribing information is available on the FDA Web site at <http://www.fda.gov/cder/approval/index.htm>.

### INTRODUCTION

Malignant mesotheliomas are highly aggressive neoplasms that arise primarily from the surface serosal cells of the pleural, peritoneal, and pericardial cavities. These malignant tumors are primarily associated with exposure to asbestos fibers (1). Risk seems to depend on the particular fiber. Crocidolite is associated with a high risk of mesothelioma in miners, manufacturers, and workers who install asbestos products; amosite has an intermediate risk; and chrysotile shows the weakest association with mesothelioma. Individuals exposed for long periods during their employment possess the highest risk, including insulation installers, asbestos producers and manufacturers, and heating and construction trade workers. The projected lifetime risk among these workers, when exposed from early adulthood, is as high as 20%. Some patients have reported only isolated or brief occupational asbestos exposures. SV40 has also been implicated in the etiology of some malignant mesotheliomas (2). In the United States, at least 60% of human mesotheliomas express SV40.

Asbestos use was banned in the United States in 1971 and the case numbers in males is expected to drop during the next 50 to 60 years to 500 new cases annually (3). The projected average annual number of female cases is 500. These trends mirror the U.S. trend in a reduction in workplace airborne asbestos levels. In the United Kingdom, mesothelioma cases are expected to increase over the next 20 years from the present total of 1,300 to >3,000 annual cases (4). Projections suggest that the number of men dying from mesothelioma in western Europe each year will almost double over the next 20 years, from 5,000 in 1998 to ~9,000 in 2018 (5). In Australia, over the next 20 years, the number of cases is expected to triple to 18,000 by 2020 (6).

Malignant pleural mesothelioma (MPM) commonly develops in the fifth to seventh decade, typically 20 to 50 years after the first documented asbestos exposure. Prognosis is poor with a median survival of 10 to 17 months from symptom onset and 9 to 13 months from diagnosis.

Received 8/3/04; revised 9/28/04; accepted 10/14/04.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

**Requests for reprints:** Maitreyee Hazarika, Division of Oncology Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, HFD-150, Room 2080, 5600 Fishers Lane, Rockville, MD 20857. Phone: 301-594-2473; Fax: 301-594-0499; E-mail: HazarikaM@cdcr.fda.gov.

©2005 American Association for Cancer Research.

MPMs are difficult to diagnose, even by expert pathologists. The Cancer Committee of the College of American Pathologists has provided a protocol for the examination of specimens from patients with MPM (7). Electron microscopy and immunohistochemistry are important adjuncts to routine microscopic evaluation in the diagnosis and classification of malignant mesothelioma.

The International Mesothelioma Interest Group staging system updated several earlier staging systems after considering the impact of the primary tumor and lymph node involvement on survival (8). Two patient series have validated the staging system (9, 10). Prospective evaluation about clinical versus operative stage has not been done.

Surgical resection is possible in a minority of patients and <15% of these patients live beyond 5 years (10–12). Radiotherapy is limited by the tumor volume to be treated and by toxicity to surrounding normal tissue (13). Chemotherapy with single agents, such as doxorubicin, methotrexate with leucovorin rescue, 5-azacitadine, 5-fluorouracil, cisplatin, and gemcitabine, have limited activity (14–16). Combination chemotherapy regimens have response rates from 0% to 48%, the highest reported for cisplatin and gemcitabine (48% in 21 patients; refs. 17, 18). Neither single agents nor combination chemotherapy regimens have shown survival improvements. In patients considered completely resectable by surgery, clinical symptoms and radiographic studies do not accurately diagnose early recurrences, making survival the most reliable indicator of drug effect (8).

Pemetrexed disodium is a structurally novel antifolate possessing a unique 6-5 fused pyrrolo[2,3-*d*]pyrimidine nucleus instead of the more common 6-6 fused pteridine or quinazoline ring structure. It is transported intracellularly predominantly through the reduced folate carrier system and metabolized to polyglutamated forms. Pemetrexed monoglutamate is a weak inhibitor of glycinamide ribonucleotide formyltransferase and a modest inhibitor of thymidylate synthase. Pemetrexed was found to be one of the best substrates for the mammalian folylpolygamma-glutamate synthetase and it is believed that polyglutamation and the polyglutamated metabolites play important roles in determining both the selectivity and the antitumor activity of this agent (19). Retained within cells for long periods, the polyglutamated forms have greater affinity for thymidylate synthase and glycinamide ribonucleotide formyltransferase than the parent drug, pemetrexed monoglutamate. The polyglutamates inhibit the enzymes, such as thymidylate synthase and glycinamide ribonucleotide formyltransferase and dihydrofolate reductase, all of which are folate-dependent enzymes involved in the *de novo* biosynthesis of thymidine and purine nucleotides (Fig. 1). The sequence of events following the addition of pemetrexed to cells is a rapid buildup of polyglutamation resulting in suppression of thymidylate synthase and cessation of oxidation of 5,10-methylenetetrahydrofolate to dihydrofolate, so that dihydrofolate levels remain low, and continued buildup of pemetrexed polyglutamates resulting in suppression of glycinamide ribonucleotide formyltransferase and inhibition of purine synthesis (20).

## CHEMISTRY

Pemetrexed for injection is supplied as a single-use sterile lyophilized powder for i.v. infusion in glass vials. Each 500 mg

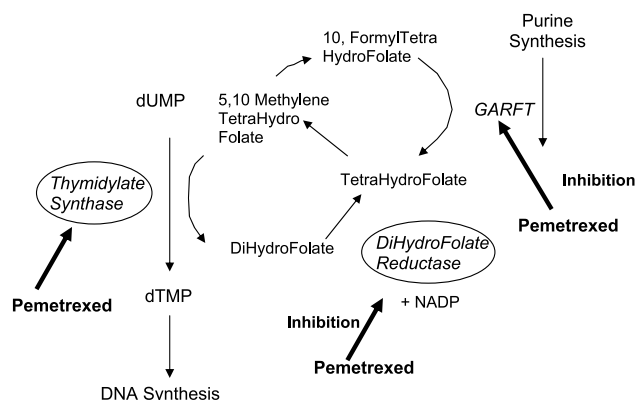


Fig. 1 Inhibition of multiple folate-requiring enzymes by pemetrexed and its polyglutamated metabolites.

vial of pemetrexed contains 713 mg pemetrexed disodium heptahydrate equivalent to 500 mg pemetrexed free acid and 500 mg mannitol. Sodium hydroxide and, if necessary, hydrochloric acid are added to adjust the pH. The drug product is manufactured by Eli Lilly and Co. (Indianapolis, IN).

Pemetrexed (molecular formula  $C_{20}H_{19}N_5O_6Na_2 \cdot 7H_2O$ , molecular weight 597.49 Da) is an organic molecule that is commercially synthesized and purified. The chemical name of pemetrexed disodium heptahydrate is L-glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl] disodium salt heptahydrate. It contains one chiral center and has seven water molecules of hydration (heptahydrate) in the solid state of the drug product. The chemical structure is shown in Fig. 2.

Each vial of pemetrexed is reconstituted with 20 mL commercially available 0.9% sodium chloride injection without preservatives to a concentration of 25 mg/mL pemetrexed as the free acid. This reconstituted pemetrexed solution should be further diluted to 100 mL with 0.9% sodium chloride injection before i.v. infusion. The final concentration of drug product solution to be administered is equivalent to 0.25 mg/mL pemetrexed as the free acid, and it should be used within 24 hours of reconstitution.

A relatively wide color range of the lyophilized and reconstituted drug product (colorless to light yellow to light green-yellow) exists. Pemetrexed vials before reconstitution should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59–86°F). Pemetrexed is not light sensitive.

## PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

When tested in a series of *in vitro* and *in vivo* (xenograft) cancer models, pemetrexed showed activity against a variety of tumor types. Pemetrexed inhibited the *in vitro* growth of mesothelioma cell lines (MSTO-211H and NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined with cisplatin, a preclinical rationale for treating mesothelioma patients with the combination.

Nonclinical toxicity studies were conducted to determine the acute and repeat-dose effects of pemetrexed when given to mice, rats, and dogs. Toxicity studies included single and

repeat-dose studies of 2 and 6 weeks (i.p.) dosing in mice and 4 and 6 weeks and 6 months (i.v.) dosing in dogs. In single-dose studies, pemetrexed showed limited acute toxicity in mice and rats; however, greater toxicity was observed in dogs. The greater toxicity in dogs was expected because rodents are poor test models for antifolates because of their high circulating folate levels in comparison with humans.

Six-week repeat-dose studies were conducted using daily, twice weekly, or weekly i.p. doses in mice and i.v. doses in dogs. Mice tolerated weekly i.p. doses of up to 944 mg/m<sup>2</sup> without death or clinical signs of toxicity, whereas weekly i.v. dosing at 2,099 mg/m<sup>2</sup> resulted in the early termination of several dogs. In dogs, repeat-dose adverse effects at higher doses were decreased food consumption, emesis, diarrhea, mucositis, decreased red cell variables, leukopenia, neutropenia, and increased hepatic enzymes. In mice, weight loss and leukopenia were the predominant drug-induced toxicities. Clinically, rash, nausea, diarrhea, asthenia, leukopenia, and neutropenia are dose limiting, consistent with the most prominent nonclinical toxicologic effects.

I.v. pemetrexed doses of  $\geq 0.3$  mg/m<sup>2</sup> caused testicular atrophy and reduced fertility. Pemetrexed was embryotoxic and teratogenic in mice at doses of 0.6 mg/m<sup>2</sup>. Pemetrexed caused no genetic damage in a standard battery of *in vitro* test mutation and clastogenicity assays, although it was clastogenic in the *in vivo* micronucleus assay. Carcinogenicity studies of pemetrexed disodium have not been conducted.

## PHARMACOKINETICS

Pemetrexed pharmacokinetics has been studied as a single-agent in doses from 0.2 to 838 mg/m<sup>2</sup> infused over 10 minutes. The total systemic exposure (area under the curve) and maximum plasma concentration ( $C_{max}$ ) increase proportionally with dose. Pemetrexed has a steady-state volume of distribution of 16.1 liters and a total systemic clearance of 91.8 mL/min. The between-patient variability in clearance is  $\sim 20\%$ . The terminal half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min as calculated by the standard Cockcroft and Gault formula). Total clearance decreases with decreasing renal function. *In vitro* studies indicate that pemetrexed is  $\sim 81\%$  bound to plasma proteins. Binding is not affected by the degree of renal impairment.

Pemetrexed is not metabolized to an appreciable extent, nor does it inhibit the cytochrome P450 isozymes 3A4, 2D6, 1A2, or 2C9. Pemetrexed is primarily eliminated in the urine, with 70% to 90% of the dose recovered as unchanged parent drug within the first 24 hours. Cisplatin, vitamin B<sub>12</sub>, and folic acid do not

affect the pharmacokinetics of pemetrexed; conversely, pemetrexed does not affect their pharmacokinetics. Moderate aspirin doses (325 mg taken four times daily) do not affect the pemetrexed pharmacokinetics, but the effect of higher doses is unknown. Ibuprofen doses (400 mg taken four times daily) reduce pemetrexed clearance by  $\sim 20\%$  (and increase area under the curve by  $\sim 20\%$ ) in patients with normal renal function. The effects of higher ibuprofen doses or of long-acting nonsteroidal anti-inflammatory drugs have not been assessed.

No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26 to 80 years. Pediatric patients were not included in clinical trials. Pemetrexed pharmacokinetics was similar for male and female patients and for Caucasians and patients of African descent.

The effect of renal impairment on the pemetrexed pharmacokinetics was assessed in 127 patients with reduced renal function treated with pemetrexed as a single agent or in combination with cisplatin. Total plasma pemetrexed clearance decreases as renal function decreases. Patients with creatinine clearance of 45 mL/min have a systemic pemetrexed area under the curve  $\sim 65\%$  higher than patients with normal creatinine clearance (100 mL/min). Because adequate dosing studies have not been done in patients with creatinine clearance of  $<45$  mL/min, these patients should not be treated with pemetrexed. Specific studies of pemetrexed pharmacokinetics in hepatically impaired patients have not been conducted, but significant effects would not be expected because the drug is predominantly renally cleared as unchanged drug. No pharmacokinetics evaluation in patients with third-space accumulations was done.

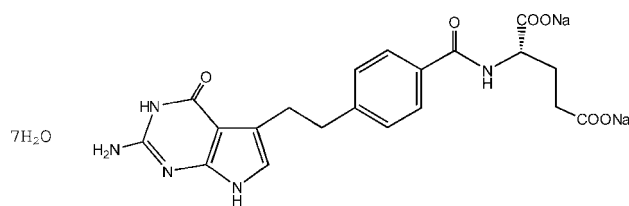
## PHASE I AND II STUDIES

Phase I studies were conducted exploring three treatment schedules: weekly times 4 every 6 weeks, daily times 5 every 3 weeks, and once every 3 weeks.

In the first schedule, 24 patients were treated with 10-minute infusions of doses from 10 to 40 mg/m<sup>2</sup>/wk. The dose-limiting toxicity was myelosuppression, particularly leukopenia and granulocytopenia. Neutropenia prevented weekly dosing in some patients. Nonhematologic toxicities included mild fatigue, anorexia, and nausea. Dose-limiting toxicity was observed at 40 mg/m<sup>2</sup>/wk, and the recommended dose for phase II evaluation was 30 mg/m<sup>2</sup>/wk. The weekly schedule was not pursued in phase II trials.

In the second schedule, 38 patients were treated at doses ranging from 0.2 to 5.2 mg/m<sup>2</sup>. The maximum tolerated dose was 4 mg/m<sup>2</sup>/d. Reversible neutropenia and liver enzyme abnormalities were dose-limiting toxicities. Other toxicities included mucositis, diarrhea, rash, fatigue, and elevated transaminases.

In the third treatment schedule, pemetrexed was administered to 37 patients as a 10-minute infusion at doses ranging from 50 to 700 mg/m<sup>2</sup>. Of the 20 patients treated at 600 mg/m<sup>2</sup>, grade 4 neutropenia and thrombocytopenia occurred in four and one patients, respectively, during the first cycle. Grade 2 toxicities at that dose level included rash, mucositis, nausea, vomiting, fatigue, anorexia, and liver transaminase elevations. Ten patients who developed rashes received dexamethasone



N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid disodium salt

Fig. 2 Chemical structure of pemetrexed disodium.

(4 mg twice daily for 3 days) in subsequent cycles starting 1 day before pemetrexed treatment, with subsequent improvement or prevention of the rash. Cumulative neutropenia, thrombocytopenia, and mucositis, presumably due to the prolonged intracellular half-life of the polyglutamate of pemetrexed, have been observed. The dose-limiting toxicities on this schedule were neutropenia, thrombocytopenia, and fatigue. Based on this study, the recommended phase II dose was 600 mg/m<sup>2</sup>.

In a phase I trial of pemetrexed in combination with cisplatin, patients with solid tumors were enrolled into one of two cohorts. The first cohort received both pemetrexed and cisplatin on day 1 of a 21-day cycle, and the second cohort received pemetrexed on day 1 and cisplatin on day 2 of a 21-day cycle. Forty patients were enrolled into the first cohort; the maximum tolerated dose was reached at 600 mg/m<sup>2</sup> pemetrexed and 100 mg/m<sup>2</sup> cisplatin, with dose-limiting toxicity of thrombocytopenia and febrile neutropenia. Eleven patients were enrolled into the second cohort. The degree of toxicity observed using the split schedule, which included two therapy-related deaths, led to the conclusion that the second schedule was inferior.

Based on the above trials, the recommended phase II dose was 600 mg/m<sup>2</sup> with both drugs given on day 1 of a 21-day cycle. The phase I studies were done without any vitamin supplementation.

Safety data from phase II trials is provided. A total of 646 patients were treated on the once every 3 weeks schedule in the phase II trials at 600 mg/m<sup>2</sup>. Hematologic toxicity was the most frequent, serious toxicity. Grade 3 and 4 hematologic toxicity included neutropenia (23% and 24%, respectively) and thrombocytopenia (7% and 5%, respectively). Although severe neutropenia was common, the incidence of serious infection was low (grade 4 infections 2%). Serious bleeding episodes were rare (<1%). Whereas 6% experienced grade 3 (5% with grade 4) skin rash, prophylactic dexamethasone was reported to ameliorate or prevent the rash in subsequent cycles. Other grade 3 and 4 nonhematologic toxicities included stomatitis, diarrhea, vomiting, and infection. Transient grade 3 and 4 elevation of liver transaminases were common but not dose limiting. No cases of persistent transaminase elevation were reported.

Due to toxicities in the above two Canadian phase II studies, the dose of pemetrexed used in these two studies was reduced from 600 to 500 mg/m<sup>2</sup> and was used in all subsequent single-agent phase II pemetrexed studies and the phase III mesothelioma trial.

Among 517 patients who received pemetrexed as a single agent at 500 mg/m<sup>2</sup> every 21 days, with dexamethasone treatment and folic acid and vitamin B<sub>12</sub> supplementation, the most common adverse events were nausea, fatigue, anorexia, and vomiting.

### PHASE III MESOTHELIOMA TRIAL

**Population.** Eligibility requirements included histologically proven diagnosis of MPM in patients not candidates for curative surgery and the presence of unidimensionally and/or bidimensionally measurable disease. The International Mesothelioma

Interest Group criteria were used for staging. Independent centralized pathology reviews were done if feasible. Patients receiving prior systemic chemotherapy or prior intracavitary cytotoxic drugs or immunomodulators were excluded, unless those agents were administered for pleurodesis. Patients receiving prior radiation therapy to the target lesion were excluded, unless the lesion was clearly progressing and the interval between the most recent radiation therapy and enrollment exceeded 4 weeks.

**Treatment.** Patients were randomized to receive either 500 mg/m<sup>2</sup> i.v. pemetrexed followed by 75 mg/m<sup>2</sup> i.v. cisplatin on day 1 of a 21-day cycle or cisplatin alone in the same dose and schedule. In the pemetrexed plus cisplatin treatment arm, 500 mg/m<sup>2</sup> pemetrexed diluted in ~100 mL normal saline as a 10-minute i.v. infusion was administered followed 30 minutes later by 75 mg/m<sup>2</sup> cisplatin over 2 hours. In an effort to blind patients to treatment, in the cisplatin alone arm, ~100 mL normal saline were given i.v. over 10 minutes followed 30 minutes later by the same dose of cisplatin.

**Supplementation with Vitamins.** Folic acid and vitamin B<sub>12</sub> supplementation were introduced into the pivotal trial for safety reasons. Foliates are required for the metabolism of total plasma homocysteine, which is converted to methionine by transfer of a methyl group from the cosubstrate 5-methyltetrahydrofolate by methionine synthase, an enzyme that also requires the cofactor methylcobalamin (vitamin B<sub>12</sub>; Fig. 3). There is a significant reciprocal association of homocysteine to serum folate and RBC folate, allowing total plasma homocysteine concentration to be used as a measure of functional status (20). Under conditions of folate and/or cobalamin deficiency, total plasma homocysteine concentrations increase. Because the enzyme L-methylmalonyl CoA mutase is vitamin B<sub>12</sub> dependent, a B<sub>12</sub> deficiency will lead to an increase in methylmalonic acid. Because of prior observations on the impact of folic acid supplementation on the toxicity profile of lometrexol, a phase I study of pemetrexed with folic acid was initiated. It was observed that elevated baseline total plasma homocysteine and methylmalonic acid levels put a patient at high risk for severe toxicity; thus, it was formulated that by reducing these levels one could substantially reduce a patient's risk for such severe toxicity.

A sponsor-initiated multivariate analysis in late 1997 assessed the relationship of vitamin metabolites, drug exposure, and other baseline patient characteristics to pemetrexed toxicity (20). Data were examined from 139 phase II patients with colon, breast, pancreas, and esophagus cancers, who had been treated with 600 mg/m<sup>2</sup> i.v. pemetrexed over 10 minutes every 21 days. These patients had homocysteine, cystathionine, and methylmalonic acid levels measured at baseline and with each subsequent cycle.

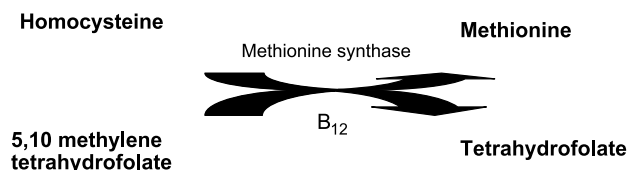


Fig. 3 Metabolism of methionine.

Stepwise regression modeling, multivariate ANOVA, and discriminant analysis were implemented to determine correlates of severe toxicity and to predict patients at high risk for experiencing severe toxicity. Pemetrexed toxicity seemed to be higher in those with elevated pre-therapy homocysteine levels, and elevated baseline homocysteine levels highly correlate with severe hematologic and nonhematologic toxicity. Because elevated pre-therapy homocysteine levels predicted toxicity, the same multivariate analysis was repeated on data from 267 patients whose baseline homocysteine levels were measured and recorded by a single laboratory. Baseline homocysteine was identified as a highly statistically significant predictor of febrile neutropenia ( $P < 0.00001$ ), grade 4 neutropenia ( $P = 0.0191$ ), grade 4 thrombocytopenia ( $P < 0.00001$ ), and grade 3/4 diarrhea ( $P < 0.00001$ ). As a result of the confirmation of the original finding by this analysis, all subsequent patients were supplemented with folic acid and vitamin B<sub>12</sub> in the ongoing phase III trial. Patients were supplemented with folic acid and vitamin B<sub>12</sub> without an increase in the pemetrexed dose, a consideration that takes into account the potential negative effect on efficacy by the addition of folic acid and vitamin B<sub>12</sub>. At this time, 112 patients had been randomized and received therapy without any vitamin supplementation, whereas 40 patients had received vitamin supplements after at least one cycle. A patient was classified as “supplemented with vitamins” if he/she received study vitamin supplement during the entire study. Vitamin supplementation in the phase III study was given to patients in both treatment arms to preserve study blinding.

Folic acid (350-1,000 µg daily) was taken orally daily starting 1 to 3 weeks before the first chemotherapy dose, continued while a patient was on therapy, and for 21 days after therapy cessation. Vitamin B<sub>12</sub> injections (1,000 µg i.m.) were started 1 to 3 weeks before the first chemotherapy dose and repeated every 9 weeks while on therapy. Patients also initiated dexamethasone on the day before chemotherapy and for 3 subsequent days to reduce the risk of skin rashes. Both vitamins and dexamethasone were given to patients on both arms.

**Analyses.** The primary analysis was comparison of survival time between the two treatment arms in the randomized and treated population, omitting eight randomized patients who received no treatment. Differences were assessed using a two-sided log-rank test. A planned interim analysis was conducted and presented to the Data Monitoring Committee. Because of this interim analysis, the final comparison of survival was tested at the  $\alpha = 0.0476$  level. Survival was also evaluated using the Wilcoxon test.

Several secondary analyses were conducted, including the impact on the survival analyses of vitamin-supplemented patients in the pemetrexed plus cisplatin arm. Subgroup survival analyses were conducted on fully supplemented, partial, non-supplemented vitamin patients and on the overall population. Survival time was analyzed by a Cox proportional hazards model, including treatment arm, supplementation group, and treatment-by-supplementation interaction.

Repeated-measures analyses were conducted on Lung Cancer Symptom Scale patient scale and pulmonary function

test variables by using linear mixed models. Lung Cancer Symptom Scale observer scale data were analyzed by the Mantel-Haenszel  $\chi^2$  test and also assessed by using simple ANOVA techniques.

The U.S. Food and Drug Administration (FDA) conducted an exploratory subgroup analysis for gender effects on survival using the Cox regression model for the multivariate analyses. The log-rank test and Wilcoxon test were used for statistical comparisons of treatments within the subgroup.

## RESULTS

**Patient Characteristics.** There were 88 principal investigators who enrolled patients in 88 study centers in 20 countries. The study was monitored by an independent Data Monitoring Committee. Between April 1999 and March 2001, 456 patients were eligible and randomized, 228 to each arm. In the intent-to-treat population of 456 patients, 8 patients did not receive any study drug due to the following reasons: patient decision (4), inclusion criteria not met (2), hypertension (1), and death from study disease (1). The sponsor did the primary analysis for safety and efficacy on the 448 randomized and treated patients.

The patient characteristics are shown in Table 1. Demographics were similar in the two treatment arms. Patients were predominantly male and Caucasian, with good performance status. Median age was 61 years (range, 19-85 years). A FDA analysis of the independent pathology review revealed the following: (a) confirmed pathology of malignant mesothelioma (67%), (b) suggestive/consistent with malignant mesothelioma (3.6%), (c) malignant mesothelioma unconfirmed (6.7%), (d) tissue unsatisfactory to confirm pathology (2.9%), and (e) samples not sent for independent review (19.4%). In the confirmed malignant mesothelioma patients, 85% had an epithelial histology and 78% had stage III or IV disease. None had received prior chemotherapy, whereas 12% had received prior radiotherapy.

Patients on the pemetrexed plus cisplatin arm received a median of 6 cycles (range, 1-12 cycles) and those on the cisplatin alone arm received a median of 4 cycles (range, 1-9 cycles). Patients not supplemented received a median of only 2 cycles of chemotherapy on both arms. The median total pemetrexed and cisplatin doses were higher in those fully supplemented. The relative dose intensity of study drugs in both arms was >90%.

**Survival.** The FDA verified the reported survival analyses using the survival data sets. The FDA Division of Scientific Investigation audited four study sites.

In the 448 randomized and treated patients, the survival time for patients treated with combination of pemetrexed plus cisplatin was longer than for those treated with single-agent cisplatin alone: 12.1 versus 9.3 months ( $P = 0.021$ ; hazard ratio, 0.77; 95% confidence interval, 0.61-0.96; Table 2). Analysis of all 456 randomized patients provided similar results with median survivals of 12.1 and 9.3 months for the combination and single-agent cisplatin groups, respectively ( $P = 0.020$ ). In the subgroup of the fully folic acid and vitamin B<sub>12</sub> supplemented patients ( $n = 331$ ), the median survivals for

Table 1 Summary of patient characteristics

Patient characteristics	Randomized and treated patients		Fully supplemented patients	
	Pemetrexed + cisplatin (n = 226)	Cisplatin (n = 222)	Pemetrexed + cisplatin (n = 168)	Cisplatin (n = 163)
Age (y)				
Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
Gender (%)				
Male	184 (81.4)	181 (81.5)	136 (81.0)	134 (82.2)
Female	42 (18.6)	41 (18.5)	32 (19.0)	29 (17.8)
Origin (%)				
Caucasian	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)
Hispanic	11 (4.9)	12 (5.4)	10 (6.0)	7 (4.3)
Asian	10 (4.4)	4 (1.9)	7 (4.2)	3 (1.8)
African descent	1 (0.4)	0	1 (0.6)	0
Stage at entry (%)				
I	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)
II	35 (15.6)	33 (15.0)	27 (16.2)	27 (16.8)
III	73 (32.4)	68 (30.6)	51 (30.5)	49 (30.4)
IV	101 (44.9)	105 (47.2)	74 (44.3)	73 (45.3)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.2)
Diagnosis/histology* (%)				
Epithelial	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)
Mixed	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)
Sarcomatoid	18 (8.0)	25 (11.3)	14 (8.3)	17 (10.4)
Other	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)
Baseline Karnofsky Performance Scale (%)				
70-80	109 (48.2)	97 (43.7)	83 (49.4)	69 (42.3)
90-100	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)

\*Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review. After independent review epithelial, mixed, and sarcomatoid were the only subtypes; there were no "other."

patients treated with the combination versus cisplatin alone were 13.3 and 10 months, respectively ( $P = 0.051$ ; hazard ratio, 0.76; 95% confidence interval, 0.57-1.0).

Sixty-seven percent of the randomized and treated patients had the diagnosis of mesothelioma confirmed by independent review. The FDA did an independent survival analysis on the pathologically confirmed mesothelioma subset. In the randomized and treated patients ( $n = 303$ ), the median survival time for patients treated with the combination versus single-agent cisplatin were 13 and 10.2 months, respectively ( $P = 0.066$ ; hazard ratio, 0.774; 95% confidence interval, 0.59-1.02). In the subgroup of the fully folic acid and vitamin B<sub>12</sub> supplemented patients ( $n = 220$ ) who were pathologically confirmed, the median survival time for those treated with the combination versus single-agent cisplatin were 14.4 and 10.3 months, respectively ( $P = 0.058$ ; hazard ratio, 0.719; 95% confidence interval, 0.51-1.01).

Kaplan-Meier survival curves for the randomized and treated group, the fully supplemented subgroup, and these same

groups in confirmed pathology mesothelioma patients are shown in Figs. 4, 5, 6, and 7.

Multivariate analysis by gender for survival showed a substantial interaction between treatment and gender ( $P = 0.072$ ) for the whole population and ( $P = 0.035$ ) for the supplemented population with a survival effect considerably greater in women. The interaction was not statistically significant for the partial-supplemented and nonsupplemented population ( $P = 0.604$ ).

The small female subgroup ( $n = 83$ ) in the randomized and treated patients and the fully folic acid and vitamin B<sub>12</sub> supplemented groups ( $n = 61$ ) each showed a statistically significant survival advantage in favor of the combination ( $P = 0.012$  and 0.010, respectively). The male population ( $n = 365$ ) was four times the female population. Although there were trends in favor of pemetrexed plus cisplatin for males in all the treatment subgroups in survival analyses, none were statistically significant (Table 3).

**Tumor Response and Time to Tumor Progression.** The radiographic studies of all responders and the data and results

Table 2 Efficacy data from the phase III trial

Efficacy variable	Randomized and treated patients		Fully supplemented patients	
	Pemetrexed + cisplatin (n = 226)	Cisplatin (n = 222)	Pemetrexed + cisplatin (n = 168)	Cisplatin (n = 163)
Median overall survival, mo (95% confidence interval)	12.1 (10.0-14.4)	9.3 (7.8-10.7)	13.3 (11.4-14.9)	10.0 (8.4-11.9)
Hazard ratio (95% confidence interval)	0.77 (0.61-0.96)		0.76 (0.57-1.0)	
$P$ (log-rank)*	0.021		0.051	
% Alive	35.8	28.4	43.5	36.8

\* $P$  is based on the two-sided log-rank test.

from the independent evaluations were reviewed by the Division of Oncology Drug Products Medical Reviewer together with the consultant radiologist. Measurability of disease was a study entry criterion. Unidimensional (rind thickness, drawn manually) and bidimensional (cross-product) measurement techniques were employed to assess pleural based disease. An index lesion was defined as one that met certain minimum size criteria for the rind thickness or lesion diameter.

Discrepancies among the investigator, the independent reviewers, and the FDA in the evaluation of response were noted. The applicant claimed that 94 (41.3%) patients in the pemetrexed plus cisplatin randomized and treated arm had an objective tumor response (complete and partial responders). Of the 94 patients in the combination treatment arm for whom the applicant claimed an objective tumor response, the FDA confirmed 47. The tumor response assessments were inconsistent between the study investigators and the two independent reviewers and were not in agreement with the FDA review. Although specific response rates could not be accurately assessed, tumor responses appeared more frequent in the pemetrexed plus cisplatin treatment group than the single-agent cisplatin treatment and a statement to this effect is included in the pemetrexed labeling, without specific numbers.

**Quality of Life.** Patients were assessed during the study using the Lung Cancer Symptom Scale. Although there were statistically significant changes favoring the combination treatment group in selected components and in the overall score, none were deemed clinically important. No claims regarding the Lung Cancer Symptom Scale were included in the label.

**Pulmonary Function.** Patients were assessed by measuring forced vital capacity (FVC), slow vital capacity, and forced expiratory volume in 1 minute. Because the primary impairment in pleural mesothelioma patients is constrictive rather than

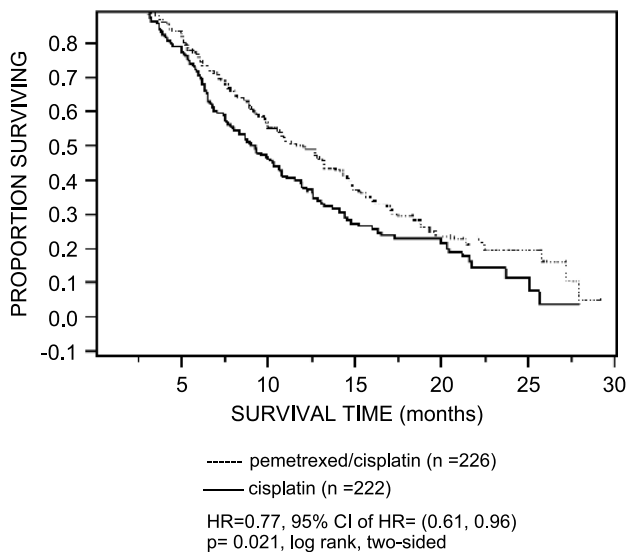


Fig. 4 Kaplan-Meier estimates of survival time for all randomized and treated patients ( $n = 448$ ).

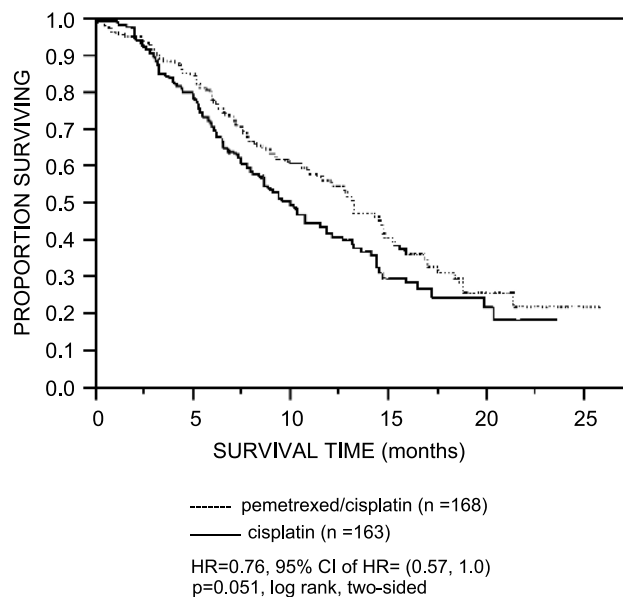


Fig. 5 Kaplan-Meier estimates of survival time for the fully supplemented randomized and treated patients ( $n = 331$ ).

obstructive, FVC was considered the most appropriate pulmonary function test in this patient population.

The applicant's analysis compared the average change from baseline in randomized and treated patients in each treatment group. The average change in FVC from baseline was +110 mL for the combination treatment and -50 mL for the cisplatin alone group. This difference was statistically significant ( $P = 0.001$ ), but because this value corresponded to the normal test variation (200 mL, American Thoracic Society) the decrement was not initially considered clinically meaningful.

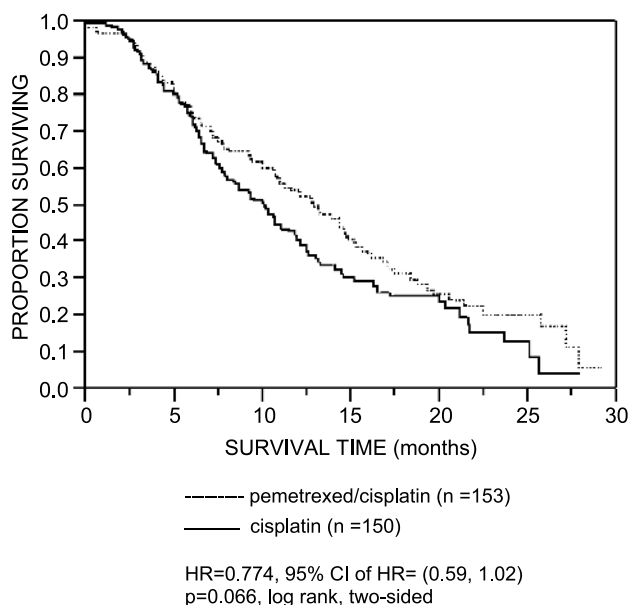


Fig. 6 Kaplan-Meier survival times for all patients with confirmed mesothelioma diagnosis ( $n = 303$ ).

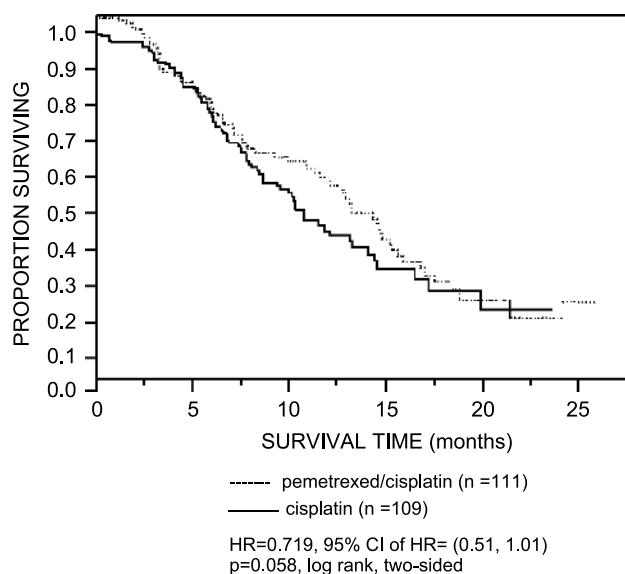


Fig. 7 Kaplan-Meier survival times for the fully supplemented subgroup patients with confirmed mesothelioma diagnosis ( $n = 220$ ).

Examination of individual responses by FDA, however, led to a different conclusion. The proportions of patients in each treatment group having an increase from baseline in FVC of  $\geq 400$  and  $\geq 500$  mL on at least one follow-up visit and on at least two follow-up visits were calculated. Follow-up visits were 6 weeks apart. A second similar analysis determined the proportions of patients in each treatment group having an increase from baseline in FVC of  $\geq 20\%$  and  $\geq 30\%$  on at least one follow-up visit and at least two follow-up visits.

In 337 of 448 (75%) randomized and treated patients who had a baseline and at least one follow-up FVC, 26.6% and 21.3% of pemetrexed plus cisplatin group patients had an increase over baseline FVC of  $\geq 400$  and  $\geq 500$  mL on at least one follow-up visit, respectively, compared with 17.9% and 11.9% in the cisplatin group, both statistically significant differences. However, only about half of the pemetrexed plus cisplatin group patients maintained these increases for at least 6 weeks. The difference between treatment groups was no longer statistically significant at 6 weeks.

In the second analysis, 28.4% and 17.2% of the combination group patients had an increase from baseline FVC of  $\geq 20\%$  and  $\geq 30\%$  on at least one follow-up visit, respectively, compared with 13.7% and 5.4% in the cisplatin alone group, both statistically significant differences. The increases in FVC were maintained for at least 6 weeks in only about half of the pemetrexed plus cisplatin group patients, but the difference

between treatment groups remained statistically significant at the 6-week analysis.

Based on these FDA analyses, a labeling claim for improvement in pulmonary function (FVC) with pemetrexed plus cisplatin treatment was permitted: “There was also improvement in lung function (forced vital capacity) in the Alimta plus cisplatin arm compared with the control arm.”

**Safety.** The primary safety analysis was done on the fully vitamin-supplemented subgroup (168 on the combination arm and 163 on the cisplatin alone arm) regardless of drug causality. In this subgroup shown in Table 4, the combination arm had higher grade 3/4 neutropenia (24.4% versus 3.1%), leucopenia (15.5% versus 0.6%), anemia (6% versus 0%), and thrombocytopenia (5.4% versus 0%). The combination arm also had higher grade 3/4 gastrointestinal symptoms, including nausea, vomiting, constipation, anorexia, stomatitis/pharyngitis, and diarrhea. Febrile neutropenia grade 3/4 and neutropenic sepsis were relatively infrequent. Supplementation with folic acid and vitamin B<sub>12</sub> reduced many of the laboratory and nonlaboratory toxicities in comparison with a never supplemented subgroup (Table 5).

The most common clinical cause of dose delay on both arms was neutropenia followed by reduced creatinine, leucopenia, anemia, stomatitis, and infection. On both treatment arms, cycle 4 was the cycle of therapy with the most clinical delays (Table 6).

## DISCUSSION

Approval was based on results of a single randomized trial showing that the addition of pemetrexed to cisplatin yields improved survival. During the trial, the addition of vitamin supplementation was made for safety concerns. The primary analysis included all patients (i.e., those who did and did not receive the vitamin supplementation). Survival analyses in all patients randomized (intent-to-treat), all patients treated, and the fully vitamin-supplemented subgroup all favored the pemetrexed plus cisplatin arm with similar advantages in median survival and risk reduction.

The FDA generally recommends external substantiation of trial results by requesting sponsors to submit two or more trials substantiating an effect on the primary end point.

Although only a single randomized trial supports this New Drug Application, this trial was multi-institutional with over 88 study centers in the United States and abroad, which enrolled 476 patients. The trial is the largest randomized study conducted in this disease and showed a substantial (3-month) survival increment. In view of the demonstrated survival superiority of the pemetrexed plus cisplatin regimen in this relatively uncommon tumor, replication of this study would not be feasible. Pemetrexed plus cisplatin is the first chemotherapeutic

Table 3 Survival analyses for gender

Group	Pemetrexed + cisplatin survival, median (mo)	Cisplatin alone survival, median (mo)	P (log rank)
Female randomized and treated ( $n = 83$ )	15.7	7.5	0.012
Female fully folic acid/vitamin B <sub>12</sub> supplemented ( $n = 61$ )	18.9	7.4	0.01
Male randomized and treated ( $n = 365$ )	11	9.4	0.176
Male fully folic acid/vitamin B <sub>12</sub> supplemented ( $n = 270$ )	12.8	10.4	0.388



Table 4 Adverse events in fully supplemented patients receiving pemetrexed and cisplatin

	All reported adverse events regardless of causality					
	Pemetrexed + cisplatin (n = 168)			Cisplatin (n = 163)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Laboratory						
Hematologic						
Neutropenia	58.3	19.0	5.4	16.0	2.5	0.6
Leukopenia	55.4	13.7	1.8	19.6	0.6	0
Anemia	32.7	5.4	0.6	14.1	0	0
Thrombocytopenia	26.8	4.2	1.2	9.8	0	0
Renal						
Creatinine	15.5	0.6	0	12.3	1.2	0
Renal failure	2.4	0	0.6	1.2	0	0
Hepatic						
Aspartate aminotransferase (SGOT)	8.3	0	0	8.6	0.6	0
Clinical						
Constitutional symptoms						
Fatigue	80.4	16.7	0	73.6	12.3	0.6
Fever	17.3	0	0	8.6	0	0
Other constitutional symptoms	10.7	1.8	0.6	8.0	0.6	0.6
Cardiovascular general						
Other cardiovascular general	11.3	0	1.2	11.0	1.8	0
Thrombosis/embolism	7.1	4.2	1.8	3.7	2.5	1.2
Gastrointestinal						
Nausea	83.9	11.3	0.6	78.5	5.5	0
Vomiting	57.7	10.1	0.6	51.5	3.7	0.6
Constipation	44.0	2.4	0.6	39.3	0.6	0
Anorexia	34.5	2.4	0	25.2	0.6	0
Stomatitis/pharyngitis	28.0	1.8	1.2	8.6	0	0
Diarrhea without colostomy	26.2	3.6	0	16.0	0.6	0
Other gastrointestinal	19.0	1.2	0.6	16.0	0.6	0
Dehydration	7.1	3.0	1.2	1.2	1.2	0
Dysphagia/esophagitis/odynophagia	6.0	1.2	0	5.5	0	0
Pulmonary						
Dyspnea	65.5	9.5	0.6	62.0	4.9	1.8
Other pulmonary	20.2	2.4	0	19.0	1.2	0.6
Pain						
Chest pain	39.9	7.7	0.6	30.1	4.9	1.2
Tumor pain	18.5	3.6	0.6	14.7	3.7	0.6
Neurology						
Neuropathy/sensory	17.3	0	0	14.7	0.6	0
Mood alteration/depression	13.7	1.2	0	9.2	0.6	0
Infection/febrile neutropenia						
Infection without neutropenia	11.3	1.2	1.2	4.3	0	0
Infection with grade 3 or 4 neutropenia	6.0	0.6	0	4.3	0	0
Infection/febrile neutropenia-other	3.0	1.2	0	1.8	0	0
Febrile neutropenia	0.6	0.6	0	0.6	0	0
Immune						
Allergic reaction/hypersensitivity	2.4	0	0	0.6	0	0
Dermatology/skin						
Rash/desquamation	22.0	0.6	0	9.2	0	0

treatment to show a survival benefit in MPM, with results that were statistically convincing and were consistent across subgroups. The results of the phase III trial were reported previously (21). An important secondary end point, improvement in pulmonary function, also supported the effect of pemetrexed.

Establishing the histologic diagnosis may be difficult. Because of the difficulties, an independent central pathology panel reviewed available slides. Because not all pathology specimens received independent review, the FDA did a subgroup survival analysis in patients with confirmed histologic diagnosis by central pathology review. Survival in this subgroup of patients with an independently reviewed pathology also favored

the pemetrexed plus cisplatin group. An additional exploratory subgroup analysis suggested an impact of gender on treatment effect. The effect in women (median survival, 15.7 months with the combination versus 7.5 months on cisplatin alone) was larger than the effect in males (median survival, 11 months with combination therapy versus 9.4 months with cisplatin alone). As with any exploratory analysis, it is not yet clear whether this difference is real or is a chance finding.

Tumor response criteria are not well established in MPM. The tumor often grows in diffuse sheets rather than more spherical configurations, complicating accurate bidimensional or unidimensional radiographic assessment. In patients with extensive lobulated disease, selection of appropriate lesions to

**Table 5** Grade 3/4 adverse events in fully supplemented versus never supplemented patients treated with pemetrexed plus cisplatin

Adverse events	Fully supplemented, % (n = 168)	Never supplemented, % (n = 32)
Neutrophils/granulocytes	24.4	37.5
Fatigue	17.3	31.3
Leukocytes	15.5	34.4
Nausea	11.9	31.3
Dyspnea	11.3	12.5
Hypertension	11.3	3.1
Vomiting	10.7	34.4
Chest pain	8.3	6.3
Hemoglobin	6.0	9.4
Thrombosis/embolism	6.0	3.1
Platelets	5.4	9.4
Tumor pain	4.8	6.3
Dehydration	4.2	9.4
Constipation	3.6	3.1
Diarrhea without colostomy	3.6	9.4
Febrile neutropenia	0.6	9.4
Infection with grade3/4 neutropenia	0.6	6.3

follow may be difficult due to lack of well-demarcated margins. The tumor burden may not be accurately represented by the lesions selected at baseline. Two independent reviewers assessed the study images with an adjudicator reviewing discrepancies. FDA reviewers also assessed tumor response rate but found the database and results unsatisfactory. Considerable discrepancy in tumor response evaluations among the study investigators, the independent reviewers, and the FDA reviewers occurred. The lack of a double-blind design may introduce bias in investigator assessments. FDA review of submitted images could confirm the tumor response in only 47 of 94 patients in the combination treatment group for whom the Applicant had ascribed a tumor response. Although precision to a response rate could not be assured, the FDA noted a higher number of responses in the combination treatment arm compared with single-agent cisplatin. Thus, a general statement regarding an improved response rate without specific numerical calculations was provided in the product label.

In the fully supplemented population, neutropenia, fatigue, and leucopenia were the most commonly reported grade 3 and 4 adverse events in the combination treatment arm. The most frequent toxicity of the combination was myelosuppression, which was reduced by folate and vitamin B<sub>12</sub> supplementation. Folate and vitamin B<sub>12</sub> supplementation allowed the administration of a greater number of chemotherapy cycles and resulted in overall less toxicity. Despite supplementation, the combination treatment produces myelosuppression, renal and gastrointestinal side effects greater than single-agent cisplatin.

## REGULATORY BASIS FOR APPROVAL

Response rate was originally proposed by the applicant as the primary end point for the randomized study. The applicant believed that unidimensional measurements would be sufficient to provide information for response. Because of uncertainty about the application of unidimensional disease for response assessments and the difficulty of measuring lesions in MPM, the FDA required that overall survival should be the primary end point of the study. In addition, an improvement in response rate has not been accepted as a surrogate for clinical benefit (i.e., improved survival or amelioration of symptoms) in this disease.

Pemetrexed was approved by the FDA on February 4, 2004 in combination with cisplatin for the treatment of patients with MPM whose disease is either unresectable or who are not otherwise candidates for curative surgery. Approval was based on an improvement in overall survival for the combination therapy of pemetrexed plus cisplatin compared with single-agent cisplatin. The recommended pemetrexed dose is 500 mg/m<sup>2</sup> administered i.v. over 10 minutes on day 1 of each 21-day cycle together with 75 mg/m<sup>2</sup> cisplatin infused over 2 hours beginning 30 minutes after the pemetrexed infusion. Folic acid (350-1,000 µg) and vitamin B<sub>12</sub> (1,000 µg) injections should be initiated before starting use of the drugs to avoid severe toxicities. Patients should also receive corticosteroids concomitant with chemotherapy to prevent skin rash. Complete prescribing information is available at the FDA Web site at <http://www.fda.gov/cder/approval/index.htm>.

**Table 6** Most common clinical reasons for dose delay—all cycles

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

## REFERENCES

1. Craighead JE, Abraham JL, Churg A, et al. The pathology of asbestos-associated diseases of the lungs and pleural cavities: diagnostic criteria and proposed grading schema. Report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health. *Arch Pathol Lab Med* 1982;106:544–96.
2. Carbone M, Fisher S, Powers A, Pass HI, Rizzo P. New molecular and epidemiological issues in mesothelioma: role of SV40. *J Cell Physiol* 1999;180:167–72.
3. Price B. Analysis of current trends in United States mesothelioma incidence. *Am J Epidemiol* 1997;145:211–8.
4. British Thoracic Society Standards of Care Committee. Statement on malignant mesothelioma in the United Kingdom. *Thorax* 2001;56:250–65.
5. Peto J, Decarli A, La Vecchia C, Levi F, Negri E. The European mesothelioma epidemic. *Br J Cancer* 1999;79:666–72.
6. Leigh J, Davidson P, Hendrie L, Berry D. Malignant mesothelioma in Australia, 1945-2000. *Am J Ind Med* 2002;41:188–201.
7. Nash G, Otis CN. Protocol for the examination of specimens from patients with malignant pleural mesothelioma: a basis for checklists. Cancer Committee, College of American Pathologists. *Arch Pathol Lab Med* 1999;123:39–44.
8. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. *Chest* 1995;108:1122–8.
9. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. *J Thorac Cardiovasc Surg* 1999;117:54–63.
10. Rusch VW, Venkatraman E. The importance of surgical staging in the treatment of malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 1996;111:815–25.
11. Pass HI, Temeck BK, Kranda K, Steinberg SM, Feuerstein IR. Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 1998;115:310–7.
12. Sugarbaker DJ, Garcia JP, Richards WG, et al. Extrapleural pneumonectomy in the multimodality therapy of malignant pleural mesothelioma. Results in 120 consecutive patients. *Ann Surg* 1996;224:288–94.
13. Maasilta P. Deterioration in lung function following hemithorax irradiation for pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 1991;20:433–8.
14. Solheim OP, Saeter G, Finnanger AM, Stenwig AE. High-dose methotrexate in the treatment of malignant mesothelioma of the pleura. A phase II study. *Br J Cancer* 1992;65:956–60.
15. Planting AS, Schellens JH, Goey SH, et al. Weekly high-dose cisplatin in malignant pleural mesothelioma. *Ann Oncol* 1994;5:373–4.
16. Kindler HL, Millard F, Herndon JE, Vogelzang NJ, Suzuki Y, Green MR. Gemcitabine for malignant mesothelioma: a phase II trial by the Cancer and Leukemia Group B. *Lung Cancer* 2001;31:311–7.
17. Chahinian AP, Antman K, Goutsou M, et al. Randomized phase II trial of cisplatin with mitomycin or doxorubicin for malignant mesothelioma by the Cancer and Leukemia Group B. *J Clin Oncol* 1993;11:1559–65.
18. Byrne MJ, Davidson JA, Musk AW, et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. *J Clin Oncol* 1999;17:25–30.
19. Shih C, Chen VJ, Gossett LS, et al. LY231514, a pyrrolo [2,3-*d*]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. *Cancer Res* 1997;57:1116–23.
20. Niyikiza C, Baker SD, Seitz DE, et al. Homocysteine and methylmalonic acid: markers to predict and avoid toxicity from pemetrexed therapy. *Mol Cancer Ther* 2002;1:545–52.
21. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636–44.