Oncologic Drugs Advisory Committee
Briefing Document

NDA 21-677
"ALIMTA as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy."

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Synopsis – NDA 21-677

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in both men and women in the United States. Chemotherapy in NSCLC prolongs survival, but few options are available after initial chemotherapy. Docetaxel is the only chemotherapy drug currently approved by the FDA in second-line NSCLC; however, docetaxel has known toxicity disadvantages, including neutropenia, febrile neutropenia, neurosensory toxicity, infection, asthenia, and alopecia. In addition, docetaxel, in combination with cisplatin, is now approved for first-line NSCLC. Thus, active agents with a better safety profile are needed to help patients who progress after prior chemotherapy.

Alimta is a novel antifolate that inhibits several folate-dependent enzymes crucial to the synthesis of pyrimidines and purines, which in turn are required for the synthesis of DNA and RNA. Alimta, in combination with cisplatin, has been approved for the treatment of malignant pleural mesothelioma (MPM), based on significantly superior overall survival.

Alimta merits approval as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy, based on a superior benefit-to-risk profile as compared with docetaxel.

Alimta demonstrates efficacy in NSCLC

In one of the largest worldwide randomized Phase 3 studies to date of second-line NSCLC (H3E-MC-JMEI [JMEI]), overall survival of patients in the Alimta arm was similar to that of docetaxel. In addition, Alimta demonstrated similar results compared with docetaxel for the secondary endpoints, which included the following:

- progression-free-survival
- time to progressive disease
- response rate and stable disease rate
- patient-reported outcomes.

Furthermore, Phase 2 studies showed that (1) single-agent Alimta has activity similar to that of other active agents in first-line NSCLC (for example, gemcitabine, paclitaxel, docetaxel, and vinorelbine), and (2) the activity of the combination of Alimta plus a platinum is within the activity range observed with other current standard platinum doublets (for example, gemcitabine plus cisplatin, paclitaxel plus cisplatin, or docetaxel plus cisplatin).

Alimta retains 102% of docetaxel's benefit over best supportive care in second-line NSCLC

Percent–benefit-retention analysis showed that Alimta retained 102% of docetaxel's relative benefit over best supportive care (BSC) in the relevant historical trial. In addition, Cox adjusted survival analysis demonstrated that Alimta retained 114% of docetaxel's benefit over BSC.

Alimta is better than historical best supportive care in second-line NSCLC
The percent—benefit-retention methodology implied that the overall survival in the Alimta arm was statistically significantly superior to that of BSC.

Efficacy of Alimta is consistently similar to docetaxel across all key subgroups
Efficacy of Alimta was consistent and similar to that of docetaxel across all patient subgroups in Study JMEI, including the three significant prognostic factors of performance status, time since last chemotherapy, and disease stage.

Alimta has an excellent safety profile and is safer than docetaxel
Treatment with Alimta showed significantly better and clinically relevant safety compared with docetaxel. Treatment with Alimta was associated with a trend for fewer deaths. Alimta therapy was related to statistically significantly less Grade 3/4 neutropenia, less neutropenia with infection, less diarrhea, and less alopecia. Alimta therapy was also associated with significantly less neurosensory toxicity, myalgia, and arthralgia. Patients in the Alimta arm required less drug-related hospitalization and supportive care utilization.

Alimta has a superior risk/benefit profile than docetaxel, based on data from the Phase 3 Study JMEI
Alimta offers an improved risk/benefit profile compared with docetaxel and merits approval in the treatment of second-line NSCLC, a devastating disease that clearly needs newer treatment options.

Summary of Efficacy and Safety Results of Pivotal Trial JMEI

Study JMEI was a large (N=571) randomized, Phase 3 registration study to compare the survival of patients treated with Alimta (N=283) with the survival of patients treated with docetaxel (N=288) in second-line NSCLC. In this study, the efficacy of Alimta was found to be similar to that of docetaxel in terms of the primary endpoint of overall survival and all secondary endpoints, as well as across all subgroup analyses. In addition, the efficacy of docetaxel observed in this study was similar to or better than that observed in previous Phase 3 docetaxel studies in the same setting.

In Study JMEI, the Kaplan-Meier (K-M) overall survival curves for the Alimta and docetaxel arms were found to be overlapping, as shown in the figure below. The hazard ratio (HR) for Alimta survival compared with docetaxel was 0.99 (confidence interval [CI], 0.82 to 1.20). The overall median survival for patients treated with Alimta (8.3 months) was similar to the overall median survival for patients treated with docetaxel (7.9 months). Docetaxel's efficacy in JMEI was similar to its efficacy in the historical trial comparing BSC to docetaxel 75 mg/m^2 (Tax 317B).

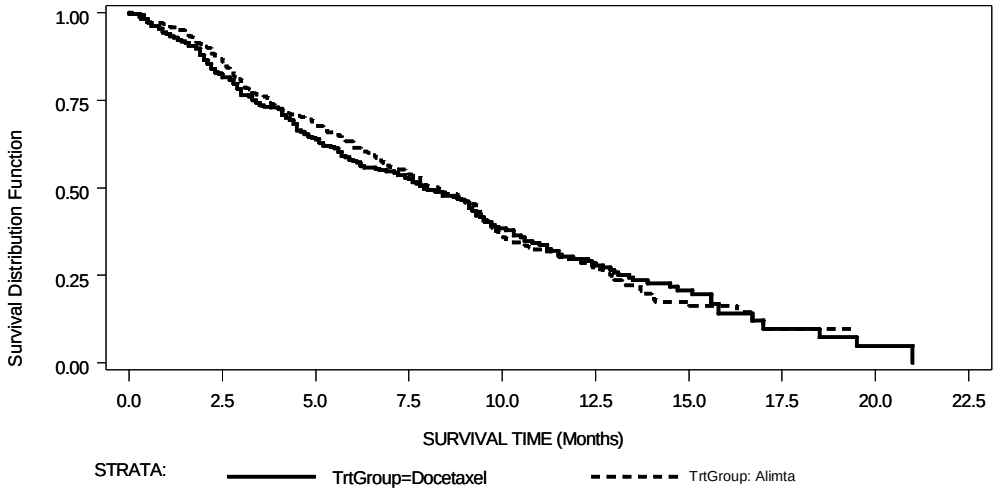


Figure Synopsis.1. Kaplan-Meier distribution of overall survival time
ITT population of Study JMEI.

Abbreviations: ITT = intent to treat; TrtGroup = treatment group.

While tests for superiority and noninferiority (based on the 1.11 margin) were not statistically significant, Alimta retained 102% (95% CI, 52% to 157%) of docetaxel's benefit over BSC. Using the lower boundary of the CI of 52%, Alimta retained statistically significantly greater than 50% of docetaxel's survival benefit over BSC (p=0.047). When considering the primary JMEI survival results in the context of the historical survival benefit of docetaxel treatment, formal statistical analyses robustly demonstrated that Alimta provides a significant survival advantage over BSC (hazard ratio [HR] = 0.55; 95% CI, 0.33 to 0.90; p=0.019).

Covariate-adjusted Cox analysis also showed a consistently similar efficacy to that of docetaxel, after adjusting for the three factors that significantly impacted survival (performance status, disease stage, and time from last chemotherapy). The percent-retention after adjustments was 114% (95% CI, 73% to 195%; p=0.016).

Results of secondary efficacy endpoints in Study JMEI were consistently indistinguishable between the Alimta and docetaxel arms:

- progression-free-survival (2.9 mo for both arms)
- time to progressive disease (3.4 mo versus 3.5 mo)
- tumor response rate (9.1% versus 8.8%)
- stable disease (45.8% versus 46.4%)

- patient-reported outcomes as characterized by the Lung Cancer Symptom Scale.

Alimta demonstrated a significantly better toxicity profile for clinically relevant toxicities compared with docetaxel in Study JMEI. The following important safety benefits were associated with the Alimta arm:

- a trend for fewer deaths (during and within 30 days of study discontinuation) (11.7% versus 14.5%)
- significantly fewer drug-related serious adverse events (10.2% versus 23.9%)
- significantly fewer hospitalizations due to adverse events (31.7% versus 40.6%)
- significantly fewer clinically relevant drug-related laboratory and nonlaboratory toxicities:
    - neutropenia (Grades 3 and 4) (5.3% versus 40.2%)
    - febrile neutropenia (Grades 3 and 4) (1.9% versus 12.7%)
    - neurosensory toxicity (Grades 2, 3, and 4) (0.8% versus 4.3%)
    - arthralgia (Grades 2, 3, and 4) (0.4% versus 5.8%)
    - myalgia (Grades 2, 3, and 4) (2.3% versus 6.9%)
    - alopecia (all grades) (6.4% versus 37.7%).
- significantly less use of granulocyte colony-stimulating factors.

In summary, Alimta shows a significant improvement in the safety profile compared with docetaxel.

Summary of Efficacy from Phase 2 Trials of Alimta in NSCLC

In Phase 2 studies, Alimta demonstrated consistent activity as a single-agent in first-line and second-line treatment of NSCLC. Platinum-based combinations with Alimta also showed efficacy comparable to current standard platinum-based chemotherapy doublets in first-line therapy for NSCLC.

- Alimta monotherapy in refractory second-line NSCLC (N=79) showed a response rate of 8.9% and a median survival of 5.7 months.
- In two studies, with a total of 87 patients, Alimta monotherapy in first-line NSCLC achieved a response rate of 16% and 23% with median survival of 7.2 and 9.2 months, respectively.

- In two studies of Alimta in combination with cisplatin in first-line NSCLC with a total of 65 patients, the response rates were 38.9% and 44.8% with the median survival of 10.9 months and 8.9 months.
- In a randomized Phase 2 study of Alimta in combination with either carboplatin or oxaliplatin in first-line NSCLC with a total of 79 patients, the response rates were 32% and 27% and the median survival was 9.9 months and 9.3 months, respectively.

1. Introduction

1.1. Non-Small Cell Lung Cancer

Lung cancer is one of the most common malignancies (12.7% of all cancers), and it continues to rise in incidence worldwide. Approximately 174,000 new cases and 160,000 lung cancer-related deaths were estimated for the year 2004 in the United States. It is also the leading cause of cancer death in both men and women in the United States. The number of deaths due to lung cancer surpasses deaths due to colorectal, breast, and prostate cancers combined. Almost 80% of lung cancers are classified as NSCLC; approximately 25% of these cases are early stage, and the remaining 75% present as locally advanced (Stage III) or metastatic disease (Stage IV) (Ihde 1992; Shepherd 1993; Walling 1994).

In the first-line setting, some patients with Stage III NSCLC receive chemotherapy as part of standard multimodality treatment. Patients with Stage IV disease, and many patients with Stage IIIB disease with pleural effusion, typically receive chemotherapy alone. Chemotherapy in the first-line setting prolongs survival and provides palliation. However, nearly all patients relapse after this therapy, with a median TTPD of 3.6 months (Schiller et al. 2002).

In the second-line setting, 40% to 50% of NSCLC patients receive chemotherapy if their performance status allows such treatment. In the United States, use of chemotherapy in this setting has increased from over 13,000 cases in 1997 to over 32,000 cases in 2003 (Tandem Anti-Cancer Drug & Tumor Audit, Synovate Healthcare).

Recently, two Phase 3 docetaxel (single-agent) studies, TAX 317 (Shepherd et al. 2000) and TAX 320 (Fossella et al. 2000), produced results that led to the approval of docetaxel as a second-line treatment of locally advanced or metastatic NSCLC. Table 1.1 compares the efficacy results from the TAX 317 and TAX 320 studies.

TAX 317 compared docetaxel with BSC in patients with NSCLC who had previously been treated with platinum-based chemotherapy. The primary study endpoint was survival. Patients were randomized to receive either 100 mg/m^2 docetaxel every 21 days or BSC. Investigators reduced the docetaxel dose to 75 mg/m^2 for the second half of the study, after an interim safety analysis revealed a high drug-related death rate in the docetaxel arm. In the postamendment cohort, 55 patients received docetaxel 75 mg/m^2 and 49 patients received BSC. The postamendment part of the study (75 mg/m^2 docetaxel) is referred as TAX 317B in this document. Patients in the BSC arm were treated with therapy judged appropriate by the treating physician, and included analgesics, transfusions, and palliative radiotherapy.

TAX 320 was an open-label, multicenter, Phase 3 trial in patients with advanced NSCLC who had progressed after platinum-containing chemotherapy. The study allowed prior paclitaxel treatment. Patients were stratified according to their best response to previous

platinum therapy and were randomized to either docetaxel 100 mg/m^2 or docetaxel 75 mg/m^2, both given as a 1-hour infusion every 3 weeks, or chemotherapy with either vinorelbine or ifosfamide (control). Vinorelbine was given at 30 mg/m^2 on Days 1, 8, and 15 of a 3-week cycle. Ifosfamide was given at 2 g/m^2/day on Days 1, 2, and 3 of a 3-week cycle. A total of 120 patients were evaluable in each docetaxel arm, and 118 patients in the control arm. Most patients on the control arm received vinorelbine.

Table 1.1. Efficacy Results from the Two Docetaxel Registration Studies in Second-Line NSCLC

	TAX 317 (Shepherd et al. 2000)				TAX 320 (Fossella et al. 2000)		
Parameter	**Doc 75[a] (N=55)**	**BSC (N=49)**	**Doc 100[a] (N=48)**	**BSC (N=51)**	**Doc 75[a] (N=120)**	**Doc 100[a] (N=120)**	**Vin/Ifo[b] (N=118)**
RR (%)	5.5	NA	6.3	NA	6.7	10.8	0.8
Median TTPD (mo)	2.8	1.6	2.1	1.4	2.0	1.9	1.8
MS (mo)	7.5*	4.6	5.9	4.6	5.7	5.5	5.6
1-year survival (%)	37*	12	19	19	32*	21	19

Abbreviations: BSC = best supportive care; Doc = docetaxel; Ifo = ifosfamide; MS = median survival; N = number of evaluable patients; NA = not available; NSCLC = non-small cell lung cancer; RR = response rate; TTPD = time to progressive disease; Vin = vinorelbine.

[a] Docetaxel doses are measured in mg/m^2.

[b] Vinorelbine doses are measured in mg/m^2; ifosfamide doses are measured in g/m^2/day.

* Statistically significant versus the control arm.

As shown in Table 1.1, treatment with docetaxel 75 mg/m^2 resulted in better overall survival compared with BSC in TAX 317. While the median survival in TAX 320 was not significantly improved with docetaxel 75 mg/m^2, the 1-year survival rate was significantly better with docetaxel 75 mg/m^2 compared with the control arm. Table 1.2 shows the toxicity results from both TAX 317 and TAX 320 as reported in the docetaxel label. Of note, Grade 3/4 neutropenia was seen in 65.3% of patients, infection was seen in 10.2%, diarrhea in 2.8%, and alopecia (all grades) in 56.3%. In addition, febrile neutropenia (Grade 4 neutropenia with fever >38°C with intravenous antibiotics and/or hospitalization) occurred in 6.3% of patients.

The approved indicated dose/schedule of docetaxel is 75 mg/m^2 once every 3 weeks.

Table 1.2. Adverse Events (%) in Studies TAX 317 and TAX 320 Regardless of Causality (N=176) (Data from Docetaxel Label)

Toxicity	Any	Grade 3/4
Neutropenia	84.1	65.3
Leukopenia	83.5	49.4
Pulmonary	40.9	21.0
Asthenia*	52.8	18.2
Infection	33.5	10.2
Anemia	91.0	9.1
Febrile neutropenia**	--	6.3
Nausea	33.5	5.1
Thrombocytopenia	8.0	2.8
Vomiting	21.6	2.8
Diarrhea	22.7	2.8
Neurosensory	23.3	1.7
Stomatitis	26.1	1.7
Skin	19.9	0.6
Alopecia (all grades)	56.3	--
Treatment-related death	2.8	--

Abbreviations: N = number of patients in the two studies receiving docetaxel 75 mg/m^2.

* Coding Symbols and Thesaurus for Adverse Reaction Terms (COSTART) classification of 'any' and 'severe.'

** Absolute Grade 4 neutropenia with fever >38°C with intravenous antibiotics or hospitalization.

In search of a better-tolerated schedule, three recent Phase 3 randomized trials (Camps et al. 2003; Gridelli et al. 2003; Schuette et al. 2004) have compared the regimen of docetaxel 75 mg/m^2 every 3 weeks with alternative weekly schedules of docetaxel (Table 1.3). The overall efficacy of the 75-mg/m^2 docetaxel regimen in these studies was comparable to that of TAX 317 (Shepherd et al. 2000).

Table 1.3. Recent Randomized Phase 3 Studies of Docetaxel 75 mg/m^2 in Second-Line NSCLC

Efficacy Parameter	Gridelli et al. 2003 (N=110)	Camps et al. 2003 (N=129)	Schuette et al. 2004[a] (N=103)
Response rate (%)	2.7	9.3	12.6
Median survival (mo)	6.7	6.6	5.8
1-year survival rate (%)	22	27	NA

Abbreviations: N = number of enrolled patients; NA = not available; NSCLC = non-small cell lung cancer.

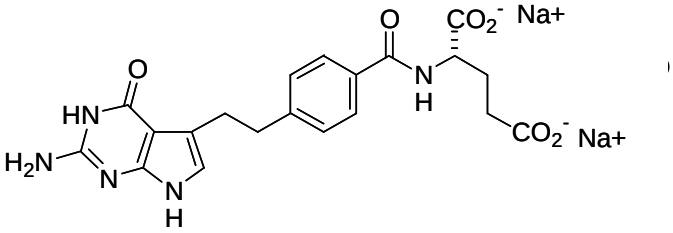
[a] Data at six months (Schuette et al. 2004).

In conclusion, docetaxel 75 mg/m^2 once every 3 weeks is the only approved therapy in the second-line treatment of NSCLC. Use of docetaxel in this setting is associated with

undesirable hematologic and other toxicities; therefore, newer, less toxic therapies are needed. With median survival in this group of 6 to 8 months, toxicity in this setting is very detrimental. In addition, the docetaxel plus cisplatin combination has recently been approved for the first-line treatment of NSCLC. Currently, in the United States, approximately 27% of all patients receiving first-line chemotherapy receive a docetaxel-based regimen (Tandem Anti-Cancer Drug & Tumor Audit, Synovate Healthcare). Patients who receive this combination therapy will need newer nontaxane-based second-line treatments.

1.2. Alimta

1.2.1. Structure and Mechanism of Action



Alimta (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) is a novel pyrrolopyrimidine-based antifolate cytotoxic agent (Taylor et al. 1992) (generic name: pemetrexed; Lilly compound number: LY231514). Figure 1.1 illustrates the mechanism of action of Alimta.

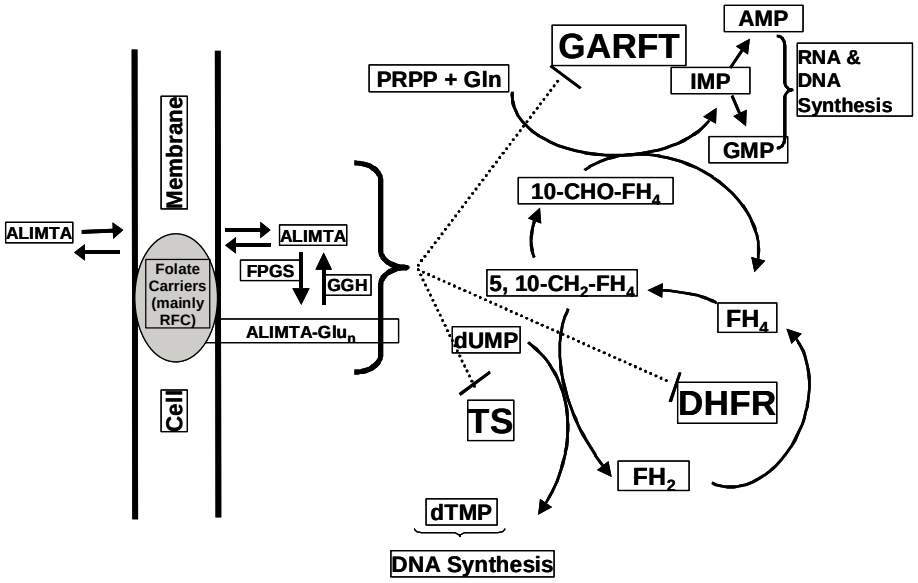


Figure 1.1. Mechanism of action of Alimta.

Abbreviations: 10-CHO-FH_4 = 10-formyl tetrahydrofolate; 5, 10-CH_2-FH_4 = 5, 10-methylene tetrahydrofolate; AMP = adenosine monophosphate; DHFR = dihydrofolate reductase; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate; FH = dihydrofolate; FPGS = folylpolyglutamate synthetase; GARFT = glycinamide ribonucleotide formyl transferase; GGH = gamma-glytamyl hydrolase; Gln = glutamine; GMP = guanosine 5'-monophosphate; IMP = inosine 5'-monophosphate; PRPP = 5-phosphoribosyl-1-pyrophosphate; RFC = reduced folate carrier; TS = thymidylate synthase.

In vitro studies have shown that the IC_{50} of Alimta against human leukemia cells is 15 nM. Intracellularly, Alimta is a good substrate for the enzyme folylpolyglutamate synthetase (Figure 1.1; Habeck et al. 1995); the resulting polyglutamated forms of Alimta are potent inhibitors of the following key folate-dependent enzymes:

- thymidylate synthase
- dihydrofolate reductase
- glycinamide ribonucleotide formyltransferase.

The pentaglutamate form of Alimta, the predominant intracellular form, has been shown to be >60-fold more potent in its inhibition of TS (catalyzes the transformation of deoxyuridine monophosphate to deoxythymidine monophosphate) than the monoglutamate (Chen et al. 1996). The multitargeted enzyme inhibitory profile of Alimta is summarized in Table 1.4 (Shih et al. 1997).

Table 1.4. Inhibition Profiles of Purified Folate-Requiring Enzymes

	K_i Values (nM ± SEM)		
	TS	**DHFR**	**GARFT**
Alimta	109 ± 9.0	7.0 ± 1.9	9300 ± 690
Alimta-$(glu)_3$	1.6 ± 0.1	7.1 ± 1.6	380 ± 92
Alimta-$(glu)_5$	1.3 ± 0.3	7.2 ± 0.4	65 ± 16

Abbreviations: DHFR = dihydrofolate reductase; GARFT = glycinamide ribonucleotide formyltransferase; SEM = standard error of the mean; TS = thymidylate synthase.

By virtue of its ability to target multiple enzymes, Alimta can strongly interfere with both RNA and DNA biosynthesis (Figure 1.1). These observations suggested that Alimta might have advantages over current antifolate therapeutic agents, such as methotrexate and raltitrexed, which are reported to inhibit only DNA synthesis.

1.2.2. Preclinical Studies

Alimta has been well characterized in preclinical experiments as a multitargeted antifolate. Human tumor xenograft studies with a wide range of tumors, including colon, breast, pancreatic, and lung cancer cells, have confirmed that Alimta possesses strong antitumor activity. In vitro growth-inhibitory experiments have also substantiated these observations. There were no unusual toxicology findings or absorption, distribution, metabolism, and excretion findings.

Preclinical studies have also assessed the potential of Alimta to elicit secondary receptor-mediated autonomic pharmacology by smooth and cardiac muscle tissue bath preparations. These in vivo assessments included several central nervous system and behavioral function tests and gastrointestinal transit evaluations in mice, renal assessments in rats, and cardiovascular assessments in anesthetized dogs. No issues expected to interfere with subsequent clinical use of Alimta in humans were identified in these studies.

1.2.3. Clinical Development

Alimta, either as a single agent or in combination with other cytotoxic agents, has been tested in several tumor types, including MPM, NSCLC, breast cancer, colorectal cancer, and pancreatic cancer.

Based on the results of Phase 1 dose-finding studies, the recommended dose of Alimta for Phase 2 and Phase 3 clinical trials was 600 mg/m^2 administered as an intravenous infusion once every 3 weeks. Subsequent safety-related clinical observations during Phase 2 testing led to a modification of the initial dosing recommendation to 500 mg/m^2 administered intravenously once every 3 weeks.

A multivariate analysis of safety data from several Alimta studies revealed an association of high baseline serum homocysteine with the probability of experiencing Grade 4

neutropenia with Grade 3/4 infection, Grade 3/4 diarrhea, or increased risk of study drug-related death (Figure 1.2; Niyikiza 2002). These data also indicated an association between the incidence of Grade 3/4 diarrhea and high baseline serum levels of methyl malonic acid (MMA). Because high serum homocysteine is known to correlate with poor folate status, and high serum MMA correlates with poor vitamin B_{12} status, the sponsor decided to supplement Alimta patients with low-dose folic acid and intramuscular vitamin B_{12}. Furthermore, the sponsor chose to supplement all treated patients because quartile analysis of baseline homocysteine and MMA revealed that the relationship between homocysteine (or MMA) and toxicity was a continuous function (Niyikiza 2002). This suggested that improvement in folic acid status in all patients would result in improved safety. Programmatic supplementation with these two vitamins was implemented in December 1999.

The rationale behind the choice of dose and duration of folic acid and vitamin B_{12} supplementation of all Alimta patients (see Section 3.1) to achieve the sponsor's goal was guided by the following considerations:

- Daily supplementation of 250 to 500 μg folic acid is known to lower homocysteine to levels below 9.0 μM within 2 weeks (Bronstrup et al. 1999; Brouwer et al. 1999).
- Intramuscular injection of 1 mg of vitamin B_{12} every 9 weeks is the recommended maintenance dose of vitamin B_{12} for patients with pernicious anemia (Walsh 1997; Hoffbrand 2000). In addition, a 10-fold decrease in MMA levels can be achieved within 5 days following one injection of 1 mg of vitamin B_{12} (Stabler et al. 1986).

Safety data obtained subsequent to supplementation showed that vitamin supplementation significantly decreased severe toxicity. These data include patients treated with Alimta monotherapy and combination therapy, and do not include JMEI results. As shown below, there was a significant reduction in neutropenia and toxic deaths.

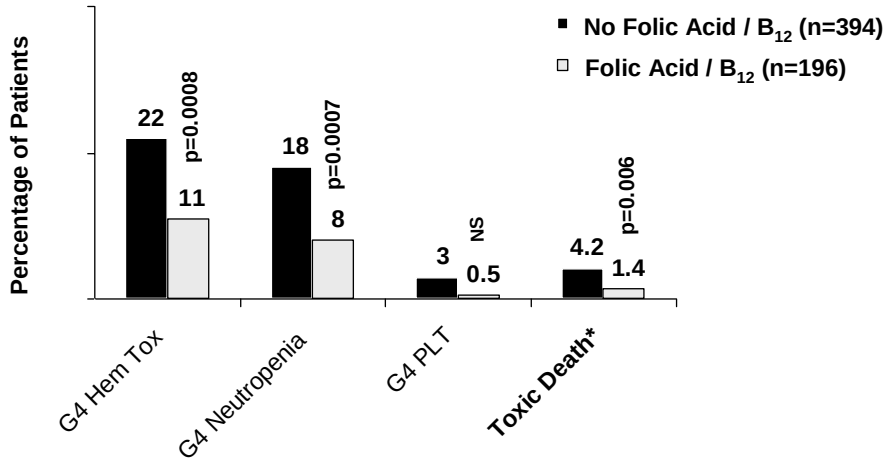


Figure 1.2. **Alimta hematologic toxicity and toxic death before and after folic acid/vitamin B12 intervention.**

Abbreviations: G = grade; HEM = hematologic; n = number of patients; NS = not significant; PLT = platelets; Tox = toxicity.
* = Drug-related death reported for all trials.

Early in the clinical development of Alimta, it was observed that prophylactic administration of dexamethasone markedly reduced skin toxicity (for example, macular papular rash with or without itching). This led to the routine administration of dexamethasone (or equivalent) in subsequent Alimta trials to patients who experienced CTC Grade 2 rash in a previous cycle. Because of the positive patient experience, starting in 1996, dexamethasone premedication was made a part of the treatment regimen for all Alimta patients in Alimta trials. Since this programmatic intervention, patients have experienced fewer, and less severe, skin toxicities.

The product label, therefore, recommends supplementation with folic acid, vitamin B_{12}, and dexamethasone as standard components of Alimta therapy.

Alimta, in combination with cisplatin, was recently approved (04 February 2004) by the FDA for the first-line treatment of patients with MPM (NDA 21-462). In a large, single-blind, multicenter, international, Phase 3 trial (H3E-MC-JMCH), treatment with Alimta plus cisplatin demonstrated a statistically significant overall survival benefit for chemotherapy-naive patients MPM compared with cisplatin monotherapy (12.1 versus 9.3 months; p=0.02). The combination regimen of Alimta plus cisplatin also showed an

improvement in measured pulmonary function, pain, and dyspnea over cisplatin alone (Gralla et al. 2003).

Current treatment options for second-line NSCLC provide only modest survival advantages, with clinically important toxicities. For that reason, new treatment strategies are needed for these patients, especially given the palliative nature of the treatment.

Alimta has now been developed for the second-line treatment of patients with locally advanced or metastatic NSCLC. In 1999, following encouraging results from Alimta Phase 2 NSCLC studies, the sponsor began a Phase 3 study, JMEI, in which single-agent Alimta was compared with single-agent docetaxel in patients who had progressed after prior chemotherapy. In Study JMEI, the sponsor did not use BSC as the control because docetaxel had been approved for second-line treatment of NSCLC; therefore, it was deemed not feasible to treat patients in the control arm with BSC. This study was not designed to test strict equivalency between Alimta and docetaxel, because doing so would have required >4000 patients (see Section 3 for more details). Therefore, the study was designed to test superiority, while allowing to test for noninferiority. This study was intended for global registration. Then, as now, the FDA and the European Authority recommended different methodologies for assessing noninferiority, percent retention, and fixed margin, respectively. As a result, the sponsor employed both methods to analyze and report the results of pivotal study JMEI.

Based on the encouraging results of similar efficacy and lower toxicity compared with docetaxel (the current treatment standard) in the pivotal study JMEI, the sponsor is seeking marketing approval for the indication of second-line treatment of NSCLC. The proposed label indication is:

> "Alimta as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy."

The label-proposed dose for this indication is Alimta 500 mg/m^2 administered intravenously over approximately 10 minutes on Day 1 of each 21-day cycle.

The timeline of some important regulatory events in the clinical development of Alimta is shown in Table 1.5.

Table 1.5. Timeline of Regulatory Events Alimta Clinical Development

Event	Date
JMEI special protocol assessment (FDA response)	23 August 2000
JMEI protocol approved	07 November 2000
JMEI protocol amendment A approved (Appendix 1)	27 November 2000
JMEI first patient enrolled	20 March 2001
JMEI protocol amendment B approved (Appendix 1)	03 August 2001
JMEI last patient enrolled	06 February 2002
JMEI statistical analysis plan (prospective) approved	24 January 2003
JMEI database locked	30 January 2003
Pre-NDA meeting for second-line NSCLC as supplemental indication	15 May 2003
ASCO oral presentation on JMEI	01 June 2003
Fast-track designation for second-line NSCLC	23 July 2003
NSCLC NDA submission	04 November 2003
120-Day Safety Update for NSCLC submission	03 March 2004
Journal of Clinical Oncology publication of JMEI	01 May 2004

1.2.3.1. Studies Supporting Efficacy of Alimta in NSCLC Patients

Table 1.6 contains a list of the sponsor's NSCLC studies that provide supporting evidence of the efficacy of Alimta in the current supplemental NDA. A total of 894 patients were enrolled in these seven studies.

Study JMEI was the pivotal Phase 3 randomized study of Alimta versus docetaxel in the second-line treatment of patients with locally advanced or metastatic NSCLC (see Section 3.1 for details). Study H3E-MC-JMBR (JMBR), a Phase 2 study of single-agent Alimta in the treatment of patients with refractory NSCLC (relapse within 3 months of first-line therapy), provides supporting efficacy evidence for this submission (Section 3.2). Table 1.6 also lists five other studies that have demonstrated clinical activity of Alimta, either as a single agent or in combination with platinum agents, in the first-line treatment of NSCLC patients (Section 3.3). Tabular overviews of all seven studies are provided in Table APP.1.1 through Table APP.1.7 of this document.

Table 1.6. Studies Supporting Efficacy of Alimta in NSCLC

Study	Phase	N	Regimen	Suppl	References	Appendix Table #
Second line						
H3E-MC-JMEI	3	571[a]	Alimta vs docetaxel	Yes	Hanna et al. 2004[b]	App.1.1
H3E-MC-JMBR	2	81	Alimta single agent	No	Smit et al. 2003[b]	App.1.2
First line						
H3E-MC-JMAL	2	59	Alimta single agent	No	Clarke et al. 2002[b]	App.1.3
H3E-MC-JMAN	2	33	Alimta single agent	No	Rusthoven et al. 1999[b]	App.1.4
H3E-MC-JMEK	2	83[c]	Alimta + carboplatin vs Alimta + oxaliplatin	Yes	Scagliotti et al. 2003 [b]	App.1.5
H3E-MC-JMAY	2	36	Alimta + cisplatin	No	Manegold et al. 2000[b]	App.1.6
H3E-MC-JMBZ	2	31	Alimta + cisplatin	No	Shepherd et al. 2001[b]	App.1.7
Total		894				

Abbreviations: N = number of enrolled patients; NSCLC = non-small cell lung cancer; Suppl = supplementation; vs = versus.

[a] Alimta: 283 patients; docetaxel: 288.

[b] A copy of this publication is provided in Appendix 6.

[c] Alimta + carboplatin: 41 patients; Alimta + oxaliplatin: 42.

In addition, recently, results from a Phase 2 study of Alimta plus carboplatin (not previously submitted to the FDA), by Koshy and colleagues, was presented at the 2004 annual meeting of the American Society of Clinical Oncology (ASCO; Koshy et al. 2004) (see Section 3.3.2 for preliminary results).

1.2.3.2. Studies Supporting Safety of Alimta in NSCLC Patients

Table 1.7 contains a list of studies that provide supporting evidence of safety of Alimta for this NDA.

Section 4.1 and Section 4.2 provide a summary of the clinical safety data of Alimta from the pivotal Phase 3 Study JMEI compared with that of docetaxel.

Section 4.3 provides a summary of the safety data from an integrated dataset compiled from Studies JMEI, JMDM, JMBT, JMEU, JMDR, and JMDS. Alimta was tested as a single agent in these studies, and the dataset included 517 vitamin-supplemented patients as of the NDA submission date (November 2003). Studies JMBR, JMAL, JMAN, JMAY, and JMBZ, shown in Table 1.6, were not part of the integrated safety database because patients in these studies were not supplemented with folic acid and vitamin B_{12}.

Tabular overviews of the studies supporting safety are provided in Table APP.1.8 through Table APP.1.12 of this document.

Table 1.7. Single-Agent Studies Supporting Safety of Alimta

Study	Phase	N	Regimen	Tumor Type	References	Appendix Table #
Second line						
H3E-MC-JMEI	3	265	Alimta vs docetaxel	NSCLC	Hanna et al. 2004[a]	App.1.1
H3E-MC-JMDM	2	60	Alimta	Breast	Mennel et al. 2001; O'Shaughnessy 2002	App.1.8
H3E-MC-JMBT	2	43	Alimta	Breast	Lilly data on file	App.1.9
H3E-MC-JMEU	2	45	Alimta	Bladder	Ongoing	App.1.10
First line						
H3E-MC-JMDR	2	43	Alimta	MPM	Lilly data on file	App.1.11
H3E-MC-JMDS	2	61	Alimta	Breast	Lilly data on file	App.1.12
Total		517				

Abbreviations: MPM = malignant pleural mesothelioma; NSCLC = non-small cell lung cancer; N = number of patients receiving Alimta plus vitamin supplementation.

[a] A copy of this publication is provided in Appendix 6.

2. Clinical Pharmacology

2.1. Overview

The pharmacokinetics of Alimta following single-agent administration were evaluated in three Phase 1 dose-escalation studies (H3E-MC-JMAA, H3E-MC-JMAB, and H3E-BP-001) and in one Phase 2 study of Alimta in combination with cisplatin (H3E-MC-JMBZ; see Table 1.6). Alimta pharmacokinetics were also assessed using population pharmacokinetic methods in 10 Phase 2 studies, including the NSCLC studies H3E-MC-JMAL and H3E-MC-JMBR, and in a Phase 3 trial (H3E-MC-JMCH) in MPM patients. These analyses included doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period to 500 cancer patients with a variety of solid tumors.

Alimta is not metabolized to an appreciable extent and is primarily eliminated as unchanged drug by renal excretion, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. Both total plasma and renal clearance correlate with measured glomerular filtration rate (GFR) and calculated renal function (standard Cockcroft-Gault method [CGCL]; Cockcroft and Gault 1976). The total systemic clearance of Alimta is approximately 91.8 mL/min, with an elimination half-life of 3.5 hours (range, 2 to 7 hours) in patients with normal renal function (CGCL 90 mL/min). Alimta pharmacokinetics are linear over the clinical dose range evaluated; therefore, total systemic exposure (area under the curve [AUC]) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of Alimta do not change over multiple treatment cycles. Alimta has a steady-state volume of distribution of 16.1 L. In vitro studies indicate that Alimta is approximately 81% bound to plasma proteins in human plasma at concentrations from 0.5 to 200 μg/L.

The effects of extrinsic factors, including coadministration of Alimta with intramuscular vitamin B_{12} and oral folic acid, cisplatin, and aspirin was evaluated, indicating no alteration in Alimta pharmacokinetics. The administration of ibuprofen 400 mg every 6 hours resulted in an approximately 17% decrease in Alimta clearance (a 20% increase in AUC). These alterations in Alimta pharmacokinetics are no greater than those observed in patients with moderate renal impairment (CGCL 45 mL/min); therefore, ibuprofen (400 mg every 6 hours) may be given concurrently with Alimta to patients with normal renal function (≥80 mL/min).

The population pharmacokinetics of Alimta were evaluated based on data combined from 10 Phase 2 studies, including two studies in NSCLC patients (Studies JMAL and JMBR). Plasma concentration-time data were evaluated by population pharmacokinetic methods using the Nonlinear Mixed Effect Modeling (NONMEM) software program. The pharmacokinetics of Alimta were best characterized by a two-compartment model parameterized in terms of clearance, central volume of distribution, intercompartmental clearance, and peripheral volume of distribution. The final population pharmacokinetic model indicated that Alimta clearance, and therefore AUC, was dependent on creatinine

clearance, as estimated by CGCL, incorporating age, body weight, and serum creatinine concentration. From this, a patient with moderately impaired renal function (CGCL 45 mL/min) would be expected to have an approximately 36% lower Alimta clearance, resulting in an approximately 56% increase in overall systemic exposure compared with the population average. Alimta central volume of distribution is dependent on body surface area, primarily reflected in peak concentrations, and is not dependent on overall systemic exposure.

The relationships between alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin as indicators of hepatic dysfunction and Alimta pharmacokinetics were evaluated in the population pharmacokinetics analyses, and no significant effect was identified. Population pharmacokinetic analyses demonstrated no significant effect of age, sex, ethnicity, smoking, or alcohol consumption on the pharmacokinetics of Alimta.

The established population pharmacokinetic model adequately described Alimta pharmacokinetics for patients with breast, cervical, esophageal, head and neck, gastric, pancreatic, colorectal, renal, or bladder cancer, MPM, or NSCLC. The results indicated that, for a given dose, the AUC would be similar for patients with all cancer types investigated, and any differences in Alimta clearance were attributable to varying renal function. Therefore, differences in response rate by cancer type are based on pharmacodynamic response, that is, sensitivity of the tumor to Alimta, and not to differences in Alimta pharmacokinetics.

2.2. Summary

- Alimta is rapidly eliminated, with a terminal elimination half-life of approximately 3.5 hours. Alimta plasma clearance correlated well between Phase 1 and Phase 2 (population-based analysis) patients, with the typical value for the population-based analysis being approximately 91.8 mL/min in patients with normal renal function (CGCL 90 mL/min).
- Alimta pharmacokinetics are linear, exhibiting no dose dependency over the clinical range evaluated and displaying no clinically significant deviations from dose proportionality.
- Coadministration of Alimta with intramuscular vitamin B_{12} and oral folic acid, cisplatin, and aspirin were evaluated, indicating no alteration in Alimta pharmacokinetics.
- Ibuprofen at 400 mg four times a day can be given concurrently with Alimta in patients with normal renal function (CGCL ≥80 mL/min).
- A two-compartment population pharmacokinetic model indicated that Alimta clearance, and therefore AUC, was dependent on creatinine clearance as estimated by CGCL.

- Population pharmacokinetic analyses demonstrated no significant effect of age, sex, ethnicity, smoking, alcohol consumption, or cancer type on the pharmacokinetics of Alimta.

3. Clinical Efficacy of Alimta in NSCLC

The major clinical efficacy claims for Alimta in NSCLC are summarized in the following points:

- In the pivotal Phase 3 study JMEI, the survival curves of Alimta and docetaxel are superimposable throughout, denoting a similar survival between the treatment arms.
- Secondary efficacy endpoints of time to progressive disease (TTPD), overall response rate, and progression-free survival (PFS), and health outcomes analyses of Study JMEI are consistently similar between Alimta and docetaxel arms.
- Docetaxel's efficacy in JMEI is similar to its efficacy in TAX 317 (docetaxel 75 mg/m^2) and is comparable to other docetaxel 75 mg/m^2 results. Using the percent-retention methodology, Alimta retained 102% of docetaxel's benefit over BSC.
- When considering the primary JMEI survival results in the context of the historical survival benefit of docetaxel treatment, formal statistical analyses robustly demonstrate that Alimta provides a superior survival advantage over historical BSC (HR=0.55, p=0.019).
- Efficacy results of Study JMEI are consistently similar between treatment arms across major subgroups including the three significant prognostic factors identified in the Cox multivariate model (Cox 1972).
- Phase 2 studies JMBR, JMAL, JMAN, JMAY, JMBZ, and JMEK provide supporting evidence of the efficacy of Alimta in NSCLC (see Table 1.6 for study details). Table App.1.2 through Table App.1.7 provide tabular overviews of these studies.

3.1. Design of Pivotal Study JMEI

3.1.1. Basic Aspects of the Study Design

Study JMEI was a randomized, Phase 3, controlled, open-label, multicenter study in patients with locally advanced or metastatic NSCLC. Patients had received previous treatment with chemotherapy. The study was conducted in 23 countries.

Figure 3.1 displays the study schema. Randomization was balanced with respect to nine factors using a minimization algorithm (Pocock and Simon 1975) with an included random component (that is, a 75% chance of randomization to the arm that minimized the overall imbalance). Two of the nine factors (Eastern Cooperative Oncology Group [ECOG] performance status and disease stage) were known to be prognostic for survival in NSCLC. Another five factors (response to prior chemotherapy, time since prior chemotherapy, number of prior chemotherapy regimens, whether prior chemotherapy

contained a platinum compound, and whether prior chemotherapy contained paclitaxel) were believed to be possible prognostic factors for survival among pretreated patients. Baseline homocysteine level was included as a factor known to be prognostic for the safety of patients treated with Alimta. Finally, investigational center was included to minimize the effect of any patient-selection biases.

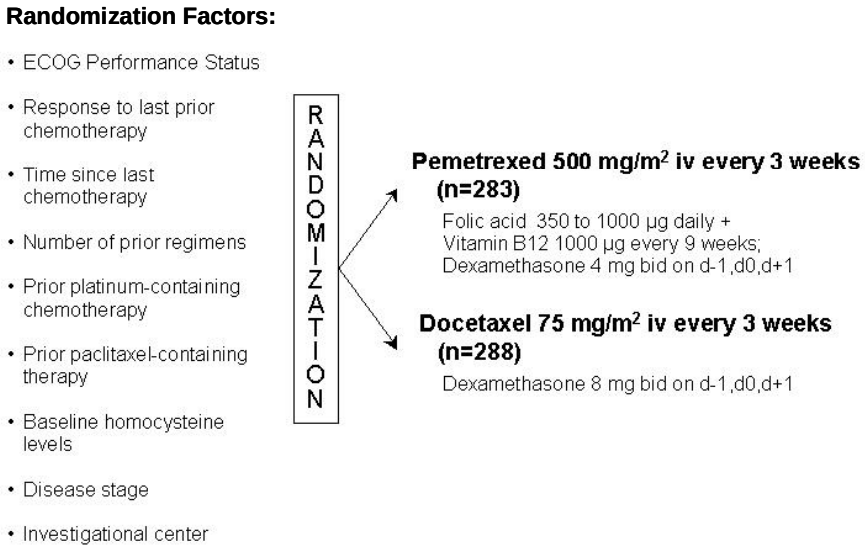


Figure 3.1. Study schema for Study JMEI.

Abbreviations: bid = twice daily; d = day; ECOG = Eastern Cooperative Oncology Group; iv = intravenous; n = number of enrolled patients.

Alimta was administered as a 500-mg/m^2 intravenous infusion on Day 1 of a 21-day cycle. Patients on this arm received folic acid supplementation, 350 to 1000 µg, or equivalent, and injections of 1000 µg vitamin B_{12}. Folic acid was to be taken orally daily beginning approximately 1 to 2 weeks before the first dose of Alimta and continued daily until 3 weeks after the last dose of Alimta. A vitamin B_{12} injection was to be given intramuscularly approximately 1 to 2 weeks before the first dose of Alimta and repeated approximately every 9 weeks until 3 weeks after the last dose of Alimta. Oral dexamethasone, 4 mg twice per day (or equivalent), was given on the day before, the day of, and the day after Alimta therapy, unless clinically contraindicated.

As the only approved therapy for second-line NSCLC, docetaxel was chosen as the active control in this study. Docetaxel was given as a 75-mg/m^2 intravenous infusion on Day 1 of a 21-day cycle, as described in the product label. Patients on this arm received oral dexamethasone, 8 mg twice daily, or an equivalent regimen, for 3 days starting the day before docetaxel administration, unless clinically contraindicated.

Patients on the docetaxel treatment arm were not required to receive folic acid or vitamin B_{12} supplementation because the docetaxel label does not prescribe the use of supplementation as part of the docetaxel regimen.

Cycles were repeated until evidence of disease progression or unacceptable toxicity occurred, the patient became pregnant, the patient requested that the therapy be discontinued, the investigator felt it was not in the patient's best interest to continue, or if the sponsor, after consultation with the investigator, decided to discontinue the patient. A patient who was receiving benefit from treatment could receive additional cycles, at the discretion of the investigator.

3.1.2. Study Objectives and Sample Size Calculations

The primary objective of the pivotal study, JMEI, was to compare the overall survival time following treatment with Alimta versus docetaxel in patients with locally advanced or metastatic (Stage IIIA/B or IV) NSCLC who had been previously treated with chemotherapy. The study was sized based on two scenarios:

1. Alimta would be judged superior to docetaxel if the 95% CI for the survival HR was entirely less than 1.00.
2. Alimta would be judged noninferior to docetaxel if the 95% CI for the survival HR was entirely less than 1.11.

The 1.11 HR margin was selected based on recommendations by the European Regulatory Authority to include a conservative noninferiority margin in the protocol design; this margin did not include any consideration for possible safety advantages.

With a final analysis that included at least 385 deaths, the study had the following operating characteristics:

- If the true survival HR of Alimta to docetaxel is 0.75, the study had at least 80% power to conclude superiority.
- If the true survival HR of Alimta to docetaxel is 0.83, the study had at least 81% power to conclude noninferiority (based on the 1.11 margin).

These considerations led to a planned enrollment of at least 520 patients.

The primary analysis was the estimation of the overall survival HR of Alimta to docetaxel in the randomized, intent-to-treat (ITT) population. The Cox proportional hazards model (Cox 1972), with study treatment arm as the only cofactor, was used to calculate a 95% CI for this overall survival HR.

The secondary objectives of the study were to compare the following between the arms:

- tumor response rate
- progression-free survival (PFS)

- time to progressive disease (TTPD)
- Lung Cancer Symptom Scale (LCSS)
- toxicity.

A secondary analysis of overall survival using a Cox proportional hazards model (Cox 1972) was performed. This prospectively defined model was constructed employing a step-wise procedure with seven randomization factors (excluding serum homocysteine level and investigational center). This model was utilized to calculate a 95% CI for overall survival HR and to determine which cofactors were prognostic for survival.

Overall survival time was defined, per patient, as the time from the date of randomization to the date of death due to any cause. Overall survival time was censored at the date of the last follow-up visit for patients who were still alive.

Progression-free survival time was defined, per patient, as the time from the date of randomization to the first date of documented disease progression or death due to any cause. Progression-free survival time was censored at the date of the last follow-up visit for patients who were still alive and who had not progressed.

Time to progressive disease was defined, per patient, as the time from the date of randomization to the first date of documented disease progression. Time to progressive disease was censored at the date of death for patients without documented disease progression. For patients who were still alive at the time of analysis, without documented disease progression, TTPD was censored at the date of the last follow-up visit.

The key inclusion criteria in Study JMEI were:

- histologic/cytologic Stage III or IV NSCLC
- previous treatment with ONLY one regimen for metastatic disease (prior adjuvant or neoadjuvant therapy allowed)
- performance status of 0 to 2 on the ECOG scale
- prior paclitaxel was allowed
- adequate organ function.

The key exclusion criteria were:

- symptomatic brain metastasis
- Grade 3 or 4 peripheral neuropathy
- weight loss ≥10% over the previous 6 weeks
- uncontrolled pleural effusions
- prior docetaxel therapy.

3.1.3. Primary Survival Analysis Plan

The primary analysis of Study JMEI was the calculation of the 95% CI for the overall survival HR of Alimta to docetaxel (prespecified as a Cox model estimate with no adjustment for prognostic cofactors).

As described in Section 3.1.2, the sample size of the study was based on the fixed margin criteria (accepted by the European Regulatory Authority). However, regarding the statistical analysis of the data, a recommendation by the FDA was incorporated to analyze the data using the percent retention method. In the United States, two oncology drugs have received marketing approval with efficacy determined by retrospective 50%-percent-retention analyses:

- docetaxel in first-line treatment breast cancer
- capecitabine in first-line colorectal cancer.

These retrospective analyses were based on percent-retention methodology (Rothmann et al. 2003). With publication of the methodology, the sponsor included a Rothmann analysis of the survival data in the statistical analysis plan (SAP) for Study JMEI prior to any treatment-assignment unblinding of the study data. The SAP specifically defined the percentage of docetaxel's survival benefit over BSC retained by Alimta as:

$$\left[1-\frac{\log \text{ HR (Alimta over Docetaxel)}}{\log \text{ HR (BSC over Docetaxel)}}\right]\times 100$$

The details of the Rothmann method were not available until immediately before datalock. A 95% CI for this percent—benefit-retained was planned prospectively in the JMEI SAP prior to any unblinding. This is a means to interpret the primary analysis of Study JMEI because it is a translation of the 95% CI for the HR to another numerical scale. See Appendices 2 and 3 for more details regarding the translation of HR to percent retention.

Based on the TAX 317B results comparing 75 mg/m^2 docetaxel with BSC, 50% retention in Study JMEI corresponds to an HR margin of 1.21. Therefore, Alimta would be judged to have retained at least 50% of docetaxel's survival benefit over BSC provided that the 95% CI for the survival HR was entirely less than 1.21.

Figure 3.2 summarizes the two noninferiority criteria (the fixed margin accepted by the European Regulatory Authority and the percent-retention margin suggested by the FDA) in terms of HR and the CI values. To interpret the primary analysis, these two criteria were applied to the upper limit of the CI of the HR.

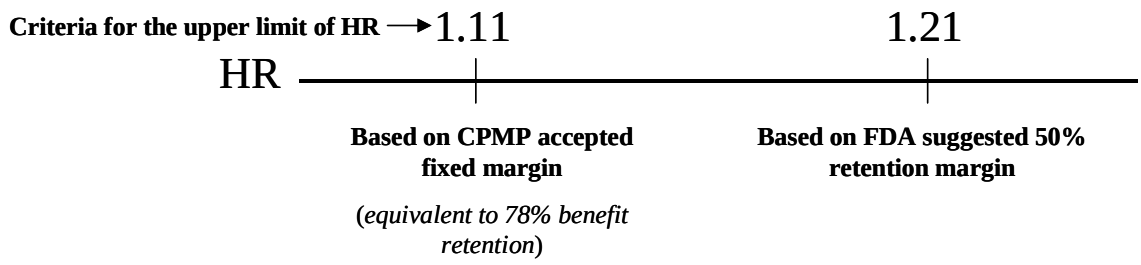


Figure 3.2. Noninferiority criteria in Study JMEI.

Note that the Rothmann analysis implies an indirect comparison of Alimta with BSC: Alimta has superior survival compared with BSC if Alimta retains ***any*** amount of docetaxel's survival benefit over BSC.

Appendix 2 contains a detailed explanation of the overall significance level of the survival analysis described in this section. Because all primary statistical conclusions would be based on the same 95% CI for the JMEI survival HR, there is no multiplicity of the false-positive error probability.

3.2. Results of Pivotal Study JMEI

3.2.1. Study Population

A total of 698 patients at 135 investigational sites in 23 countries were entered (signed the informed consent) in Study JMEI. Of these, 571 (81.8%) patients were randomly assigned (enrolled) to the Alimta arm or the docetaxel arm. Of the 127 patients who were not enrolled, 114 patients did not meet the inclusion criteria, and 13 were excluded for reasons not specified by the investigational sites.

Efficacy analyses were primarily based on the randomized, ITT population. The ITT population was defined as all patients randomly assigned to a treatment arm, whether or not they received study drug. The ITT population in this study consisted of 283 patients in the Alimta arm and 288 patients in the docetaxel arm. To test the robustness of the efficacy results, additional efficacy analyses were performed on the subgroup of patients who were randomized and treated with at least one cycle of therapy (RT). Of the 571 ITT patients, 541 were qualified for RT analyses (Alimta: 265; docetaxel: 276).

Table 3.1 shows the balance of baseline covariates between treatment arms. The two treatment arms were well balanced with respect to all demographic characteristics.

Table 3.1. Summary of Baseline Patient and Disease Characteristics ITT Population Study JMEI

Patient Characteristic	Alimta (N=283)	Docetaxel (N=288)
Median age, years (range)	59 (22-81)	57 (28-87)
	Percentage of Patients	
Sex		
Women	31.4	24.7
Men	68.6	75.3
ECOG PS 0 or 1	88.6	87.6
Stage IV disease	74.9	74.7
Homocysteine level <12 μm	71.4	68.9
Histology		
Adenocarcinoma	54.4	49.3
Squamous	27.6	32.3
Best response to prior chemotherapy		
CR/PR	35.6	36.5
Time since last chemotherapy		
<3 mo	50.4	48.1
>3 mo	49.6	51.9
Prior therapy		
Prior paclitaxel	25.8	27.8
Prior platinum	92.6	89.9

Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; N = number of ITT patients; PR = partial response; PS = performance status.

Adenocarcinoma was the predominant histological subtype, followed by squamous cell carcinoma. In both treatment arms, most patients had Stage IV disease and a good ECOG performance status (0 to 1).

Table 3.2 presents a summary of reported prior therapies; the two treatment arms were well balanced with respect to all prior therapy categories.

Table 3.2. Summary of Reported Prior Therapies ITT Population Study JMEI

Prior Therapy	Alimta (N=283) n (%)	Docetaxel (N=288) n (%)
Prior surgery	64 (22.6)	67 (23.3)
Prior radiotherapy	125 (44.2)	131 (45.5)
Prior immunotherapy	1 (0.4)	1 (0.3)
Prior chemotherapy	283 (100)	288 (100)
Adjuvant setting	21 (7.4)	18 (6.3)
Neoadjuvant setting	26 (9.2)	23 (8.0)
Locally advanced setting	101 (35.7)	111 (38.5)
Metastatic setting	147 (51.9)	148 (51.4)
One line of therapy	143 (50.5)	146 (50.7)
Two lines of therapy	4 (1.4)	2 (0.7)
Drug therapy needing classification	1 (0.4)	0

Abbreviations: ITT = intent to treat; n = number of patients who received the specified prior therapy; N = number of ITT patients.

3.2.2. Study Drug Exposure

Patients in the Alimta arm received 96.6% of the planned dose intensity, whereas patients in the docetaxel arm received 94.4% of the planned dose intensity. A median of four treatment cycles was delivered in both arms, with a range of 1 to 20 cycles in the Alimta arm and 1 to 14 cycles in the docetaxel arm. See Section 4.1.3 for further details on study-drug exposure for both arms.

3.2.3. Results of the Primary Survival Analysis

The primary analysis of Study JMEI was the calculation of the 95% CI for the overall survival HR of Alimta to docetaxel. The estimated HR was 0.99, with a 95% CI of 0.82 to 1.20. The K-M estimates for median survival were 8.3 months for Alimta and 7.9 months for docetaxel (Kaplan and Meier 1958). The 1-year survival rate on each arm was 29.7%.

Figure 3.3 displays the K-M (Kaplan and Meier 1958) survival time graphs for the ITT population. Graphs of survival distributions for Alimta and docetaxel arms were superimposable, overlapping several times.

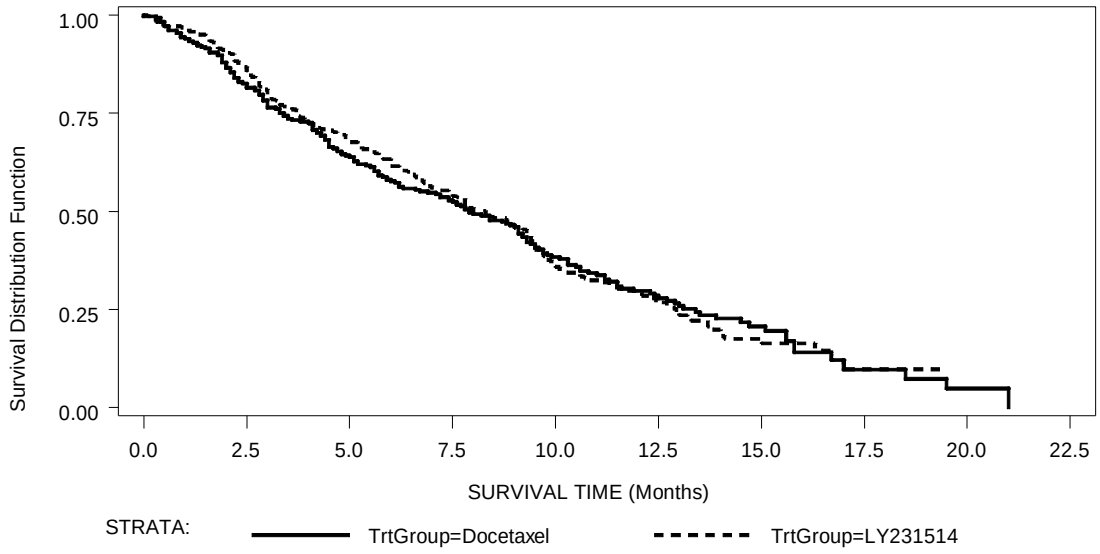


Figure 3.3. Kaplan-Meier distribution of overall survival time: ITT population of Study JMEI.

Abbreviations: ITT = intent to treat; TrtGroup = treatment group.

While tests for superiority and noninferiority (based on the 1.11 margin) were not statistically significant, Alimta preserved 102% (95% CI, 52% to 157%) of docetaxel's advantage over BSC. Using the lower limit of the CI of 52%, Alimta retained statistically significantly greater than 50% of docetaxel's survival benefit over BSC (p=0.047). When considering the primary JMEI survival results in the framework of the historical survival benefit of docetaxel treatment, formal statistical analyses demonstrated that Alimta provided a significant survival advantage over BSC (HR=0.55; 95% CI, 0.33 to 0.90; p=0.019). Valid use of the percent-retention analysis requires the assumption that the historical TAX 317B results are comparable with what would have been obtained if a BSC arm had been included in Study JMEI. While there are some minor differences between the TAX 317 and JMEI patient populations, there does not appear to be any overall prognostic advantage to either population. The survival and censoring distributions for the docetaxel arms from the two studies appear very comparable (Figure 3.4). The rest of this section discusses these points in detail.

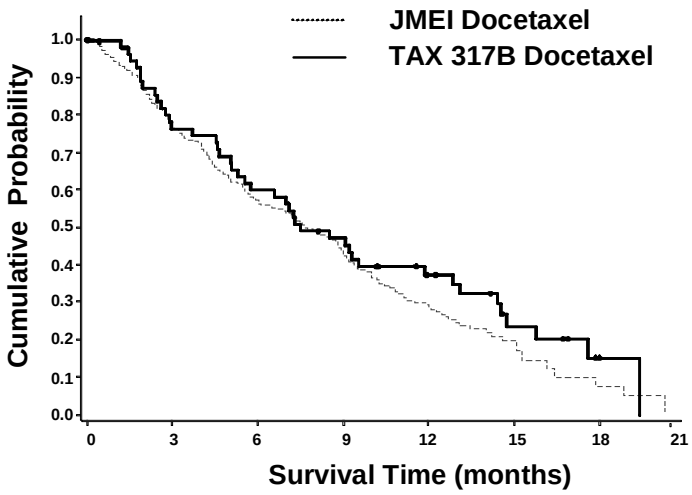


Figure 3.4. **Kaplan-Meier distributions of overall survival time, 75 mg/m^2 docetaxel: comparison of Study JMEI with TAX 317B.**

Table 3.3 compares the JMEI and TAX 317 study populations receiving docetaxel at 75 mg/m^2. Although several numerical differences can be observed, there are no large, clinically relevant discrepancies. Study JMEI had a greater percentage of patients with performance status of 0 or 1, as well as a slightly greater percentage of Stage III patients. These two factors suggest a possible prognostic advantage for Study JMEI. However, JMEI also had a smaller percentage of women and included patients with prior paclitaxel treatment and patients without prior platinum treatment, which suggests possible prognostic advantages for TAX 317. Thus, overall, prognostic differences appear to balance out. Further, the K-M survival results for the 75-mg/m^2 docetaxel arms of the two studies overlap, with a higher median survival (7.9 months) observed in Study JMEI compared with the median survival (7.5 months) reported in Study TAX 317 (Figure 3.4).

Table 3.3. Summary of Baseline Patient and Disease Characteristics Study JMEI Compared with TAX 317

Patient Characteristic	JMEI (N=571)	TAX 317 (N=204)
Median age, years (range)	58 (22-87)	61 (28-77)
	Percentage of Patients	
Sex		
Women	28.0	32.8
Men	72.0	67.2
ECOG PS		
0 or 1	88.1	75.5
2	11.9	24.5
Stage of disease		
III	25.2	21.1
IV	74.8	78.9
Best response to prior chemotherapy		
CR/PR	36.1	35.3
Other	63.9	64.7
Prior therapy		
Prior paclitaxel	26.8	0
Prior platinum	91.2	100
≥2 Prior chemotherapy regimens	6.0	25.0

Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; N = number of ITT patients; PR = partial response;.

Furthermore, recent data from Shepherd and colleagues (Shepherd et al. 2004, ASCO annual meeting) for erlotinib versus BSC confirm that the performance of BSC in NSCLC has not changed over time (median survival of the second- and third-line BSC patients, N=243, is 4.7 months).

Therefore, it is reasonable to assume that the historical results of docetaxel relative to BSC are comparable over time. This enables testing of the effectiveness of Alimta over BSC using the historical trial TAX 317B. Alimta resulted in significantly superior survival time compared with BSC (HR=0.55; 95% CI, 0.33 to 0.90; p=0.019, Figure 3.5).

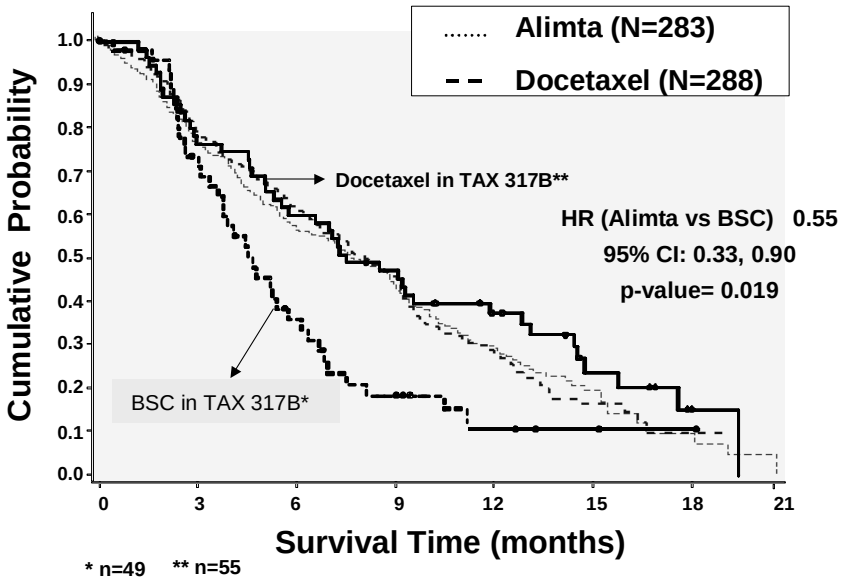


Figure 3.5. Kaplan-Meier distributions of overall survival time, Alimta versus BSC: comparison of Study JMEI with TAX 317B.

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; n = number of patients; N = number of intent-to-treat patients in Study JMEI.

Figure 3.6 summarizes the primary survival results for Alimta versus docetaxel. The 95% CI for the survival HR demonstrates that:

- Overall survival in the Alimta arm was 22% better than that in the docetaxel arm in the best-case scenario and 17% worse in the worst-case scenario.
- Protocol-defined tests for superiority and noninferiority (based on the 1.11 margin) were not statistically significant.
- Alimta retained 102% (95% CI, 52% to 157%) of the survival benefit of docetaxel over BSC. Alimta retained statistically significantly greater than 50% of docetaxel's survival benefit over BSC (p=0.047).
- Survival with Alimta is statistically significantly superior to BSC (HR=0.55; 95% CI, 0.33 to 0.90; p=0.019).

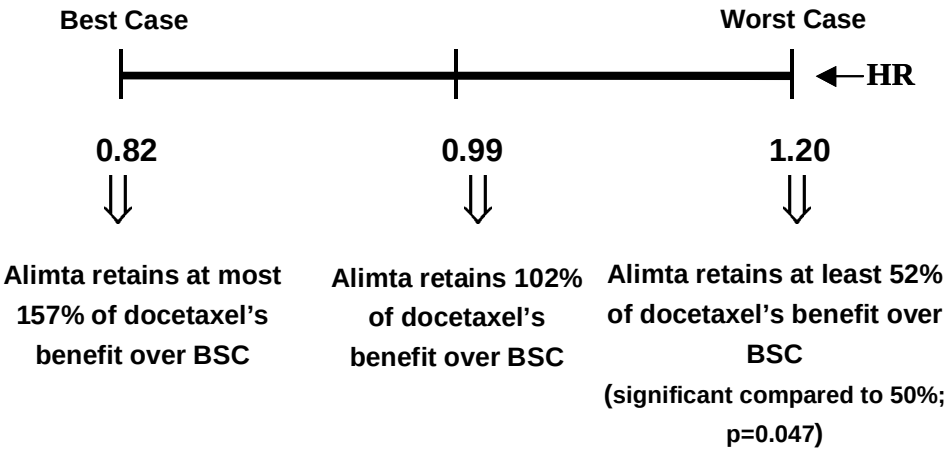


Figure 3.6. Summary of primary analysis of Alimta versus docetaxel.

Abbreviation: BSC = best supportive care.

Table 3.4 summarizes survival results. See Appendix 3 for details of the percent-retention analysis and the comparison of Alimta with BSC.

**Table 3.4. Summary of Survival Time (Months)
ITT Population
Study JMEI**

	ITT Population (N=571)	
	Alimta (n=283)	**Docetaxel (n=288)**
Median	8.3	7.9
95% CI for median	7.0-9.4	6.3–9.2
Percentage of patients surviving at least:		
6 months	61.5	57.6
12 months	29.7	29.7
Percentage censored	27.2	29.5
HR, Alimta to docetaxel	0.99	
95% CI for HR	0.82–1.20	
%-retention based on HR		
% efficacy retained by Alimta	102%	
95% CI of % benefit retained	52%-157%	
p-value for testing 50% retention	0.047	
HR, Alimta to BSC	0.55	
95% CI of HR, Alimta to BSC	0.33–0.90	
p-value for superiority to BSC	0.019	

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = number of patients in the treatment arm; N = number of patients in the population.

3.2.4. Cox Covariate-Adjusted Survival Analysis

Cox multiple regression analysis (Cox 1972) was used to identify factors, other than treatment intervention, that affected the overall survival time, and to estimate the treatment effect adjusting for these factors in the ITT population. This analysis was conducted with data from the 532 patients who had data for at least one of the factors in the model. Cox modeling was performed using the stepwise elimination method to reduce the number of factors included in the model. This method is not a source of bias with respect to the treatment effect because the elimination step is carried out before adding treatment to the model (Edwards 1999). Therefore, the resulting model provides the best estimate of comparative survival, adjusted for the variability due to the factors predictive of survival time.

The following seven baseline characteristics were assessed for the model using the stepwise procedure:

- prior platinum chemotherapy (Yes or No)
- disease stage (IIIA/IIIB or IV)
- ECOG performance status (2 or 0/1)

- prior paclitaxel (excluding docetaxel) chemotherapy (Yes or No)
- number of prior chemotherapies (1 or 2)
- time since last chemotherapy (≥3 or <3 months)
- best response to prior chemotherapy (complete response [CR]/partial response [PR] or stable disease [SD] or progressive disease [PD]/unknown).

After nonsignificant factors were eliminated, the final Cox model showed that the following three factors were predictive of longer survival time (Table 3.5):

- ECOG performance status of 0 or 1 compared with 2
- Stage IIIA or IIIB compared with IV
- ≥3 months since last chemotherapy compared with <3 months.

Table 3.5. Summary of Model Selection on Overall Survival Time ITT Population Study JMEI

Variable	p-Value	HR (95% CI)
ECOG performance status (0 or 1 over 2)	<0.001	0.25 (0.19-0.34)
Time since last chemotherapy (≥3 over <3 mo)	0.004	0.74 (0.60-0.90)
Stage (III over IV)	0.026	0.77 (0.60-0.97)
Treatment effect + Above 3 factors	0.051	0.93 (0.76-1.13)

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio (adjusted); ITT = intent to treat.

The final Cox model, with the treatment effect added to the three significant factors, showed an HR of 0.93 (95% CI, 0.76 to 1.13) with a borderline statistical significance for the 1.11 fixed-margin noninferiority test (p=0.051). Thus, the adjusted Cox model supports the interpretation of a very similar survival benefit for Alimta and docetaxel seen in unadjusted survival analysis. The HR of 0.93 corresponds to Alimta retaining 114% of docetaxel benefit over BSC, and the upper 95% CI of 1.13, corresponds to Alimta retaining at least 73% of the docetaxel survival benefit over BSC. The statistical test for 50% retention was statistically significant with p=0.016.

Figure 3.7 illustrates the summary of the Cox adjusted overall survival analysis.

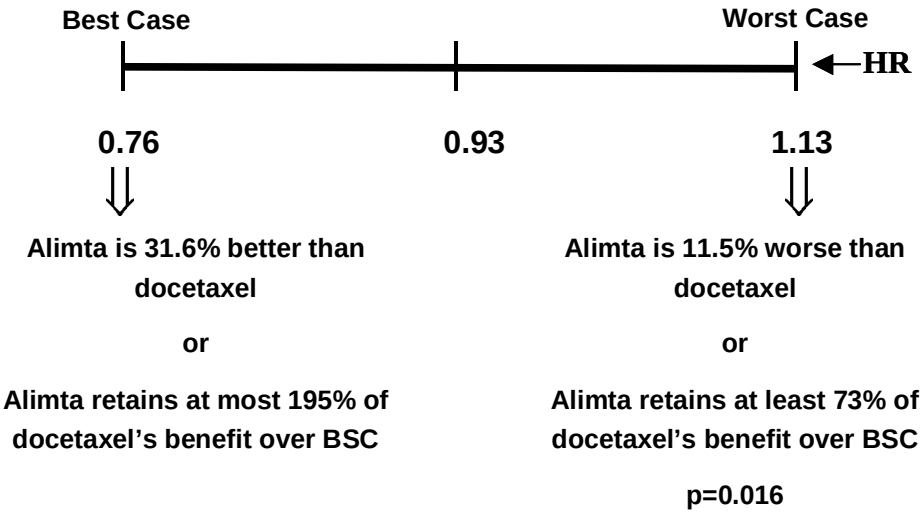


Figure 3.7. Summary of Cox adjusted survival analysis of Alimta versus docetaxel.

Abbreviation: BSC = best supportive care.

3.2.5. Other Supporting Survival Analyses

Table 3.6 summarizes survival results for the RT population. Survival summaries for the RT population were consistent with those for the ITT population.

A retrospective percent-retention analysis was also performed based on the 1-year survival rates. Using the TAX 317B results, and using the difference in 1-year survival rates as the measure of benefit, the estimate of the percentage of benefit (docetaxel over BSC) retained by Alimta was 100%. The lower bound of this 95% CI was 57%. Thus, this retrospective analysis of 1-year survival benefit is consistent with the primary analysis of overall survival.

Table 3.6. Summary of Survival Time (Months) Randomized and Treated Population Study JMEI

	Alimta (N=265)	Docetaxel (N=276)
Median	8.4	8.0
95% CI for median	7.4–9.4	6.7–9.2
Percentage of patients surviving at least:		
6 months	62.9	58.3
12 months	30.6	29.8
Percentage censored	27.6	28.3
HR, Alimta to docetaxel	0.97	
95% CI for HR	0.80–1.18	
%-retention based on HR		
% efficacy retained by Alimta	105%	
95% CI of % benefit retained	58%-168%	
p-value for testing 50% retention	0.036	
HR, Alimta to BSC	0.54	
95% CI of HR, Alimta to BSC	0.33–0.89	
p-value for superiority to BSC	0.015	

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; N = number of randomized and treated patients in the treatment arm; N = number of patients in the population.

3.2.6. Poststudy Anticancer Therapy

Table 3.7 presents a summary of the RT patients who received poststudy anticancer therapy. In the RT population, 156 (58.9%) patients on the Alimta arm and 148 (53.6%) patients on the docetaxel arm received at least one poststudy anticancer treatment. Docetaxel was the most frequent poststudy anticancer therapy for patients on the Alimta arm, and gemcitabine was most frequent for patients on the docetaxel arm. It is not surprising that docetaxel was the most commonly prescribed poststudy treatment because docetaxel is approved in patients who have received a prior chemotherapy regimen.

Table 3.7. Summary of Poststudy Anticancer Therapy Randomized and Treated Population Study JMEI

	Number (%) of Patients	
Poststudy Therapy	**Alimta (N=265)**	**Docetaxel (N=276)**
All poststudy anticancer therapy[1]	156 (58.9)	148 (53.6)
Surgery, radiation, or other treatment	56 (21.1)	69 (25)
Poststudy chemotherapy[1]	126 (47.5)	107 (38.8)
Platinum		
Carboplatin	5 (1.9)	7 (2.5)
Cisplatin	4 (1.5)	8 (2.9)
Docetaxel	85 (32.1)	11 (4.0)
Paclitaxel	4 (1.5)	3 (1.1)
Vinorelbine	6 (2.3)	25 (9.1)
Gemcitabine	17 (6.4)	32 (11.6)
Gefitinib	5 (1.9)	21 (7.6)
Etoposide	2 (0.8)	5 (1.8)
Mitomycin	1 (0.4)	5 (1.8)
Other chemotherapy	19 (7.2)	24 (8.7)

Abbreviation: N = number of randomized and treated patients.

[1] Patients may have received more than one form of therapy.

Post hoc analyses were performed examining the relationship between poststudy therapy and patient survival. These analyses should be considered exploratory, since a benefit from poststudy therapy cannot be determined conclusively from these outcome-based, nonrandomized comparisons.

Kaplan-Meier survival estimates were obtained for subgroups of patients who (1) did not receive poststudy chemotherapy, (2) received poststudy docetaxel chemotherapy, and (3) received other poststudy chemotherapy (Table 3.8). The results showed that patients who received poststudy chemotherapy, regardless of whether it was with docetaxel or other chemotherapy agents, had a longer survival than those who did not. Furthermore, survival for patients receiving poststudy docetaxel chemotherapy was similar to those receiving other agents. The median survival of patients in the Alimta arm who received poststudy docetaxel was actually 1 month lower than the median survival of those who received other poststudy chemotherapy (9.6 months versus 10.6 months).

Table 3.8. Overall Survival of Patients Who Received Poststudy Chemotherapy
Randomized and Treated Population
Study JMEI

	Alimta (N=265)		Docetaxel (N=276)	
Poststudy Chemotherapy	**n (%)**	**MS (mo)**	**n (%)**	**MS (mo)**
No poststudy chemotherapy	139 (52.4)	6.2	169 (61.2)	5.0
Poststudy chemotherapy	126 (47.5)	9.8	107 (38.8)	10.8
Docetaxel-containing [1]	85 (32.1)	9.6	11 (4.0)	10.1
Regimens without docetaxel	41 (15.5)	10.6	96 (34.8)	11.2

Abbreviations: ITT = intention to treat; MS = median survival; n = number of patients in the subgroup; N = number of randomized and treated patients.

[1] Patients may have received other drugs in addition to docetaxel.

An additional post hoc analysis (Table 3.9) of overall survival was performed by censoring patients at their poststudy chemotherapy date. While this analysis may violate statistical assumptions of random censoring, it is an attempt to consider patient survival independent of the confounding factor of poststudy chemotherapy. Although exploratory, the comparative results between Alimta and docetaxel are consistent with the primary analysis of survival discussed in Section 3.2.3.

Table 3.9. Summary of Survival Time (Months) Censored at Poststudy Chemotherapy Date
ITT Population
Study JMEI

	ITT Population (N=571)	
	Alimta (n=283)	**Docetaxel (n=288)**
Median survival (mo)	9.3	9.1
95% CI for median	7.8-9.8	7.1–9.8
Percentage of patients surviving at least:		
6 months	65.2	59.7
12 months	36.2	31.0
Percentage censored	59.7	52.4
HR, Alimta to docetaxel	0.86	
95% CI for HR	0.67–1.11	

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = number of patients in the treatment arm; N = number of patients in the population.

In conclusion, there is no evidence that poststudy chemotherapy has biased the results of Study JMEI in any way.

3.2.7. Secondary Efficacy Analyses

3.2.7.1. Progression-Free Survival Time

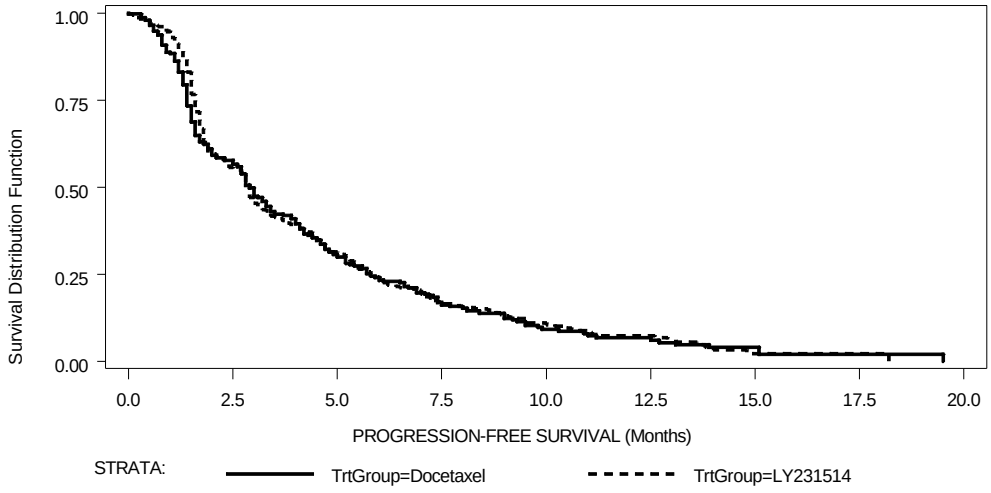
Table 3.10 presents a summary of progression-free survival time for the ITT population and RT population of Study JMEI. Progression-free survival time was defined as the time from randomization to the first observation of PD or death due to any cause. In the ITT population, progression-free survival time for patients on the Alimta arm was analogous to that of patients on the docetaxel arm (median, 2.9 versus 2.9 months); the HR was 0.97, with a 95% HR CI of 0.82 to 1.16. Progression-free survival time results for the RT population were similar to those for the ITT population.

Figure 3.8 displays the K-M curves for progression-free survival time for the ITT population. The progression-free survival time curves were similar for the two treatment arms. Results for the RT population were consistent with the ITT population.

Table 3.10. Summary of Progression-Free Survival Time (Months) ITT Population and RT Population Study JMEI

	ITT Patients (N=571)		RT Patients (N=541)	
	Alimta (n=283)	Docetaxel (n=288)	Alimta (n=265)	Docetaxel (n=276)
Minimum	0	0	0.3	0.3
25th percentile	1.6	1.4	1.6	1.4
Median	2.9	2.9	2.9	3.0
75th percentile	5.8	5.8	5.6	5.8
Maximum	18.2	19.5	18.2	19.5
Percentage of patients with progression-free survival of at least:				
3 months	45.3	47.3	45.3	47.8
6 months	23.2	23.3	22.3	23.3
9 months	13.0	12.3	12.0	12.1
Percentage of patients censored	6.4	10.4	5.7	8.3
Hazard ratio	0.97		0.98	
95% CI for hazard ratio	(0.82-1.16)		(0.82-1.17)	
Wald p-value	0.759		0.821	

Abbreviations: CI = confidence interval; ITT = intent to treat; n = number of patients in the treatment arm; N = number of patients in the population; RT = randomized and treated.



Program name: km_tte.SAS. Population: itt Parameter: timepdps

Figure 3.8. Kaplan-Meier distribution of progression-free survival: ITT population of Study JMEI.

Abbreviations: ITT = intent to treat; TrtGroup = treatment group.

3.2.7.2. Time to Progressive Disease

Table 3.11 presents a summary of TTPD for the ITT population and RT population. Time to progressive disease was defined as the time from randomization to the first date of documented disease progression.

In the ITT population, the TTPD for patients on the Alimta arm was similar to that for patients on the docetaxel arm (median, 3.4 versus 3.5 months). The HR was 0.97, with a 95% HR CI of 0.80 to 1.17.

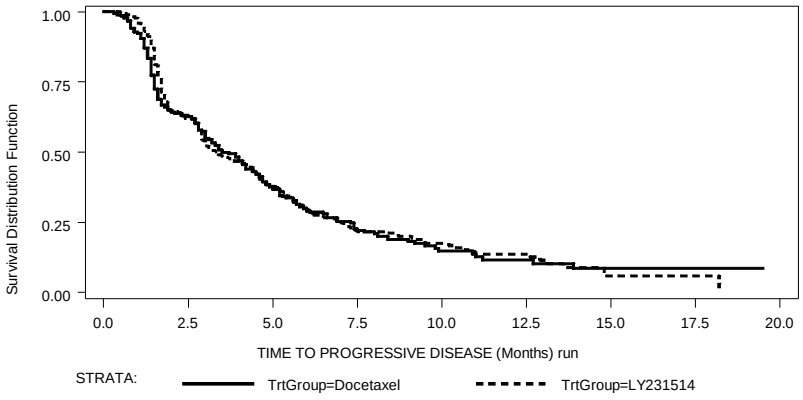
Results for the RT population were similar to those for the ITT population.

Figure 3.9 displays the K-M curves for TTPD for the ITT population. The TTPD curves were identical for the two treatment arms. Results for the RT population were consistent with those for the ITT population.

Table 3.11. Summary of Time to Progressive Disease (Months) ITT Population and RT Population Study JMEI

	ITT Patients (N=571)		RT Patients (N=541)	
	Alimta (n=283)	Docetaxel (n=288)	Alimta (n=265)	Docetaxel (n=276)
Minimum	0.5	0.3	0.5	0.3
25th percentile	1.7	1.5	1.7	1.5
Median	3.4	3.5	3.1	3.5
75th percentile	7.0	7.3	6.4	6.9
Maximum	18.2	19.5	18.2	19.5
Percentage of patients without progressive disease at:				
3 months	52.2	55.0	50.6	54.5
6 months	29.4	29.1	27.3	28.6
9 months	20.1	18.2	17.8	17.7
Percentage of patients censored	24.7	27.8	20.0	24.6
Hazard ratio	0.97		1.01	
95% CI for hazard ratio	(0.80-1.17)		(0.83-1.22)	
Wald p-value	0.721		0.951	

Abbreviations: CI = confidence interval; ITT = intent to treat; n = number of patients in the treatment arm; N = number of patients in the population; RT = randomized and treated.



Program name: KM_TTPD.SAS. Population: itt Parameter: timepdps

Figure 3.9. Kaplan-Meier distribution of time to progressive disease: ITT population of Study JMEI.

Abbreviations: ITT = intent to treat; TrtGroup = treatment group.

3.2.7.3. Tumor Response Rate

A total of 264 patients in the Alimta arm and 274 patients in the docetaxel arm were qualified for protocol-defined tumor response (QR) analyses. Tumor response was evaluated by applying a modified standard Southwest Oncology Group (SWOG) criteria (Green and Weiss 1992). In the QR population, the number of patients with a best

response of CR, PR, partial response in nonmeasurable disease (PRNM), or SD was similar between the treatment arms (Alimta: 9.1%; docetaxel: 8.8%; Table 3.12).

Table 3.12. Summary of Tumor Response QR Population Study JMEI

	Alimta (N=264)	Docetaxel (N=274)	p-Value
Response (%) (CR+PR+PRNM)	24 (9.1)	24 (8.8)	>0.999
95% CI for response rate	(5.9-13.2)	(5.7-12.8)	-
CR (%)	1 (0.4)	0	-
PR (%)	20 (7.6)	24 (8.8)	-
PRNM (%)	3 (1.1)	0	-
SD (%)	121 (45.8)	127 (46.4)	0.931

Abbreviations: CI = confidence interval; CR = complete response; N = number of patients in the treatment arm; PR = partial response; PRNM = partial response in nonmeasurable disease; QR = qualified for response analysis; SD = stable disease.

3.2.7.4. Lung Cancer Symptom Scale

3.2.7.4.1. Patient Scale

The patient Lung Cancer Symptom Scale (LCSS) consists of nine 100-mm visual analogue scales. Scores are reported from 0 to 100, with zero representing the best score. The average symptom burden index is calculated from the average of the six symptom items (anorexia, fatigue, cough, dyspnea, hemoptysis, and pain). A total score is determined from the average of the values from the nine LCSS visual analogue scales. Compliance was 89.0% for the Alimta arm and 85.1% for the docetaxel arm.

When data were analyzed at the group level, no differences were identified between the treatment arms in any of the patient scales (Table 3.13). Patients on both arms reported initial increases in anorexia, fatigue, dyspnea, and pain, which subsequently stabilized. Scores for cough and hemoptysis were relatively unchanged. Both treatment arms reported initial increases in average symptom burden index, symptom distress, and interference with activity level, which subsequently stabilized. Both arms reported initial deterioration in global quality of life (QoL) and total LCSS scores, which subsequently stabilized. When data were analyzed at the patient level, there was no difference in the rates of patients with improved or stable symptoms, as measured by the average symptom burden index (Table 3.13).

In the second-line setting, the TAX 317 trial comparing docetaxel with BSC demonstrated symptom palliation with docetaxel (Dancey et al. 2004). A retrospective analysis of JMEI LCSS scores was performed to assess the relationship between response (CR, PR, and SD) and symptom improvement (De Marinis et al. 2004). In this analysis, responding patients had a significant improvement in symptom scores, regardless of treatment arm, compared with nonresponders. Of note, >50% of assessable patients (n=484) had some degree of symptom improvement, with greater improvement for CR and PR patients compared with SD patients.

3.2.7.4.2. Observer Scale

The LCSS observer scale (a five-point categorical scale) is completed by study site personnel. Scores are reported on a scale from 0 to 100, with 100 representing the best possible score. The observers in Study JMEI rated six individual symptoms: anorexia, fatigue, cough, dyspnea, hemoptysis, and pain. A total score is calculated from the average of the six LCSS values.

Data from 239 patients (84.5%) in the Alimta arm and 232 (80.5%) in the docetaxel arm were included in the observer scale analysis. Patients were included in the analysis only if they had data for the baseline period and from at least one cycle. Baseline symptom and total scores were well balanced between the treatment arms.

Table 3.13 presents a summary of the changes in observer total LCSS scores by treatment arm. No differences were observed in the distribution of changes in observer scale scores between the treatment arms. Scores for most patients remained stable.

Table 3.13. Summary of LCSS Analyses Study JMEI

	Number (%) of Patients		
Average Symptom Burden Index	**Alimta (N=283)**	**Docetaxel (N=288)**	**p-Value[1]**
Patient Scale			
Number of responding patients	227	247	
Improved/Stable	115 (50.7)	114 (46.2)	0.327
Worsened/Unknown	112 (49.3)	133 (53.9)	-
Observer Scale			
Number of patients assessed	239	232	
Improved/Stable	108 (45.2)	113 (48.7)	0.444
Worsened/Unknown	131 (54.8)	119 (51.3)	-

Abbreviations: LCSS = Lung Cancer Symptom Scale; N = number of patients in the treatment arm.

1 Chi-square p-value.

3.2.8. Sensitivity Analysis of Efficacy

To evaluate the robustness of the effectiveness of Alimta in NSCLC, alternative analyses were performed. This included examination of different endpoints, various subgroups, and additional historical data.

3.2.8.1. Alimta versus Historical BSC

In addition to considering the comparability of the JMEI and TAX 317B trials for overall survival, the robustness of the superiority result for Alimta over BSC was examined by considering the entire TAX 317 trial (both A and B parts of the study, representing the pre- and postamendment cohorts) and the secondary endpoint of TTPD. Figure 3.10 shows the HR and the 95% confidence limits for the HR for Alimta over BSC in all these different analyses. The results show that Alimta is superior to BSC consistently and this superiority is not sensitive to the choice of endpoints, method of analysis, or choice of historical data.

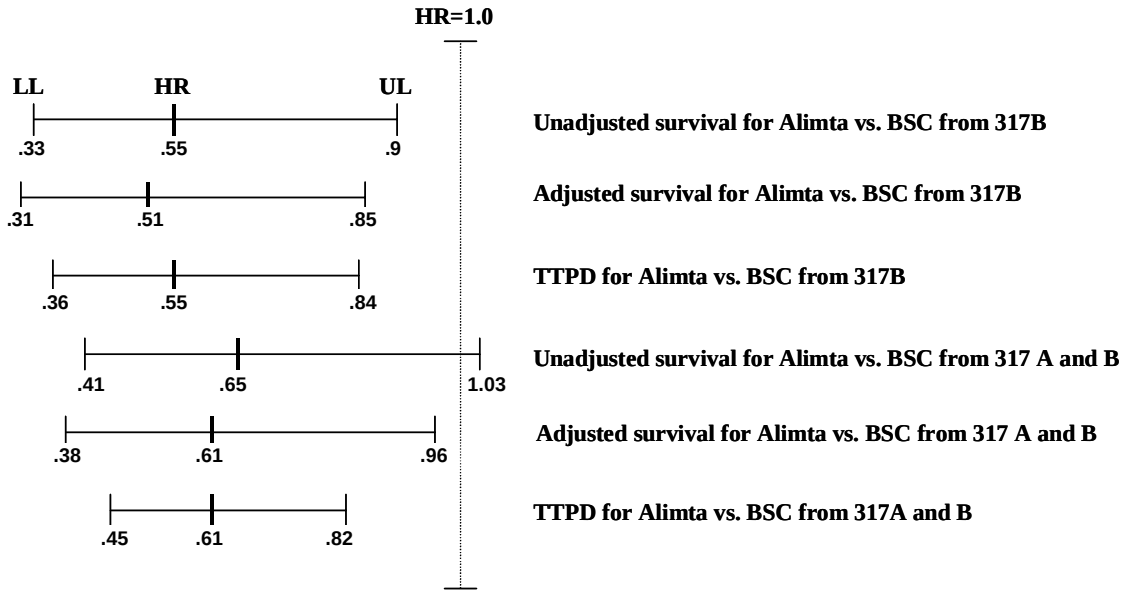


Figure 3.10. Six analyses comparing Alimta with historical BSC (TAX 317).

Abbreviations: BSC = best supportive care; HR = hazard ratio; LL = lower limit; TTPD = time to progressive disease; UL = upper limit; vs = versus.

3.2.8.2. Alimta versus Docetaxel

Table 3.14 illustrates the overall survival for the key subgroups related to three prognostic factors (stage, performance status and time since last chemotherapy). Prior therapy status was also considered in this subgroup analysis because it is an important clinical factor in this setting. The results show that Alimta is similar to docetaxel consistently and not sensitive to the choice of subgroups or choice of data.

Table 3.14. Survival in Key Subgroups
ITT Population
Study JMEI

	# of Pts	HR
Prior Platinum	**521**	**1.03**
No Prior Platinum	**50**	**0. 74**
No Prior Taxane	**418**	**1.03**
Prior Taxane	**153**	**0.97**
Performance Status 0 or 1	**474**	**1.00**
Performance Status 2	**64**	**0.75**
Stage III	**144**	**1.01**
Stage IV	**427**	**0.99**
< 3 mo since last chemo	**277**	**1.06**
≥ 3 mo since last chemo	**286**	**0.92**

Abbreviations: chemo = chemotherapy; HR = hazard ratio; ITT = intent to treat; Pts = patients.

3.2.9. Overall Efficacy for Study JMEI

Study JMEI was a large (N=571) randomized, Phase 3, multicenter trial comparing the efficacy of Alimta and docetaxel in patients with locally advanced or metastatic NSCLC who had been previously treated with chemotherapy. Overall, the baseline patient and disease characteristics and prognostic factors were well balanced between the treatment arms. The majority of patients had Stage IV disease and good ECOG performance status (0 or 1). Approximately 90% of the patients had received prior platinum-containing regimens.

- In this trial, the performance of docetaxel was at least as good as any previously reported Phase 3 trial in this patient population. Survival time was similar between the two treatment arms for all randomized patients with respect to median survival (Alimta: 8.3 months; docetaxel: 7.9 months; HR=0.99; 95% CI, 0.82 to 1.20). Overall survival in the Alimta arm was 22% better than that in the docetaxel arm in the best-case scenario and 17% worse in the worst-case scenario.
- Alimta provides statistically significantly superior survival to BSC (HR=0.55; 95% CI, 0.33 to 0.90; p=0.019). From the same analysis, Alimta retained 102% of docetaxel's survival benefit over BSC, with a 95% CI of 52% to 157%, p=0.047).

- The Cox multiple regression analysis confirmed that increased survival was associated with good performance status, locally advanced disease, and longer time since last chemotherapy. This model showed a somewhat stronger result for Alimta in overall survival after adjusting for the three significant prognostic factors (HR=0.93; 95% CI, 0.76 to 1.13). Overall adjusted survival in the Alimta arm was 32% better than that in the docetaxel arm in the best-case scenario and 12% worse in the worst-case scenario.
- Adjusted results show that Alimta provides statistically significantly superior survival to BSC (HR=0.51; 95% CI, 0.31 to 0.85; p=0.009). Alimta retained 114% of docetaxel's survival benefit over BSC, with a 95% CI of 73% to 195%, p=0.016.
- The results of other time-to-event endpoints were similar between the treatment arms. Progression-free survival was superimposable between the treatment arms (2.9 months; HR=0.97; 95% CI, 0.82 to 1.16). Time to progressive disease was also overlapping between the treatment arms (Alimta: 3.4 months; docetaxel: 3.5 months; HR=0.97; 95% CI, 0.80 to 1.17).
- For patients who were qualified for tumor response analysis (N=538), the response rates were similar between the treatment arms (Alimta: 9.1%; docetaxel: 8.8%).
- Sensitivity analysis shows that Alimta is superior to historical BSC irrespective of choice of endpoints or historical data.
- Quality of life was assessed with the LCSS, an instrument that focuses on disease-related symptoms and, therefore, is considered another measure of efficacy. Analyses of patient scale data on both the individual patient and aggregate levels showed no difference between the treatment arms. Over 50% of assessable patients in both arms achieved an improvement in maximum symptom scores. Analysis of the observer scale data also did not show any difference between the treatment arms.

The overall efficacy conclusions of the pivotal trial, JMEI, are as follows:

- Docetaxel performs as well as reported in the literature.
- Alimta and docetaxel show equivalent benefits for pretreated patients with NSCLC, as seen consistently in all efficacy parameters and major subgroups:
    - overall survival
    - adjusted survival
    - progression-free survival
    - time to progressive disease

  - response rate
  - Lung Cancer Symptom Scale scores
  - major subgroups.

- When considering the survival results of Study JMEI in the context of the historical survival benefit of docetaxel treatment, formal multiple sensitivity analyses robustly demonstrate that Alimta provides a survival advantage over BSC in:
  - unadjusted survival from TAX 317B
  - adjusted survival from TAX 317B
  - TTPD from TAX 317B
  - unadjusted survival from TAX 317A and TAX 317B
  - adjusted survival from TAX 317A and TAX 317B
  - TTPD from TAX 317A and TAX 317B.

3.3. Studies Supporting Efficacy

Table 1.6 lists the Phase 2 clinical studies in NSCLC that provided the supporting efficacy evidence for this submission.

3.3.1. Efficacy Results from Single-Agent Studies (Phase 2)

The activity of Alimta in the treatment of NSCLC was demonstrated in three Phase 2 studies in which Alimta was administered as a single-agent to patients who had received prior chemotherapy (Study JMBR) or to chemotherapy naive patients (Studies JMAL and JMAN). All three of these studies were carried out prior to the implementation of programmatic vitamin supplementation. The results from these studies showed that Alimta is as active as any other cytotoxic agent currently available for the treatment of NSCLC.

In Study JMBR, Alimta was administered at 500 mg/m^2 every 3 weeks in patients with NSCLC whose disease was refractory to prior chemotherapy (Table 3.15; Smit et al. 2003 [Appendix 6]).

Of the 79 evaluable patients, 44 (55.7%) patients had received prior platinum and 52 (65.8%) patients had stopped prior chemotherapy within 1 month prior to study start. A total of 65 (82.3%) patients had Stage IV disease. The overall median survival time and the tumor response rate in this study were 5.7 months and 8.9%, respectively. The 1-year survival rate was 23%.

Table 3.15. Summary of Efficacy Study H3E-MC-JMBR

	All Patients	Prior Platinum	No Prior Platinum
Evaluable patients	79	44	35
CR (%)	1 (1.3)	0	1 (2.9)
PR (%)	6 (7.6)	2 (4.5)	4 (11.4)
SD (%)	25 (32)	16 (36)	9 (26)
PD (%)	30 (38)	18 (41)	12 (34)
N/A (%)	17 (22)	8 (18)	9 (26)
Median survival (mo)	5.7	6.4	4.0
Median progression-free interval (mo)	2.0	2.3	1.6
Median duration of response (mo)	2.0	1.6	6.8

Abbreviations: CR = complete response; N/A = unknown or not assessed; PR = partial response; SD = stable disease; PD = progressive disease.

Reference: Smit et al. 2003. A copy of this reference is provided in Appendix 6.

In Study JMAL (Table 3.16) (Clarke et al. 2002 [Appendix 6]), Alimta was administered at 600 mg/m^2 every 3 weeks to chemotherapy-naive NSCLC patients. Fifty-seven patients were evaluable for tumor response rate. The median age of all evaluable patients was 59 years. Almost a third of patients (27.5%) had poor performance status (2 on the World Health Organization scale). Sixteen percent of patients had a tumor response. The median TTPD was 4.4 months, and the median survival time was 7.2 months.

In Study JMAN (Table 3.16) (Rusthoven et al. 1999 [Appendix 6]), Alimta was administered at 500 mg/m^2 every 3 weeks to chemotherapy-naive NSCLC patients. Thirty patients were evaluable for tumor response. The median age of all evaluable patients was 63 years. All but 1 patient had an ECOG performance status of 0 to 1. A good tumor response rate (23.3%) was observed in this study; median TTPD was 3.8 months, and median survival time was 9.2 months.

Table 3.16. Single-Agent Alimta as First-Line Therapy Studies H3E-MC-JMAL and H3E-MC-JMAN

	JMAL Clarke et al. 2002[a]	JMAN Rusthoven et al. 1999[a]
Dose (mg/m^2)	600	500
Evaluable patients	57	30
Stage III/IV (n)	18/39	5/25
Overall response rate	16%	23%
PR (n)	9	7
Performance status = 2	32%	3%
Median TTPD (mo)	4.4	3.8
Median survival (mo)	7.2	9.2
Median duration of response (mo)	4.9	3.1

Abbreviations: n = number of patients; PR =partial response; TTPD = time to progressive disease.

[a] A copy of this publication is provided in Appendix 6.

3.3.2. Efficacy Results from Phase 2 Combination Therapy Studies

Three other Phase 2 studies, JMAY (Table 3.17; Manegold et al. 2000 [Appendix 6]), JMBZ (Table 3.17; Shepherd et al. 2001 [Appendix 6]), and JMEK (Table 3.18), examined the efficacy of Alimta in combination with platinum in the first-line treatment of patients with NSCLC. Studies JMAY and JMBZ were completed before the implementation of programmatic vitamin supplementation. Patients in Study JMEK received vitamin supplementation. The results presented below show that the combination regimen of Alimta and a platinum has efficacy comparable to other platinum doublets such as gemcitabine plus cisplatin, paclitaxel plus cisplatin, or docetaxel plus cisplatin.

In Studies JMAY and JMBZ, Alimta 500 mg/m^2 plus cisplatin 75 mg/m^2 was administered every 3 weeks. The overall response rates for evaluable patients were 38.9% and 44.8%, respectively. Median survival times were 10.9 and 8.9 months, respectively.

Table 3.17. Alimta Plus Cisplatin as First-Line Therapy Studies H3E-MC-JMAY and H3E-MC-JMBZ

	JMAY Manegold et al. 2000[a]	JMBZ Shepherd et al. 2001[a]
Dose (mg/m^2)	Alimta: 500 Cisplatin: 75	Alimta: 500 Cisplatin: 75
Evaluable patients[1] (n)	36	29
Stage III/IV (n)	18/18	5/26
Overall response rate	38.9%	44.8%
PR (n)	14	13
Performance status = 2	3%	16%
Median TTPD (mo)	6.3	N/R
Median survival (mo)	10.9	8.9
Median duration of response (mo)	10.4	6.1

Abbreviations: n = number of patients; N/R = not reported; PR = partial response; TTPD = time to progressive disease.

[a] A copy of this publication is provided in Appendix 6.

[1] Evaluable for response.

In the randomized Phase 2 Study JMEK (Table 3.18), patients were randomized to Alimta plus carboplatin or Alimta plus oxaliplatin. Patients in this study received folic acid and vitamin B_{12} supplementation. The overall response rate in the Alimta plus carboplatin arm was 31.6% and in the Alimta plus oxaliplatin arm was 26.8%. The corresponding median survival times were 9.9 months and 9.3 months, respectively.

Table 3.18. Alimta Plus Carboplatin or Alimta Plus Oxaliplatin First-Line NSCLC Study H3E-MC-JMEK

Regimen (mg/m^2)	N	ORR (%) (CR+PR)	MDR (mo)	MS (mo)
Alimta 500 + Carboplatin AUC 6	38	32	6.7	9.9
Alimta 500 + Oxaliplatin 120	41	27	4.4	9.3

Abbreviations: AUC = area under the curve; CR = complete response; MDR = median duration of response; MS = median survival; N = number of evaluable patients; ORR = overall response rate; PR = partial response.

Reference: Scagliotti et al. 2003 (Appendix 6); Zinner et al. 2003.

The results of a Phase 2 study of Alimta plus carboplatin in previously untreated advanced NSCLC was recently reported at ASCO (data from this study are not part of the current sNDA). Fifty patients were treated with Alimta 500 mg/m^2 and carboplatin 6 AUC along with vitamin supplementation. The response rate was 28%, median TTPD was 4.9 months, and the estimated median and 1-year survival were 13.5 months and 55.3%, respectively (Koshy et al. 2004).

3.4. Efficacy Conclusions for Alimta in NSCLC

I. Alimta demonstrates efficacy in NSCLC

In a large, worldwide, randomized Phase 3 study of second-line NSCLC (JMEI), the survival of Alimta was similar to that of docetaxel (HR=0.99; 95% CI, 0.82 to 1.20). In addition, Alimta showed similar results compared with docetaxel for the following:

- progression-free-survival, (HR=0.97; 95% CI, 0.82 to 1.16)
- time to progressive disease (HR=0.97; 95% CI, 0.80 to 1.17)
- response rate (9.1% versus 8.8%) and stable disease rate (45.8% versus 46.4%)
- patient-reported outcomes (LCSS)

Additionally, in Phase 2 studies, Alimta achieved comparable activity in first-line NSCLC as a single agent (response rates of 16% and 23%) and in combination with platinum compounds (response rates from 27% to 44.8%).

II. Alimta preserves 102% of docetaxel's advantage over best supportive care in second-line NSCLC

Percent–benefit-retention analysis revealed that Alimta retained 102% (95% CI, 52% to 157%) of docetaxel's relative gain over BSC in the only historical trial including BSC.

III. Alimta is better than historical best supportive care in second-line NSCLC

The percent–benefit-retention methodology implies that the overall survival in the Alimta arm was statistically significantly superior to that of historical BSC (HR=0.55; 95% CI, 0.33 to 0.90 p=0.019).

IV. Efficacy of Alimta is consistently similar to docetaxel across all key subgroups

Efficacy of Alimta was consistent and similar to that of docetaxel across all patient subgroups in Study JMEI, including the three significant prognostic factors of performance status, time since last chemotherapy, and disease stage. In addition, Cox adjusted-survival analysis showed that Alimta retained 114% (95% CI, 73% to 195%) of docetaxel's benefit over BSC.

4. Safety

The major clinical safety claims for Alimta in NSCLC are summarized below:

Results from Study JMEI:

- fewer deaths
- significantly less neutropenia and febrile neutropenia
- significantly less neutropenia with infection
- significantly less alopecia and diarrhea
- significantly less neurosensory toxicity, myalgia, and arthralgia
- significantly fewer drug-related serious adverse events (SAEs)
- significantly fewer hospitalizations due to adverse events.

Results from integrated safety data:

- Three (0.6%) patients died from study drug-related causes (cardiac arrest, hepatic failure, and pneumonia/sepsis; previously reported in Study JMEI).
- Nine (1.7%) patients experienced serious and unexpected adverse events thought to be related to study therapy.
- Twenty-six (5%) patients discontinued therapy because of adverse events. Events relating to renal dysfunction remain the most common adverse events leading to discontinuation.
- Grade 3 and 4 transaminase elevations occurred in fewer than 10% of patients. Neutropenia rarely resulted in clinical sequelae; the rate of febrile neutropenia was only 1.9%.
- Fatigue was the most common Grade 3 or 4 toxicity, occurring in 4.7% of patients.
- Subgroup analyses of clinically relevant treatment-emergent adverse events (TEAEs) showed that decreased creatinine clearance and anemia were reported more commonly in older patients. Anorexia, decreased hemoglobin, and rash occurred significantly more frequently in men; vomiting and diarrhea occurred more often in women. Analyses of clinically relevant CTC Grade 3 and 4 toxicities showed no significant differences between either age or sex subgroups.

4.1. Safety Results from Study JMEI

4.1.1. Study Objectives, Design, and Treatment

The safety objective of Study JMEI was to characterize the qualitative and quantitative toxicities of Alimta 500 mg/m^2 compared with docetaxel 75 mg/m^2 administered once every 21 days. Patients in the Alimta arm received prophylactic dexamethasone and supplementation with folic acid and vitamin B_{12}. Patients in the docetaxel arm received dexamethasone per the docetaxel label (twice the dosage compared with the Alimta arm). Dose adjustments and dose delays were allowed based on laboratory and nonlaboratory toxicities.

4.1.2. Demographic and Other Characteristics

All patients who received at least one dose of Alimta or docetaxel were evaluated for safety (RT population; N=541) in Study JMEI.

Demographic and other patient characteristics are presented in Section 3.2.1.

4.1.3. Overall Extent of Exposure

Analysis of dose and duration included all patients who received at least one dose of study medication.

Key exposure data from Phase 3 Study JMEI are as follows:

- A total of 1164 doses (cycles) were administered to patients in the Alimta arm, and 1085 doses (cycles) were administered to patients in the docetaxel arm.
- A median of four cycles of therapy was administered to patients on both treatment arms.
- Dose reductions were significantly less frequent in patients treated with Alimta: 14 doses (1.2% of doses administered) in the Alimta arm compared with 61 doses (5.6% of doses administered) in the docetaxel arm ($p<0.001$). Of the 61 doses reduced in the docetaxel arm, 34 (3.1% of all doses) were reduced because of febrile neutropenia or neutropenia. In the Alimta arm, only one dose (0.1% of all doses) was reduced because of neutropenia, and none were reduced because of febrile neutropenia. These differences were observed despite more G-CSF use in the docetaxel arm.

- A total of 231 dose delays (19.8% of 1164 doses) were reported in the Alimta arm, and 193 dose delays (17.8% of 1085 doses) were reported in the docetaxel arm. Scheduling conflict was the most common reason for dose delays on both treatment arms. Decreased creatinine clearance, which caused 13 dose delays in 7 patients (1.1% of all cycles administered), was the second most common reason for dose delays in the Alimta arm. Three of the 7 patients had a baseline creatinine clearance rate of 47 to 52 mL/min, which was very close to the protocol-defined lower limit of 45 mL/min. In Study JMEI, there were no CTC Grade 3/4 renal toxicities. Infection was the second most common reason for dose delays in the docetaxel arm.

4.1.4. Adverse Events

An adverse event was defined as any undesirable experience that occurred after the patient received the first dose of study drug, without regard to the possibility of a causal relationship.

At the first visit, study site personnel questioned each patient and noted the occurrence and nature of presenting and preexisting conditions. At subsequent visits, site personnel again questioned the patient, noting any changes in the presenting or preexisting conditions and the occurrence and nature of any adverse events. The investigator was requested to assess the causality of any adverse event that was reported during the study. All TEAEs and SAEs in Study JMEI were reported using Medical Dictionary for Regulatory Activities (MedDRA®; Version 5.1) terminology.

Table 4.1 summarizes the overall adverse event profile for Alimta versus docetaxel in Study JMEI. In general, patients in the Alimta arm experienced fewer SAEs, deaths, and discontinuations due to adverse events. Drug-related SAEs were statistically significantly fewer in the Alimta arm (Table 4.3).

Table 4.1. Overview of Adverse Events Randomized and Treated Population Study JMEI

Adverse Event	Number (%) of Patients with an Event			
	Regardless of Drug Causality		Possibly Drug Related	
	Alimta (N=265)	Docetaxel (N=276)	Alimta (N=265)	Docetaxel (N=276)
Deaths	31 (11.7)	40 (14.5)	3 (1.1)	5 (1.8)
Patients with ≥1 SAE	99 (37.4)	120 (43.5)	27 (10.2)	66 (23.9)
SUR events	5 (1.9)	9 (3.3)	5 (1.9)	9 (3.3)
Nonserious, clinically significant adverse events (discontinuations)	5 (1.9)	11 (4.0)	4 (1.5)	9 (3.3)
Discontinuations due to SAEs	13 (4.9)	14 (5.1)	3 (1.1)	9 (3.3)

Abbreviations: N = number of randomized and treated patients; SAE = serious adverse event; SUR = serious, unexpected, and reportable.

4.1.4.1. Treatment-Emergent Adverse Events

Treatment-emergent adverse events were defined as events that first occurred or, if present at the time of enrollment, worsened, after administration of at least one dose of study drug.

Table App.5.1 displays the TEAEs experienced by ≥10% of the patients, regardless of causality, and Table App.5.2 displays the TEAEs that were considered study drug-related and were experienced by ≥10% of the patients.

In general, the occurrence of TEAEs, regardless of drug causality, was similar between treatment arms. However, the drug-related TEAEs were significantly fewer in the Alimta arm compared with the docetaxel arm (78.1% versus 85.9%, p=0.025).

The key findings for Study JMEI were as follows:

- The five most commonly reported drug-related TEAEs in the Alimta arm were nausea (30.2% of patients), fatigue (24.5%), anorexia (20.4%), anemia (18.1%), and vomiting (16.2%).
- The five most commonly reported drug-related TEAEs in the docetaxel arm were neutropenia (43.8% of patients), alopecia (38.4%), leukopenia (33.7%), fatigue (23.9%), and diarrhea (23.6%).
- The incidence of neutropenia ($p<0.001$) and leukopenia ($p<0.001$) was significantly lower in the Alimta arm, while the incidence of transaminase elevation ($p<0.001$) was significantly lower in the docetaxel arm.

- The incidence of alopecia ($p<0.001$) and diarrhea ($p=0.001$) was significantly lower in the Alimta arm, and the incidence of nausea ($p<0.001$) and rash ($p=0.009$) was significantly lower in the docetaxel arm.

  The difference in the incidence of nausea may be attributed to the higher dosage with corticosteroids (as premedication) in the docetaxel arm, which was twice that of Alimta arm. Also, slightly more patients in the docetaxel arm received HT_3 antagonists (37.5% versus 32.5%). The majority of these events were mild. The incidence of CTC (version 2.0; NCI 1998) Grade 3/4 nausea was not significantly different between the two arms (Alimta 2.6% of patients, docetaxel 1.8%; $p=0.570$).

- More patients in the docetaxel arm experienced drug-related TEAEs of the blood and lymphatic system (Alimta 26.0%, docetaxel 59.1%; $p<0.001$). In addition to neutropenia and leukopenia, the incidence of febrile neutropenia (Alimta 1.9%, docetaxel 13.4%; $p<0.001$) was statistically significantly higher in the docetaxel arm. Thrombocytopenia (Alimta 8.7%, docetaxel 1.1%; $p<0.001$) was significantly lower in the docetaxel arm compared with the Alimta arm.

4.1.4.2. Deaths

During the active treatment phase of Study JMEI, deaths were rare (Table 4.2); 31 patients died on the Alimta arm compared with 40 on the docetaxel arm. More drug-related deaths were reported in the docetaxel arm than in the Alimta arm (1.8% and 1.1%, respectively). This difference was not statistically significant.

Three study drug-related deaths were reported in the Alimta arm compared with five in the docetaxel arm. One patient in the Alimta arm died from hepatic failure, 1 died from cardiac arrest, and 1 died from pneumonia/sepsis. In the docetaxel arm, 2 patients died from sepsis or septic shock, 1 from pulmonary embolism, 1 from lung disorder, and 1 from pneumonia. Table 4.2 provides a summary of the deaths in Study JMEI.

Table 4.2. Summary of Deaths Randomized and Treated Population Study JMEI

Cause of Death	Alimta (N=265) n (%)	Docetaxel (N=276) n (%)
Study-Drug Related	3 (1.1)	5 (1.8)
Cardiac arrest	1 (0.4)	0
Hepatic failure	1 (0.4)	0
Pulmonary embolism	0	1 (0.4)
Lung disorder	0	1 (0.4)
Pneumonia	0	1 (0.4)
Pneumonia and sepsis	1 (0.4)	0
Sepsis	0	1 (0.4)
Septic shock	0	1 (0.4)
Other Causes	10 (3.8)	9 (3.3)
Pulmonary embolism	2 (0.8)	0
ARDS	1 (0.4)	0
Cardiopulmonary failure	1 (0.4)	2 (0.7)
Dyspnea	1 (0.4)	0
Myocardial infarction	3 (1.1)	0
Pneumonia	2 (0.8)	1 (0.4)
Cardiac tamponade	0	1 (0.4)
Cardiovascular disorder	0	1 (0.4)
Cerebrovascular accident	0	1 (0.4)
Chronic obstructive airways disease	0	1 (0.4)
Unexplained	0	1 (0.4)
Superior vena caval occlusion	0	1 (0.4)
Study Disease	18 (6.8)	26 (9.4)
Total	31 (11.7)	40 (14.5)

Abbreviations: ARDS = acute respiratory distress syndrome; n = number of patients who died; N = number of randomized and treated patients.

4.1.4.3. Serious Adverse Events

An adverse event was considered serious (SAE) if it resulted in death, hospitalization, severe or permanent disability, or cancer (other than cancers diagnosed prior to enrollment); constituted a congenital anomaly; was life threatening; or was significant for any other reason. Study site investigators relied upon their clinical judgment to discern and document whether the event was causally related to study therapy. Serious unexpected reportable (SUR) events are also included in this section.

Table 4.3 displays the SAEs experienced by ≥2% of the patients, regardless of causality, and SAEs that were considered study-drug related. Table 4.4 displays the SAEs that led to discontinuation.

The key findings for SAEs in Study JMEI are as follows:

- In general, the occurrence of SAEs, regardless of drug causality, was similar between the treatment arms. However, study drug-related SAEs were significantly lower in the Alimta arm (10.2% versus 23.9%; $p<0.001$) (Table 4.3).
- In the docetaxel arm, the five most commonly reported SAEs, regardless of causality, were febrile neutropenia (11.2%), dyspnea (9.1%), neutropenia (6.2%), pneumonia (5.1%), and pyrexia (3.6%). The incidences of neutropenia and febrile neutropenia were statistically significantly higher in the docetaxel arm ($p<0.001$). In the Alimta arm, the five most frequently reported SAEs, regardless of causality, were pneumonia (6.8%), dyspnea (4.9%), pyrexia (4.5%), anemia (3.8%), and abdominal pain (2.3%). No patients in the Alimta arm experienced neutropenia as an SAE (Table 4.3).
- The percentage of patients hospitalized because of adverse events was significantly lower in the Alimta arm (Alimta 31.7%, docetaxel 40.6%; $p=0.032$), particularly for drug-related febrile neutropenia (Alimta 1.5%, docetaxel 13.4%; $p<0.001$) (Table 4.8).
- More patients in the docetaxel arm than in the Alimta arm discontinued because of an SAE (Table 4.4). Thirteen (4.9%) patients in the Alimta arm discontinued because of an SAE; three (1.1%) of these discontinuations were considered study-drug related. In the docetaxel arm, 14 (5.1%) patients discontinued because of an SAE; nine (3.3%) of these discontinuations were considered study-drug related.
- The most common SAE resulting in discontinuation in the Alimta arm was fatigue (0.8%); in the docetaxel arm, febrile neutropenia (1.1%) and pyrexia (0.7%) (Table 4.4).
- More patients in the docetaxel arm experienced SURs than did patients in the Alimta arm (3.3% versus 1.9%) (Table 4.1). Two patients on each arm had more than one event, including 1 patient in the docetaxel arm who experienced four SURs.

Table 4.3. Serious Adverse Events Experienced by at Least 2% Patients Randomized and Treated Population Study JMEI

Event	Alimta (N=265) n (%)	Docetaxel (N=276) n (%)	Significant p-Values
Study Drug-Related			
Patients with ≥1 event	27 (10.2)	66 (23.9)	<0.001
Anemia	7 (2.6)	7 (2.5)	-
Febrile neutropenia	4 (1.5)	31 (11.2)	<0.001
Pyrexia	3 (1.1)	8 (2.9)	-
Neutropenia	0 (0.0)	17 (6.2)	<0.001
Regardless of Causality			
Patients with ≥1 event	99 (37.4)	120 (43.5)	-
Pneumonia	18 (6.8)	14 (5.1)	-
Dyspnea	13 (4.9)	25 (9.1)	-
Pyrexia	12 (4.5)	10 (3.6)	-
Anemia	10 (3.8)	7 (2.5)	-
Abdominal pain	6 (2.3)	0 (0.0)	0.013
Febrile neutropenia	4 (1.5)	31 (11.2)	<0.001
Asthenia	4 (1.5)	8 (2.9)	-
Pleural effusion	1 (0.4)	6 (2.2)	-
Neutropenia	0 (0.0)	17 (6.2)	<0.001

Abbreviations: n = number of patients with serious adverse events; N = number of randomized and treated patients.

Table 4.4. Discontinuations due to Serious Adverse Events Randomized and Treated Population Study JMEI

	Number of Patients			
	Regardless of Causality		Possibly Study-Drug Related	
Event	**Alimta**	**Docetaxel**	**Alimta**	**Docetaxel**
Acquired tracheo-esophageal fistula	-	1	-	-
Acute diverticulitis	-	1	-	-
Arthralgia	-	1	-	1
Cardiac failure	-	1	-	-
Cerebrovascular accident	1	-	-	-
Chronic obstructive airway disease	1	-	-	-
Confusion	1	-	-	-
Cytolytic hepatitis	1	-	1	-
Dyspnea	-	1	-	-
Exanthem	1	-	1	-
Fatigue	2	-	-	-
Febrile neutropenia	-	3	-	3
General physical health deterioration	-	1	-	-
Hepatitis B	1	-	-	-
Hypercalcemia	1	-	-	-
Loss of consciousness	-	1	-	1
Pneumonia	1	-	-	-
Polyneuropathy	-	1	-	1
Pyrexia	-	2	-	2
Renal failure	1	-	1	-
Respiratory tract infection	1	-	-	-
Reversible ischemic neurological deficiency	-	1	-	1
Thrombosis	1	-	-	-
Total	**13**	**14**	**3**	**9**

4.1.4.4. Other Significant Adverse Events

Adverse events that resulted in study discontinuation were classified as "nonserious, clinically significant adverse events." Investigators were required to document the reasons for discontinuation. Table 4.5 summarizes discontinuations due to nonserious adverse events.

The key findings for Study JMEI are as follows:

- More patients in the docetaxel arm (4.0%) discontinued from the study because of nonserious, clinically significant adverse events than patients in the Alimta arm (1.9%). In the docetaxel arm and Alimta arm, respectively, 3.3% and 1.5% of patients discontinued because of study drug-related events (Table 4.5).
- The most frequent reason for study drug-related discontinuation was decreased creatinine clearance (0.8%) in the Alimta arm and fatigue (1.4%) on docetaxel arm.

Table 4.5. Discontinuations due to Adverse Events (Nonserious, Clinically Significant)
Randomized and Treated Population
Study JMEI

	Number of Patients			
	Regardless of Causality		Possibly Study Drug-Related	
Event	**Alimta**	**Docetaxel**	**Alimta**	**Docetaxel**
Blood alkaline phosphate increased	1	-	-	-
Blood creatinine increased	1	-	1	-
Bone pain	-	1	-	-
Creatine clearance decreased	2	-	2	-
Dyspnea	-	1	-	-
Fatigue	1	3	1	3
Localized infection	-	1	-	1
Dermatitis allergic	-	1	-	1
Neuropathy	-	1	-	1
Stomatitis	-	1	-	1
Paresthesia	-	1	-	1
Hyponatremia	-	1	-	1
Total	**5**	**11**	**4**	**9**

4.1.5. Clinical Laboratory and Nonlaboratory Evaluations

Investigators were asked to assess the drug causality of each laboratory and nonlaboratory adverse event and to assign a grade to the event using the CTC reporting guidelines (version 2.0; NCI 1998).

There were no differences in the incidence of Grade 1 and 2 laboratory and nonlaboratory toxicities. However, patients in the Alimta arm had significantly fewer Grade 3 and Grade 4 toxicities compared with patients in the docetaxel arm.

4.1.5.1. Laboratory Toxicities

Table 4.6 summarizes selected CTC Grade 3 and 4 laboratory toxicities in Study JMEI.

The key findings for study drug-related laboratory toxicities for Study JMEI are as follows:

- Neutropenia was the most common Grade 3 or 4 hematologic toxicity and was reported at a significantly higher rate in the docetaxel arm (40.2%) than in the Alimta arm (5.3%, $p<0.001$). Significantly fewer patients in the Alimta arm received G-CSFs concomitantly (Alimta 2.6%; docetaxel 19.2%, $p<0.001$) (Table 4.10).
- The incidence of Grade 3 and 4 thrombocytopenia was low in both arms (Alimta 1.9%; docetaxel 0.4%). Grade 3 and 4 anemia was similar between the treatment arms (Alimta 4.2%; docetaxel 4.3%). More patients in the Alimta arm received red blood cell transfusions (16.6% versus 11.6%; Table 4.12), and more patients in the docetaxel arm received erythropoietin (6.8% versus 10.1%; Table 4.11) concomitantly.
- The overall incidence of Grade 3 and 4 nonhematologic laboratory toxicities was low in both arms. In the Alimta arm, the most common Grade 3 or 4 nonhematologic toxicities were increased ALT and AST, occurring in 1.9% and 1.1% of the patients, respectively. However, these increases in ALT and AST levels were not associated with a significant increase in bilirubin levels (0.4%). No Grade 3 or 4 elevations of ALT were reported in the docetaxel arm ($p=0.028$) (Table 4.6).

In summary, Alimta had significantly fewer Grade 3 and Grade 4 laboratory toxicities related or regardless of causality ($p<0.001$).

Table 4.6. Summary of Selected Grade 3 and 4 Laboratory Toxicities Randomized and Treated Population Study JMEI

	Percentage of Patients		
Toxicity	Alimta (N=265)	Docetaxel (N=276)	p-Value
Study-drug related			
Neutropenia	5.3	40.2	<0.001
Anemia	4.2	4.3	1.0
Thrombocytopenia	1.9	0.4	0.116
Creatinine	0	0	1.0
Increased AST	1.1	0	-
Increased ALT	1.9	0	0.028
Bilirubin	0.4	0	-
Regardless of causality			
Neutropenia	5.3	40.2	<0.001
Anemia	7.5	6.2	0.610
Thrombocytopenia	1.9	0.7	0.277
Creatinine	0	0	1.0
Increased AST	1.1	0.4	0.364
Increased ALT	2.6	0.4	0.034

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; N = number of randomized and treated patients.

4.1.5.2. Nonlaboratory Toxicities

Table 4.7 summarizes selected CTC Grade 3 and 4 nonlaboratory toxicities in Study JMEI.

The key findings for study drug-related nonlaboratory toxicities for Study JMEI:

- Grade 3 and 4 febrile neutropenia was the most common toxicity in the docetaxel arm, experienced by significantly more patients compared with the Alimta arm (12.7% versus 1.9%; p<0.001). The majority of cases of febrile neutropenia in the docetaxel arm (23 patients, 8.3%) occurred during Cycle 1.
- Grade 3 and 4 fatigue (5.3%) was the most commonly reported nonlaboratory toxicity in the Alimta arm. The incidence of fatigue in the docetaxel arm was similar (5.4%).
- Infection with Grade 3 or 4 neutropenia was significantly different between the treatment arms (Alimta 0, docetaxel 3.3%; p=0.004).
- Grade 3 and 4 toxicities, including nausea, vomiting, anorexia, fatigue, and stomatitis, were similar in the two arms.
- Alimta patients had significantly less (p=0.012) Grade 2 to 4 neuropathy (sensory) (0.8%) than docetaxel patients (4.3%).

- Grade 2 to 4 arthralgia was reported in significantly fewer patients in the Alimta arm compared with the docetaxel arm (0.4% versus 5.8%; p<0.001). Grade 2 to 4 myalgia was reported in significantly fewer patients in the Alimta arm compared with the docetaxel arm (2.3% versus 6.9%; p=0.013). Alopecia (all grades) was significantly higher in the docetaxel arm (37.7% versus 6.4%; p<0.001).

In summary, the Alimta arm had significantly fewer Grade 3 and 4 drug-related nonlaboratory toxicities (p<0.001).

Table 4.7. Summary of Selected Grade 3 and 4 Nonlaboratory Toxicities Randomized and Treated Population Study JMEI

	Percentage of Patients		
Toxicity	**Alimta (N=265)**	**Docetaxel (N=276)**	**p-Value**
Study-Drug Related			
Febrile neutropenia	1.9	12.7	<0.001
Infection with Grade 3 or 4 neutropenia	0	3.3	0.004
Fatigue	5.3	5.4	1.0
Nausea	2.6	1.8	0.570
Vomiting	1.5	1.1	0.720
Stomatitis	1.1	1.1	1.0
Diarrhea	0.4	2.5	0.069
Pulmonary toxicity	0	1.4	0.124
Neurosensory (Grade 2–4)	0.8	4.3	0.012
Alopecia (all grades)	6.4	37.7	<0.001
Arthralgia (Grade 2–4)	0.4	5.8	<0.001
Myalgia (Grade 2–4)	2.3	6.9	0.013
Regardless of Causality			
Febrile neutropenia	1.9	12.7	<0.001
Infection with Grade 3 or 4 neutropenia	0	5.8	<0.001
Fatigue	15.8	16.7	0.817
Nausea	3.8	2.5	0.466
Vomiting	1.5	1.4	1.0
Stomatitis	1.1	1.1	1.0
Diarrhea	0.4	4.0	0.006
Pulmonary toxicity	6.8	9.8	0.217
Neurosensory (Grade 2–4)	7.5	9.8	0.365
Alopecia (all grades)	11.3	42.4	<0.001

Abbreviation: N = number of randomized and treated patients.

4.1.6. Hospitalizations

Table 4.8 displays a summary of reasons patients were hospitalized during the study. Significantly fewer hospitalizations associated with adverse events occurred in the Alimta arm ($p=0.032$), particularly for febrile neutropenia ($p<0.001$). The most commonly reported nondrug-related events with hospitalization were dyspnea and pneumonia.

More admissions and days of hospitalization for social reasons were reported in the Alimta arm. This type of hospitalization accounts for the days that a patient remained in the hospital between protocol events for convenience and not because of adverse events. Hospitalization for social reasons is more likely to be related to a specific local health care system or to individual patient needs (for example, distance from the patient's home to the investigational site or the availability of a caregiver). Social reasons were reported most commonly at sites in Germany, Pakistan, and Russia. Four of the 5 patients enrolled in Russia, all in the Alimta arm, accounted for 135 days of hospitalization.

Table 4.8. Summary of Hospitalizations Randomized and Treated Population Study JMEI

Reason for Hospitalization[1]	Number (%) of Patients: Alimta (N=265)	Number (%) of Patients: Docetaxel (N=276)	p-Value
All reasons	129 (48.7)	146 (52.9)	0.345
Study drug administration	53 (20.0)	57 (20.7)	-
Adverse events (all)	84 (31.7)	112 (40.6)	0.032
Drug-related AEs[2]	19 (7.2)	60 (21.7)	<0.001
Febrile neutropenia[2]	4 (1.5)	37 (13.4)	<0.001
Other drug-related AEs[2]	17 (6.4)	29 (10.5)	0.092
Nondrug-related AEs[2]	69 (26.0)	66 (23.9)	-
Protocol tests	43 (16.2)	31 (11.2)	-
Social reasons	17 (6.4)	16 (5.8)	-
Number of admissions	337	364	-
Study drug administration	123	151	-
Adverse events (all)	113	147	-
Febrile neutropenia[2]	4	43	-
Other drug-related[2]	17	29	-
Nondrug-related[2]	92	75	-
Protocol tests	72	49	-
Social reasons	29	17	-
Days of hospitalization	1722	1410	-
Study drug administration	314	314	-
Adverse events (all)	885	833	-
Febrile neutropenia[2]	29	195	-
Other drug-related[2]	131	151	-
Nondrug-related[2]	725	487	-
Protocol tests	143	100	-
Social reasons	380	163	-

Abbreviations: AEs = adverse events; N = number of randomized and treated patients.

1 Patients may have been admitted for multiple reasons.

2 Relatedness was determined by the investigator.

Study JMEI was a global study, and there are known differences in approaches to healthcare between North America and other regions. Therefore, further analysis of hospitalization data was carried out for the patients enrolled in North America. This analysis has shown that no hospitalizations in Study JMEI occurred for reasons other than adverse events (Table 4.9). The number of patients hospitalized because of adverse events was higher in the docetaxel arm.

Overall, hospitalization due to drug-related adverse events was significantly lower in the Alimta arm. This observation is consistent with the safety profile of the two drugs and suggests that Alimta is better tolerated than docetaxel with respect to life-threatening

events leading to hospitalization. Table 4.9 summarizes the hospitalizations for North America.

Table 4.9. Summary of Hospitalizations for North America (United States and Canada) Randomized and Treated Population Study JMEI

	Number (%) of Patients	
Reason for Hospitalization[1]	**Alimta (N=68)**	**Docetaxel (N=67)**
All reasons	20 (29.4)	25 (37.3)
Study drug administration	0	0
Adverse events (all)	20 (29.4)	25 (37.3)
Febrile neutropenia	1 (1.5)	9 (13.4)
Other study drug-related AEs[2]	1 (1.5)	4 (6.0)
Nondrug-related AEs[2]	18 (26.5)	14 (20.9)
Protocol tests	0	0
Social reasons	0	0
Number of admissions	27	32
Adverse events (all)	27	32
Febrile neutropenia	1	12
Other study drug-related[2]	1	4
Nondrug-related[2]	25	16
Days of hospitalization	157	199
Adverse events (all)	157	199
Febrile neutropenia	5	38
Other study drug-related[2]	5	14
Nondrug-related[2]	147	147

Abbreviations: AE = adverse event; N = number of randomized and treated patients.

1 Patients may have been admitted for multiple reasons.

2 Relatedness was determined by investigator.

4.1.7. Concomitant Medication

The concomitant medications considered in Study JMEI included 5-HT_3 antagonists, granulocyte colony-stimulating factors (G-CSFs), erythropoietin, and parenteral antibiotics (Table 4.10). Table 4.10 summarizes selected concomitant drug therapy used for supportive care. In general, a greater percentage of patients in the docetaxel arm received concomitant medications compared with the Alimta arm.

Table 4.10. Summary of Selected Concomitant Drug Therapy Used for Supportive Care
Randomized and Treated Population
Study JMEI

	Number (%) of Patients	
Categories	**Alimta (N=265)**	**Docetaxel (N=276)**
Corticosteroids (systemic)	264 (99.6)	276 (100)
5-HT_3 antagonists	92 (34.7)	108 (39.1)
Metoclopramide	72 (27.2)	76 (27.5)
H_2 antagonists and proton pump inhibitors	102 (38.5)	129 (46.7)
Opioids	150 (56.6)	156 (56.5)
Erythropoietin	18 (6.8)	28 (10.1)
G-CSFs	7 (2.6)	53 (19.2)
Antibiotics (systemic)	120 (45.3)	150 (54.4)
Antibiotics (iv or im only)	52 (19.6)	70 (25.4)

Abbreviations: G-CSF = granulocyte colony-stimulating factor; iv = intravenous; im = intramuscular; N = number of randomized and treated patients.

Table 4.11 summarizes the number of courses given for selected concomitant medications. Patients in the docetaxel arm received more courses of G-CSFs and parenteral antibiotics than did patients in the Alimta arm; the difference between the arms for G-CSFs was statistically significant ($p<0.001$).

Table 4.11. Summary of Courses of Therapy for Selected Concomitant Medications Randomized and Treated Population Study JMEI

	Alimta (N=265)		Docetaxel (N=276)	
Medication/Reason Given	**n (%)**	**Courses**	**n (%)**	**Courses**
G-CSFs	7 (2.6)	10	53 (19.2)	100
Erythropoietin	18 (6.8)	48[a]	28 (10.1)	58[b]
Antibiotics (iv or im)	52 (19.6)	106	70 (25.4)	151
Febrile neutropenia	3 (1.1)	6	19 (6.9)	38
Neutropenia/leukopenia	0	0	5 (1.8)	16
Pneumonia	12 (4.5)	21	12 (4.3)	28
Pyrexia	9 (3.4)	23	10 (3.6)	24
Sepsis	0	0	2 (0.7)	6

Abbreviation: G-CSF = granulocyte colony-stimulating factor, im = intramuscular; iv = intravenous; n = number of patients who received the specified concomitant medication; N = number of randomized and treated patients.

[a] One patient received erythropoietin intermittently over 25 courses.

[b] One patient received erythropoietin intermittently over 22 courses.

4.1.8. Transfusions

Table 4.12 summarizes the number of patients who received transfusions and the number of units received by treatment arm in Study JMEI. The number of transfusions in the study was small: 45 (17%) patients on the Alimta arm and 32 (11.6%) patients on the docetaxel arm received one or more transfusions.

On both treatment arms, red blood cell transfusions were most common. Although the incidence of CTC 3 and 4 anemia was similar between the arms (Table 4.6), more patients on the Alimta arm received transfusions of red blood cells, and more patients on the docetaxel arm received erythropoietin.

The number of patients receiving platelet transfusions in this study was small; this may reflect the low incidence of CTC Grade 3 or 4 thrombocytopenia observed in this study (Table 4.6).

Table 4.12. Summary of On-Study Transfusions Randomized and Treated Population Study JMEI

Type of Transfusion	Alimta (N=265)		Docetaxel (N=276)	
Patients with ≥1 transfusion[1] (%)	45 (17.0)		32 (11.6)	
	Units	**n (%)**	**Units**	**n (%)**
RBC transfusions[2]	148	44 (16.6)	81	32 (11.6)
Plasma transfusions	8	2 (0.8)	4	1 (0.4)
Platelet transfusions[3]	44	3 (1.1)	0	0

Abbreviations: n = number of patients who received the specified type of transfusion; N = number of randomized and treated patients; RBC = red blood cell.

1 Patients may have received more than one type of transfusion.

2 Patients received 1 to 3 units of RBCs per transfusion; 1 unit = 1 bag of packed RBC.

3 Patients received 6 to 15 units of platelets per transfusion.

4.2. Safety Conclusions from Study JMEI

From a safety standpoint, Alimta represents a superior treatment option in the second-line treatment of NSCLC.

Although both regimens could be given at the prescribed dose and schedule, important safety profile benefits occurred in the group randomized to Alimta:

- fewer deaths
- significantly less neutropenia and febrile neutropenia
- significantly less neutropenia with infection
- significantly less alopecia and diarrhea
- significantly less neurotoxicity, myalgia, and arthralgia
- significantly fewer drug-related SAEs
- significantly fewer hospitalizations due to adverse events.

Patients on both arms received a similar number of cycles of treatment (median, 4). Statistically significantly more dose reductions occurred in the docetaxel arm compared with the Alimta arm ($p<0.001$). Most reductions were associated with neutropenia or febrile neutropenia.

Five study drug-related deaths (all on study) occurred on the docetaxel arm, and three (two on study and one poststudy) occurred on the Alimta arm. Drug-related TEAEs and drug-related SAEs were statistically higher in the docetaxel arm compared with the Alimta arm.

The incidence of any CTC Grade 3 or 4 laboratory toxicity was very low in the Alimta arm compared with the docetaxel arm. There were statistically significantly fewer Grade 3 and 4 toxicities of neutropenia on the Alimta arm compared with docetaxel arm (5.3% versus 40.2%). Grade 3 and 4 elevations of ALT and AST occurred in 1.9% and 1.1% patients in the Alimta arm compared with none in the docetaxel arm; the difference in the incidence of ALT elevations was statistically significant (p=0.028). No clinically significant conclusions could be drawn from the low incidence of increased ALT and AST. The incidence of Grade 3 or 4 thrombocytopenia was low, and the incidence of Grade 3 or 4 anemia was similar on the two treatment arms. More patients on the docetaxel arm received erythropoietin, and more patients on the Alimta arm received red blood cell transfusions.

The incidence of any Grade 3 or 4 nonlaboratory toxicity was very low in the Alimta arm compared with docetaxel. Infection with Grade 3 or 4 neutropenia, febrile neutropenia, and alopecia (all grades) were significantly less frequent in the Alimta arm. Grade 2 to 4 myalgia, arthralgia, and neuropathy (sensory) were significantly lower in the Alimta arm. Other clinically important events such as diarrhea, vomiting, nausea, fatigue, and hypersensitivity occurred at a similar frequency in the two treatment arms. The incidence of diarrhea (regardless of causality) was statistically significantly lower in the Alimta arm (Table 4.7).

The requirement for G-CSFs, antibiotics, and hospitalizations for investigator-determined drug-related events was greater in the docetaxel arm. The number of patients who received G-CSFs and antibiotics was significantly lower in the Alimta arm compared with the docetaxel arm. The number of patients hospitalized for drug-related adverse events, particularly febrile neutropenia, was significantly lower in the Alimta arm than in the docetaxel arm. More admissions and days of hospitalization were attributed to febrile neutropenia (43 versus 4 admissions, 195 versus 29 days) and other drug-related adverse events (29 versus 17 admissions, 151 versus 131 days) in the docetaxel arm than in the Alimta arm.

4.3. Integrated Safety Data from Phase 2 and 3 Alimta Single-Agent Studies

This section presents A summary of safety data integrated from the six clinical studies (JMEI, JMBT, JMDM, JMDS, JMDR, and JMEU) outlined in Table 1.7. A total of 517 patients in these studies received single-agent 500-mg/m^2 Alimta every 21 days, plus daily folic acid, a vitamin B_{12} injection every 9 weeks, and dexamethasone.

Overviews of these studies are provided in Appendix 1 (Table App.1.1 and Table App.1.8 through Table App.1.12).

Qualitative and quantitative comparison of data from vitamin-supplemented and -nonsupplemented patients receiving 500 mg/m^2 Alimta in Phase 2 and Phase 3 trials

reveals that supplementation with folic acid and vitamin B_{12} improves the safety profile of Alimta.

Table 4.13 illustrates the trend toward reduction of deaths, SAEs, and other adverse events when supplementation was added to the treatment regimen. A similar safety profile is observed in the laboratory and nonlaboratory CTC toxicities (Table 4.14). Table 4.14 shows the safety results for single-agent Alimta.

Table 4.13. Integrated Analysis of Supplemented and Nonsupplemented Alimta Patients Deaths, SAEs, Discontinuations

	Number (%) of Patients	
Event	**Supplemented Patients (500 mg/m^2) (N=517)**	**Nonsupplemented Patients (500 mg/m^2) (N=286)**
Study drug-related deaths	3 (0.6)	12 (4.2)
Patients with ≥1 related SAE	48 (9.3)	67 (23.4)
Discontinuations due to AE	26 (5)	24 (8.4)
Patients with ≥1 related TEAE	426 (82.4)	265 (92.7)

Abbreviations: AE = adverse event; N = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 4.14. Alimta Single-Agent Safety Results

	Percentage of Patients	
CTC Grade 3 or 4 Event	**Supplemented Patients Alimta 500 mg/m^2 (N=43)**	**Nonsupplemented Patients Alimta 500 mg/m^2 (N=242)**
Neutropenia	27.9	46.3
Leukopenia	23.3	41.7
Anemia	0.0	19.0
Platelets	2.3	13.2
Neurosensory	0.0	6.2
Infection	2.3	4.1
Stomatitis	0.0	2.9
Pulmonary	2.3	2.9
Vomiting	0.0	2.9
Nausea	0.0	2.1
Diarrhea	0.0	2.1
Hematologic + nonlaboratory toxicity	0.0	6.2

Abbreviations: CTC = Common Toxicity Criteria; N = number of patients.

The following are safety conclusions from the integrated dataset:

- Three (0.6%) patients died from study drug-related causes (cardiac arrest, hepatic failure, and pneumonia/sepsis; previously reported in Study JMEI).
- Nine (1.7%) patients experienced serious and unexpected adverse events thought to be related to study therapy.
- Twenty-six (5%) patients discontinued therapy because of adverse events. Events relating to renal dysfunction remain the most common adverse events leading to discontinuation.
- Grade 3 and 4 transaminase elevations occurred in fewer than 10% of patients. Neutropenia rarely resulted in clinical sequelae; the rate of febrile neutropenia was only 1.9%, very similar to the previously reported rate of 2%.
- Fatigue was the most common Grade 3 or 4 toxicity, occurring in 4.7% of patients.
- Subgroup analyses of clinically relevant TEAEs showed that decreased creatinine clearance and anemia were reported more commonly in older patients. Anorexia, decreased hemoglobin, and rash occurred significantly more frequently in men; vomiting and diarrhea occurred more often in women. Analyses of clinically relevant CTC Grade 3 and 4 toxicities showed no significant differences between either age or sex subgroups.

This integrated analysis illustrates that the safety profile of single-agent Alimta, with folic acid and vitamin B_{12} supplementation and prophylactic dexamethasone, is improved compared with the results of single-agent Alimta trials without vitamin supplementation, in which Grade 3 or 4 neutropenia was observed in as many as 42% of patients (Clarke et al. 2002 [Appendix 6]).

5. Summary

This section summarizes the reasons Alimta merits approval in second-line NSCLC patients.

Few treatment options exist for NSCLC patients who progress after first-line chemotherapy; docetaxel is currently the only chemotherapy drug approved for treatment in second-line NSCLC patients. When administered to this patient group, docetaxel is associated with clinically important toxicity, especially neutropenia and febrile neutropenia. Approximately one half of patients with NSCLC who receive docetaxel for second-line treatment develop Grade 3 or 4 neutropenia. This is particularly undesirable when associated with hospitalization in this population with a short expected survival. As a result, there is need for improvement in both efficacy and toxicity. In addition, docetaxel has recently been approved for first-line treatment of NSCLC, thus creating a need for alternate second-line regimens with better safety profiles.

Alimta is an antifolate that targets at least three folate-dependent enzymes essential for pyrimidine and purine biosynthesis; its mode of action is different from that of taxane, which interferes with microtubule assembly during cell division. These mechanistic differences minimize the development of cross-resistance in patients and render Alimta a good alternative after prior paclitaxel treatment.

Alimta is efficacious in NSCLC

In the pivotal study JMEI, the efficacy of single-agent Alimta, as determined by overall survival, was similar to that of docetaxel, the drug currently approved in this setting, in both adjusted and unadjusted analyses. This similarity was consistent across all secondary endpoints, including PFS, TTPD, response rate, stable disease, and patient-reported outcomes and reinforces the clinical relevance and robustness of the results in Study JMEI.

Results from Phase 2 studies have shown that single-agent Alimta is as active as other agents in NSCLC, with a response rate of 9% in the second-line setting and 16% to 23% in the first-line setting. In addition, several Phase 2 studies of Alimta in combination with cisplatin, oxaliplatin, or carboplatin have shown efficacy similar to other standard platinum doublets, with response rate of 27% to 45% and median survival of 8.9 to 10.9 months.

Alimta retains 102% of docetaxel's benefit over historical BSC in second-line NSCLC

Percent–benefit-retention analysis showed that Alimta retained 102% of docetaxel's relative benefit over BSC in the relevant historical trial. In addition, Cox adjusted survival analysis demonstrated that Alimta retained 114% of docetaxel's benefit over BSC in TAX 317 (p=0.016).

Survival in Alimta arm superior to BSC
Overall survival in the Alimta arm in Study JMEI was significantly superior to BSC (HR=0.55; p=0.019).

Results from Study JMEI are consistent across all subgroups
In Study JMEI, the efficacy of Alimta was consistent in all the subgroups, including the three significant prognostic factors of performance status, time since last chemotherapy, and disease stage.

Alimta has an excellent safety profile and is safer than docetaxel
Single-agent Alimta showed a clinically better safety profile than single-agent docetaxel in patients with previously treated NSCLC in the pivotal study, JMEI. This improvement was demonstrated through lower toxicity, fewer deaths on study, and less neutropenia and its clinically important sequelae such as febrile neutropenia, a particularly devastating complication in this palliative setting. Other important toxicities observed less frequently with Alimta included alopecia, diarrhea, and fewer drug-related SAEs (which, by definition, noticeably affect a patient's daily activities). Again, in a palliative setting, hair loss and diarrhea are very relevant to patients. Although some laboratory toxicities, such as rash and elevation of transaminase and serum creatinine levels, were more common on the Alimta arm, these were not as clinically pertinent.

Patients treated on the Alimta arm required less drug-related resource utilization, such as use of growth factors and hospitalization due to adverse events or febrile neutropenia.

Alimta has a better risk/benefit profile than docetaxel based on data from the Phase 3 Study JMEI
Alimta offers a better risk/benefit profile compared with docetaxel and merits approval in the treatment of second-line NSCLC, a devastating disease that clearly needs newer treatment options.

To quantify the risk/benefit profile of Alimta, a retrospective analysis of toxicity-free survival time was performed. This is defined as the time from the date of randomization to the first date of any Grade 4 toxicity or death due to any cause. Toxicity-free survival time was censored at the date of the last follow-up visit for patients who were still alive and who had not experienced any Grade 4 toxicity. This incorporates both time to severe toxicity and survival endpoints. Results demonstrated a statistically significantly longer toxicity-free survival for Alimta compared with docetaxel (Figure 5.1), with a median toxicity-free survival time of 7.5 months for Alimta versus 2.3 months for docetaxel (HR=0.57; p<0.001).

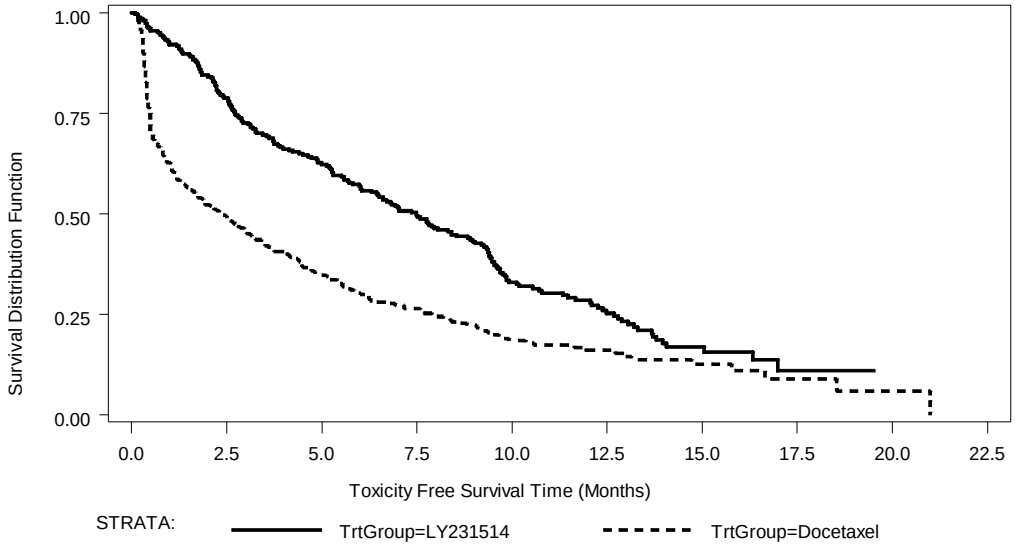


Figure 5.1. **Toxicity-free survival curve for Alimta and docetaxel in Study JMEI.**

Therefore, Alimta as a single agent should be indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.

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7. Abbreviations

Abbreviation	Term
ALT	alanine transaminase
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
AUC	area under the curve
BSC	best supportive care
CGCL	Cockroft Gault creatinine clearance
CI	confidence interval
CPMP	Committee for Proprietary Medicinal Products (European Regulatory Authority)
CR	complete response
CTC	Common Toxicity Criteria
DHFR	dihydrofolate reductase
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GARFT	glycinamide ribonucleotide formyltransferase
GFR	glomerular filtration rate
HR	hazard ratio
ITT	intent to treat
KM	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMA	methyl malonic acid
MPM	malignant pleural mesothelioma
MS	median survival
NCI	National Cancer Institute
NONMEM	Nonlinear Mixed Effect Modeling
NSCLC	non-small cell lung cancer
ORR	overall response rate
PD	progressive disease
PFS	progression-free survival
PR	partial response
PRNM	partial response in nonmeasurable disease
QoL	quality of life
QR	qualified for response analysis
RT	randomized and treated with at least one cycle of therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SUR	serious, unexpected, related adverse event
SWOG	Southwest Oncology Group
TEAE	treatment-emergent adverse event
TS	thymidylate synthase
TTPD	time to progressive disease

Appendix 1: Tabular Overview of Clinical Studies

Table App.1.1. Study H3E-MC-JMEI

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMEI **Status:** Completed	**Primary:** • Compare overall survival **Secondary:** • Characterize and compare toxicities • Compare the objective tumor response rate • Compare time-to-event efficacy variables • Compare changes in average symptom burden index	**Phase 3** Multicenter, controlled, open-label, randomized study of Alimta vs docetaxel in patients with locally advanced or metastatic (Stage IIIA, IIIB, or IV) NSCLC who were previously treated with chemotherapy. The study protocol was amended twice (see below for reasons for amendment)	**Alimta Formulation:** Aqueous at start of study, then lyophilized **Regimen:** **Alimta Arm** Alimta 500 mg/m^2 iv on Day 1 every 21 days **Docetaxel Arm** Docetaxel 75 mg/m^2 iv on Day 1 every 21 days **Vitamins:** Supplemented with folic acid 350-600 µg po and B_{12} 1000 µg im (Alimta patients only) **Dexamethasone:** **Alimta Arm** Prophylactic dexamethasone administered **Docetaxel Arm** Premedicated per docetaxel label	**Enrolled:** 571 **Treated:** 541 Arm A: 265 Arm B: 276 **Vitamin:** Arm A: 265 Arm B: 0 **Nonvitamin:** Arm A: 0 Arm B: 276

Abbreviations: ID = identification; im = intramuscular; iv = intravenous; NSCLC = non-small cell lung cancer; po = oral.

Reasons for Amendment A, Study JMEI

- to encourage the use of oral dexamethasone
- to allow treatment to continue until unacceptable toxicity, disease progression, physician believes discontinuation from study therapy is in the patient's best interest, or patient requests discontinuation from study therapy.
- to more clearly define the prior chemotherapy allowed in the desired patient population.
- to balance randomization with regard to the number of prior chemotherapy regimens
- to better define partial response in nonmeasurable disease
- to clarify that "follow-up" begins upon discontinuation from study therapy
- to change the timing for the first baseline electrocardiogram to "… approximately 1 week prior to the first ALIMTA dose."

Reasons for Amendment B, Study JMEI

- to replace the liquid formulation of LY231514 with the lyophilized preparation.
- to further explain the statistical methodology
- to make independent review of a patient's response status optional rather than required.

Table App.1.2. Study H3E-MC-JMBR

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMBR **Status:** Completed	**Primary:** • Response rate **Secondary:** • Characterize the quantitative and qualitative toxicities • Measure time-to-event efficacy variables • Evaluate changes in QoL over time	**Phase 2** Single-arm, open-label, non-randomized trial of Alimta in patients with NSCLC who had failed previous chemotherapy (with or without a platinum-containing agent)	**Alimta Formulation:** Lyophilized **Regimen:** Alimta 500 mg/m^2 iv on Day 1 every 21 days **Vitamins:** No vitamin supplementation **Dexamethasone:** Prophylactic dexamethasone administered	**Enrolled:** 81 **Treated:** 81 **Prior Platinum Agent:** 45 **No Prior Platinum Agent:** 36

Abbreviations: ID = identification; iv = intravenous; NSCLC = non-small cell lung cancer; QoL = quality of life.

Table App.1.3. Study H3E-MC-JMAL

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMAL **Status:** Completed	**Primary:** • Response rate **Secondary:** • Characterize the nature of the toxicity • Assess pharmacodynamics and population PK • Measure time-to-event efficacy variables	**Phase 2** Multicenter, single-arm, open-label, non-randomized study of Alimta in patients with inoperable, locally advanced, recurrent, or metastatic NSCLC	**Alimta Formulation:** Lyophilized **Regimen:** • Alimta 600 mg/m^2 iv on Day 1 every 21 days • Maximum of 12 cycles unless unacceptable toxicity **Vitamins:** No vitamin supplementation **Dexamethasone:** No prophylactic dexamethasone unless ≥Grade 2 rash occurred	**Enrolled:** 59 **Treated:** 59

Abbreviations: ID = identification; iv = intravenous; NSCLC = non-small cell lung cancer; PK = pharmacokinetics.

Table App.1.4. Study H3E-MC-JMAN

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMAN **Status:** Completed	**Primary:** • Response rate • Response duration **Secondary:** • Determine the toxicity	**Phase 2** Open-label, nonrandomized trial of Alimta in patients with advanced NSCLC	**Alimta Formulation:** Lyophilized **Regimen:** • Alimta 600 mg/m^2 iv on Day 1 every 21 days • Protocol was amended and the dose reduced to 500 mg/m^2 because of toxicity in patients on this study and on Study JMAO **Vitamins:** No vitamin supplementation **Dexamethasone:** No prophylactic dexamethasone unless ≥Grade 2 rash occurred	**Enrolled:** 33 **Treated:** 33

Abbreviations: ID = identification; iv = intravenous; NSCLC = non-small cell lung cancer.

Table App.1.5. Study H3E-MC-JMEK

Study ID/Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMEK **Status:** Completed	**Primary:** • Response rate **Secondary:** • Measure time-to-event efficacy variables • Characterize toxicities in each arm • Measure change in average symptom burden index for patients	**Phase 2** Multicenter, randomized, open-label, study of Alimta plus carboplatin or Alimta plus oxaliplatin in front line chemotherapy patients with locally advanced or metastatic (Stage IIIB or IV) NSCLC	**Alimta Formulation:** Aqueous at start of study, then lyophilized **Regimen:** **<u>Alimta plus Carboplatin</u>** • Alimta 500 mg/m^2 iv on Day 1 of a 21-day cycle for 6 cycles • Carboplatin iv AUC 6 after Alimta on Day 1 of a 21-day cycle **<u>Alimta plus Oxaliplatin</u>** • Alimta 500 mg/m^2 iv on Day 1 of a 21-day cycle for 6 cycles • Oxaliplatin 120 mg/m^2 iv after Alimta on Day 1 of a 21-day cycle **Vitamins:** Supplemented with folic acid 350-1000 µg po and B_{12} 1000 µg im **Dexamethasone:** Prophylactic dexamethasone administered	**Entered:** 91 **Treated:** 80 **Vitamin:** 80 **Nonvitamin:** 0

Abbreviations: AUC = area under the concentration curve; ID = identification; im = intramuscular; iv = intravenous; NSCLC = non-small cell lung cancer; po = oral.

Table App.1.6. Study H3E-MC-JMAY

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMAY **Status:** Completed	**Primary:** • Response rate **Secondary:** • Characterize the nature of the toxicity of Alimta in combination with cisplatin in this patient group • Measure time-to-event efficacy variables	**Phase 2** Multicenter, single-arm, open-label, nonrandomized trial of Alimta with cisplatin in patients with Stage IIIb or IV NSCLC	**Alimta Formulation:** Lyophilized **Regimen:** • Alimta 500 mg/m^2 iv on Day 1 every 21 days • Cisplatin 75 mg/m^2 iv 30 minutes after Alimta on Day 1 every 21 days **Vitamins:** No vitamin supplementation **Dexamethasone:** Prophylactic dexamethasone administered	**Enrolled:** 36 **Treated:** 36

Abbreviations: ID = identification; iv = intravenous; NSCLC = non-small cell lung cancer.

Table App.1.7. Study H3E-MC-JMBZ

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMBZ **Status:** Completed	• Assess the efficacy of Alimta in combination with cisplatin • Determine response rate and response duration • Determine the toxicity of Alimta in combination with cisplatin given sequentially	**Phase 2** Multicenter, open-label, nonrandomized study of Alimta plus cisplatin in patients with advanced NSCLC	**Alimta Formulation:** Lyophilized **Regimen:** • Alimta 500 mg/m^2 iv on Day 1 every 21 days • Cisplatin 75 mg/m^2 iv after Alimta on Day 1 every 21 days **Vitamins:** No vitamin supplementation **Dexamethasone:** Prophylactic dexamethasone required	**Enrolled:** 31 **Treated:** 31

Abbreviations: ID = identification; iv = intravenous; NSCLC = non-small cell lung cancer.

Table App.1.8. Study H3E-MC-JMDM

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMDM **Status:** Completed	**Primary:** • Response rate **Secondary:** • Characterize the toxicities of Alimta • Measure time-to-event efficacy variables • Characterize rate and duration of sustained improvement of disease-related symptoms • Characterize the rate of clinical benefit	**Phase 2** Open-label, non-randomized trial of Alimta in patients with advanced breast cancer who had been previously treated with an anthracycline, a paclitaxel, and capecitabine	**Alimta Formulation:** Lyophilized **Regimen:** Alimta 500 mg/m^2 iv on Day 1 of a 21-day cycle **Vitamins:** Supplemented with folic acid 350-600 μg po and B_{12} 1000 μg im **Dexamethasone:** Prophylactic dexamethasone administered	**Enrolled:** 80 **Vitamin:** 60 **Nonvitamin:** 20

Abbreviations: ID = identification; im = intramuscular; iv = intravenous; po = oral.

Table App.1.9. Study H3E-MC-JMBT

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMBT **Status:** Completed	**Primary:** • Response rate **Secondary:** • Characterize toxicity • Measure time-to-event efficacy variables • Evaluate changes in QoL over time	**Phase 2** Multicenter open-label, nonrandomized study of Alimta in patients with locally advanced or metastatic breast cancer who have received prior treatment with an anthracycline (or anthracenedione) containing regimen and a paclitaxel	**Alimta Formulation:** Lyophilized **Regimen:** Alimta 500 mg/m^2 iv on Day 1 every 21 days **Vitamins:** Supplemented with folic acid 350-600 μg po and B_{12} 1000 μg im **Dexamethasone:** Prophylactic dexamethasone administered	**Enrolled:** 79 **Vitamin:** 43 **Nonvitamin:** 36

Abbreviations: ID = identification; im = intramuscular; iv = intravenous; po = oral; QoL = quality of life.

Table App.1.10. Study H3E-MC-JMEU

Study ID/Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMEU **Status:** Ongoing **Study Conducted:** United States	**Primary:** • Response rate **Secondary:** • Measure time-to-event efficacy variables • Characterize toxicities	**Phase 2** Single-center, open-label, nonrandomized study of Alimta as second line therapy in patients with locally advanced or metastatic transitional cell carcinoma of the urothelium	**Alimta Formulation:** Lyophilized **Regimen:** • Alimta 500 mg/m^2 iv on Day 1 every 21 days **Vitamins:** Supplemented with folic acid 350-600 μg po and B_{12} 1000 μg im **Dexamethasone:** Prophylactic dexamethasone administered	**Enrolled:** 46

Abbreviations: ID = identification; im = intramuscular; iv = intravenous; po = oral.

Table App.1.11. Study H3E-MC-JMDR

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMDR **Status:** Completed	**Primary:** • Response rate **Secondary:** • Characterize the quantitative and qualitative toxicities • Measure time-to-event efficacy variables • Evaluate clinical benefit • Evaluate changes in pulmonary function test scores • Evaluate changes in lung density determinations in approximately 40 patients • Assess the vitamin metabolite status of patients • Evaluate changes in LCSS scores	**Phase 2** Multicenter non-randomized, open-label study of Alimta in patients with malignant pleural mesothelioma	**Alimta Formulation:** Aqueous **Regimen:** Alimta 500 mg/m^2 iv on Day 1 every 21 days **Vitamins:** Supplemented with folic acid 350-1000 µg po and B_{12} 1000 µg im **Dexamethasone:** Prophylactic dexamethasone administered	**Enrolled:** 64 **Vitamin:** 43 **Nonvitamin:** 21

Abbreviations: ID = identification; im = intramuscular; iv = intravenous; LCSS = Lung Cancer Symptom Scale; po = oral.

Table App.1.12. Study H3E-MC-JMDS

Study ID/ Trial Status/ Report Type	Objective	Trial Design	Regimen/Vitamin Supplementation/ Dexamethasone	Demographics
Study ID: H3E-MC-JMDS **Status:** Completed	**Primary:** • Determine relationship between levels of multiple molecular markers, including (but not limited to) TS, DHFR, GARFT, p53, and erbB2 expression, in breast cancer and normal tissues, and the patient's response to Alimta therapy **Secondary:** • Tumor response • Characterize toxicities • Determine how treatment with Alimta modulates the levels of multiple molecular markers	**Phase 2** Single-center, open-label, nonrandomized study of Alimta in the neoadjuvant setting in patients with previously untreated advanced breast cancer	**Alimta Formulation:** Aqueous at start of study, then lyophilized **Regimen:** • Alimta 500 mg/m^2 iv over 10 minutes on Day 1 every 3 weeks for a maximum of 3 cycles • Biopsies conducted before and after the first cycle • Surgical samples of tissue obtained after the third cycle **Vitamins:** Supplemented with folic acid 350-600 µg po and B_{12} 1000 µg im **Dexamethasone:** Prophylactic dexamethasone administered	**Enrolled:** 61 **Vitamin:** 61

Abbreviations: DHFR = dihydrofolate reductase; ID = identification; im = intramuscular; iv = intravenous; po = oral; TS = thymidylate synthase.

Appendix 2: Overall Significance Level for JMEI Primary Survival Analysis

Overall Significance Level of Primary Survival Tests

The primary analysis of Study JMEI was the calculation of the 95% CI for the survival HR (Alimta to docetaxel). From this one CI, primary statistical inference can be drawn regarding the degree of efficacy (that is, tests for superiority to docetaxel, noninferiority to docetaxel, retention of 50% of docetaxel benefit, and superiority to BSC) without multiplicity of the false-positive probability (fixed at alpha = 5% because of the fixed 95% CI).

The overall alpha level is fixed at 5%, which can also be seen from the following mathematical proof. Consider three primary (one-sided) statistical tests based on the JMEI survival data. The null hypotheses for these tests (written in terms of the log HR scale) are listed below:

Log HR(Alimta/docetaxel) ≥ 0	(superiority test)
Log HR(Alimta/docetaxel) ≥ 0.10436	(1.11 HR margin test)
Log HR(Alimta/docetaxel) ≥ (0.5)Log HR(BSC/docetaxel)	(50%-retention test)

Rothmann and colleagues (Rothmann et al. 2003) show that the null hypothesis for the 50% retention test can be approximated by:

$$H_{03}: \quad \text{Log HR (Alimta / docetaxel)} \geq [2(1.96)/\sqrt{\text{N}}] + (0.5)L - (1.96)\sqrt{(4/N + S^2/4)} = 0.18782$$

where L=0.59 is the historic estimate of log HR(BSC/docetaxel), S=0.235 is the standard error of L, and N=409 is the number of events in the JMEI analysis. The values of L, S, and N do not depend on any treatment-assignment unblinding of the JMEI data, and therefore these values are treated as known constants in the JMEI survival analysis. H_{03} is therefore a fixed-margin hypothesis, and so all three null hypotheses are fixed-margin hypotheses:

H_{01}: Log HR(Alimta/docetaxel) ≥ 0	(superiority test)
H_{02}: Log HR(Alimta/docetaxel) ≥ 0.10436	(10% noninferiority test)
H_{03}: Log HR(Alimta/docetaxel) ≥ 0.18782	(50%-retention test)

It is necessary to control the "type-1" (false-positive) error probability of the JMEI study. Each test individually has a (one-sided) false-positive probability of 0.025. It is reasonable to define the overall (one-sided) false-positive probability as:

(Overall alpha) = probability of a false-positive error on any of the threes tests.

The hypotheses are "nested" in the sense that H_{03} implies H_{02}, and that H_{02} implies H_{01}. Further, rejecting H_{01} implies rejecting H_{02}, which in turn implies rejecting H_{03}.

Case 1: Assume H_{03} is true. Then rejecting any of the three hypotheses would be a false-positive error. The following is true:

(Overall alpha) = Prob(rejecting any of the null hypotheses), given H_{03}

= Prob(rejecting H_{03}), given H_{03} [due to the nested hypotheses]

= 0.025

Case 2: Assume H_{02} is true, while H_{03} is false. Then rejecting H_{01} or H_{02} would be a false-positive error. The following is true:

(Overall alpha) = Prob(rejecting H_{01} or H_{02}), given H_{02}

= Prob(rejecting H_{02}), given H_{02} [due to the nested hypotheses]

= 0.025

Case 3: Assume H_{01} is true, while H_{02} is false. Then rejecting H_{01} would be a false-positive error. The following is true:

(Overall alpha) = P(rejecting H_{01}), given H_{01}

= 0.025

This proves mathematically, that without adjustment, the overall one-sided alpha is at most 0.025 (or equivalently, that the overall two-sided alpha is at most 0.05).

Appendix 3: Calculations Involving Historical Estimates

Historical data

Prior to the JMEI trial, two randomized trials (TAX 317 and TAX 320) studied the 21-day schedules of 75 mg/m^2 docetaxel. TAX 317 showed evidence of an overall survival benefit for patients treated with 75 mg/m^2 docetaxel compared with BSC. TAX 320 did not show a statistically significant survival advantage over patients treated with 75 mg/m^2 docetaxel compared with control chemotherapy (vinorelbine or ifosfamide). No supporting evidence demonstrates that treatment with vinorelbine or ifosfamide is equivalent to BSC.

The TAX 317 trial had two distinct subpopulations. Initially, patients were randomly assigned to 100 mg/m^2 docetaxel versus BSC. However, concerns were noted regarding the low tolerability of the 100 mg/m^2 dose, with five possibly treatment-related deaths among the first 49 patients randomly assigned to docetaxel (Shepherd et al. 2000). In addition, the median number of delivered cycles of 100 mg/m^2 docetaxel was only two cycles. An amendment was introduced to randomize patients to 75 mg/m^2 docetaxel (n=55) versus BSC (n=49). At the new dose, the median number of cycles delivered was four, and the final survival analysis showed that patients receiving 100 mg/m^2 docetaxel had an estimated 20% lower median survival (5.9 months) than patients receiving 75 mg/m^2 docetaxel (7.5 months). Because of the distinct differences in both tolerability and efficacy before and after the amendment, it is necessary to distinguish patients treated with 75 mg/m^2 docetaxel as a separate population from those treated with 100 mg/m^2 docetaxel.

So the only directly informative historical data for comparing Alimta with BSC is the 104-patient, postamendment cohort of the TAX 317 trial, referred to as TAX 317B. Therefore, the JMEI primary analysis was extended to include estimating the percentage of the docetaxel survival advantage over BSC (from TAX317B) retained by Alimta in JMEI.

Key numerical estimates used for the percent-retention calculation and comparison to BSC are given in the following table. The 95% CI for the HR of docetaxel over BSC from the docetaxel label was 0.35 to 0.88. From these results, it may be inferred that the estimated natural logarithm of the HR (BSC over docetaxel) was 0.589, with a standard error of 0.235.

Study	Log HR	St Error
TAX 317 (75 mg/m^2 docetaxel versus BSC)	0.589	0.235
JMEI (Alimta versus 75 mg/m^2 docetaxel)	-0.010	0.100

Percent-Retention Statistic and Confidence Interval

Let δ denote the percentage of the docetaxel survival benefit over BSC retained by Alimta. Consider also the following definitions:

L_1 = natural log HR (BSC over docetaxel)

L_2 = natural log HR (Alimta over docetaxel)

V_1 = variance of L_1

V_2 = variance of L_2

$L_1 - L_2$ = natural log HR (BSC over Alimta)

The percent-retention method as applied in JMEI defines δ as $(L_1 - L_2)/ L_1$.

To test H_0: $\delta = 0.5$, or equivalently H_0: $L_2 - (1-0.5) L_1 = 0$, the statistic Z is compared with a standard normal distribution:

$$Z = [L_2 - (1-0.5) L_1] / [\text{sqrt} (V_2 + (1-0.5)^2 V_1)].$$

The 95% CI for δ will be (δ_1, δ_2), where δ_1 is the minimum value of δ such that

$$-1.96 \leq [L_2 - (1-\delta) L_1] / [\text{sqrt} (V_1 + (1-\delta)^2 V_2)]$$

and δ_2 is the maximum value of δ such that

$$L_2 - (1-\delta) L_1]/[\text{sqrt} (V_1 + (1-\delta)^2 V_2)] \leq 1.96.$$

Comparison of Alimta with BSC

The upper bound of the 95% CI for the HR of BSC over Alimta is

$$\text{EXP} [(L_1 - L_2) + 1.96*\text{sqrt} (V_1 + V_2)].$$

The lower bound of the 95% CI for the HR of BSC over Alimta is

$$\text{EXP} [(L_1 - L_2) - 1.96*\text{sqrt} (V_1 + V_2)].$$

To test the superiority of Alimta over BSC, compare $(L_1 - L_2) / \text{sqrt} (V_1 + V_2)$ to a standard normal distribution.

Application of Percent-Retention Method to JMEI and TAX 317 Trial Results

L_1=0.589, V_1=0.055, L_2= -0.01, V_2=0.01, and there were 409 deaths on JMEI.

Using these estimates, δ is estimated to be 1.02, with Z = –1.985 (p=0.047). The 95% CI for δ is 52% to 157%. Therefore, there is a statistically significant retention of over 50% of the survival benefit.

Appendix 4: Patient Summaries

Patient 071-7214, a 49-year-old Caucasian man with metastatic NSCLC, initially diagnosed 18.9 months before enrollment in this study, was randomly assigned to receive ALIMTA at the starting dose of 500 mg/m^2.

The patient had received radiotherapy to the right upper lobe in 2000. He progressed with two cycles of chemotherapy with carboplatin and paclitaxel in February 2001 and received radiotherapy to the chest wall in April 2001, and to the right upper lobe in May 2001.

The patient's performance status at the time of enrollment was 2 on the Eastern Cooperative Group (ECOG) scale. Before enrollment, he had reported Grade 1 dyspnea and asthenia, tumor pain, and Grade 3 neuropathy. The patient was taking diclofenac and morphine for pain control and amitriptyline and gabapentin for the neuropathy.

During Cycle 1, the patient had CTC Grade 3 asthenia, which was not drug related, CTC Grade 3 decrease in leucocytes, neutropenia and lymphocytopenia, which were study drug related. During Cycle 2, 2 days after study drug administration, the patient experienced Grade 2 fever and diarrhea and was hospitalized. Stool culture was negative and diarrhea resolved after 2 days. On the next day, 3 days after study drug, the patient had CTC Grade 3 dermatitis and mucositis/stomatitis, which were possibly related to study drug.

The patient received several medications for the treatment of the dermatitis and mucositis including: dexamethasone, metoclopramide, ceftriaxone, metronidazole, vitamin K, leucovorin, oxycodone-paracetamol, hyoscine butylbromide, and haloperidol.

His condition worsened 2 days after the onset of mucositis/stomatitis, ulcerated lesions developed, then hemorrhagic lesions and crust on all surfaces in mouth and on lips, his abdomen was distended.

He completed two cycles of therapy. The last dose of ALIMTA was administered on 01 November 2001.

The patient died on 19 November 2001. Death was due to mucositis/stomatitis that led on to a cardiac respiratory arrest. An autopsy was not performed. While the cardio-respiratory arrest itself was not documented as study drug related, the increasing mucositis/stomatitis, which led to the patient's death was considered study drug related in the investigator's opinion.

Patient 114-0141, a 64-year-old Caucasian woman with metastatic NSCLC, initially diagnosed 11.3 months before enrollment in this study, was randomly assigned to receive ALIMTA at the starting dose of 500 mg/m^2.

The patient had received prior chemotherapy with gemcitabine and paclitaxel (14 cycles) from August 2000 to June 2001 with a best response of PR.

The patient's performance status at the time of enrollment was 1 on the Eastern Cooperative Group (ECOG) scale. Her historical illnesses included tuberculosis, tachyarrhythmia, and removal of malignant melanoma in 1991. Before enrollment, she had reported hypothyroidism, anemia, cough, emphysema, fatigue, low back pain, sensory neuropathy, and shortness of breath. Relevant concomitant medications were famotidine, folic acid, levofloxacin, levothyroxine sodium, lorazepam, estrogen medroxyprogesterone acetate, morphine sulfate, naproxen, paracetamol, paracetamol/hydrocodone, and promethazine.

During Cycle 1, the patient had CTC Grade 3 agitation, nausea, and right upper quadrant pain. At the end of Cycle 1, the patient also had CTC Grade 4 toxicities of hepatic failure, elevated serum glutamic-oxaloacetic transaminase (12260/µL) and increased serum glutamic-pyruvic transaminase (9810/µL), elevated lipase, elevated total bilirubin (2.1 mg/dL), elevated amylase (100/µL), and lethargy. The time of onset of the event in relation to administration on the study drug was 18 days after study drug infusion and for the liver failure 28 days after study drug infusion. In the opinion of the investigator, all events with the exception of agitation, lethargy, and right upper quadrant pain, were related to study drug.

The patient received hydrocodone/acetaminophen, levofloxacin, levothyroxine, famotidine, epoetin alfa, promethazine, diazepam, lorazepam, droperidol, and morphine. The patient required hospitalization for a CTC Grade 2 fever, weakness, and fatigue 16 days after study drug. Fever had started at Day 7, was considered tumor fever and treated with naproxen. The next day the patient appeared jaundiced, labs were drawn showing significantly elevated liver enzymes, which were normal at the time of enrollment. The patient had no liver metastasis. The patient became less responsive and went into lethargy 28 days after study drug and was discharged to home hospice care.

She completed one cycle of therapy. The last dose of ALIMTA was administered on 20 July 2001.

The patient died on study at 15 August 2001. Death was due to hepatic failure. The physician speculated that the hepatic failure was consistent with an acute infective or chemical liver injury leading to hepatic decompensation, but etiology was not clear. Her viral serology results were positive for HB core and HBS antibody, negative for HBS antigen, and Hep A antibody. The timing of the hepatic failure is a little late to be easily contributable to ALIMTA. An autopsy was not performed. In the opinion of the investigator, the death was possibly related to study drug. Survival from start of treatment was 1.1 months.

Patient 406-4122, a 71-year-old Caucasian man with locally advanced NSCLC, initially diagnosed 8.5 months before enrollment in this study, was randomly assigned to receive ALIMTA at the starting dose of 500 mg/m^2.

The patient had received 6 cycles of an adjuvant chemotherapy of paclitaxel (total dose 1216 mg) and carboplatin (total dose 1248 mg) with a best response of PR before study enrollment.

He had received radiotherapy (mediastinum 56 GY) before study enrollment.

The patient's performance status at the time of enrollment was 1 on the Eastern Cooperative Group (ECOG) scale. Before enrollment, he had reported an aortic stenosis in 1996 and a percutan transluminal coronary angioplasty in 1990. Clinically significant baseline conditions were coronary heart disease, hypertension, diabetes mellitus, benign prostate hypertrophy, cough, sputum, pneumonitis, dyspnea, fatigue, and decreased general condition. Relevant concomitant medication: human insulin, glibenclamide, captopril, codeine phosphate, molsidomine, ipratropiumbromide, isosorbide mononitrate, and potassium-sodium-hydrogen citrate.

During Cycle 2, the patient had atrial arrythmia (CTC Grade 3). The investigator believed that this event was not related to study drug administration, but to preexisting cardiac disease. He was hospitalized due to this event. Atrial arrhythmia reduced to CTC Grade 2 from Cycle 3 onwards. During Cycle 6, his general conditions decreased to CTC Grade 3 and he developed a CTC Grade 2 urinary tract infection with fever (CTC Grade 3), for which he was hospitalized. The tumor was reassessed and the patient discontinued study treatment due to disease progression. Five days later, he developed a pneumonia and general sepsis, pneumonia was considered by the investigator as not study drug related, the sepsis as study drug related. However, the Lilly physician considered both the pneumonia and sepsis as unexpected and possibly related to study drug and thus both serious adverse events were classified as reportable. Pneumonia and general sepsis caused his death on 21 May 2002, 5 days after study discontinuation and 26 days after last study drug application. The death was attributed to disease progression and was not related to study drug in the investigator's opinion, however the generalized sepsis was seen as study-drug related by the investigator. Lilly assessment resulted in pneumonia and general sepsis as reason for death to be considered as possibly related to study drug.

He completed six cycles of therapy without dose modification or delays. The last dose of ALIMTA was administered on 25 April 2002. Survival from start of treatment was 4.8 months.

Appendix 5: Treatment-Emergent Adverse Event Tables

Table App.5.1. Summary of Treatment-Emergent Adverse Events by System Organ Class Regardless of Causality Occurring in at Least 10% of Patients in Study JMEI

MedDRA Preferred Term System Organ Class	Alimta (N=265) n (%)	Docetaxel (N=276) n (%)	p-Value
All patients with ≥1 event	259 (97.7)	272 (98.6)	
Blood and lymphatic system disorders			
Patients with ≥1 event	97 (36.6)	172 (62.3)	<0.001
Neutropenia	27 (10.2)	121 (43.8)	<0.001
Anemia	76 (28.7)	71 (25.7)	
Leukopenia	33 (12.5)	93 (33.7)	<0.001
Febrile neutropenia	5 (1.9)	37 (13.4)	<0.001
Thrombocytopenia	24 (9.1)	5 (1.8)	<0.001
Cardiac disorders			
Patients with ≥1 event	32 (12.1)	35 (12.7)	
Cardiac failure	4 (1.5)	3 (1.1)	
Cardiac failure congestive	2 (0.8)	0 (0.0)	
Cardiac arrest	1 (0.4)	0 (0.0)	
Eye disorders			
Patients with ≥1 event	35 (13.2)	20 (7.2)	0.023
Gastrointestinal disorders			
Patients with ≥1 event	179 (67.5)	171 (62.0)	
Nausea	98 (37.0)	59 (21.4)	<0.001
Diarrhea	60 (22.6)	91 (33.0)	0.010
Vomiting	65 (24.5)	48 (17.4)	0.045
Constipation	58 (21.9)	34 (12.3)	0.004
Stomatitis	23 (8.7)	34 (12.3)	
Abdominal pain	21 (7.9)	23 (8.3)	
General disorders and administration site conditions			
Patients with ≥1 event	212 (80.0)	199 (72.1)	0.035
Fatigue	133 (50.2)	115 (41.7)	0.048
Pyrexia	70 (26.4)	58 (21.0)	
Chest pain	43 (16.2)	36 (13.0)	
Asthenia	35 (13.2)	41 (14.9)	
Mucosal inflammation	19 (7.2)	21 (7.6)	
Edema	14 (5.3)	23 (8.3)	
Hepatobiliary disorders			
Hepatic failure	1 (0.4)	0 (0.0)	
Immune system disorders			
Hypersensitivity	3 (1.1)	5 (1.8)	
Infections and infestations			
Patients with ≥1 event	77 (29.1)	78 (28.3)	
Sepsis	1 (0.4)	5 (1.8)	

(continued)

Table App.5.1. Summary of Treatment-Emergent Adverse Events by System Organ Class Regardless of Causality Occurring in at Least 10% of Patients in Study JMEI (concluded)

MedDRA Preferred Term System Organ Class	Alimta (N=265) n (%)	Docetaxel (N=276) n (%)	p-Value
Investigations			
Patients with ≥1 event	76 (28.7)	44 (15.9)	<0.001
Weight decreased	22 (8.3)	20 (7.2)	
Alanine aminotransferase increased	23 (8.7%)	6 (2.2)	<0.001
Aspartate aminotransferase increased	20 (7.5)	3 (1.1)	<0.001
Creatinine renal clearance decreased	12 (4.5)	1 (0.4)	0.001
Blood creatinine increased	6 (2.3)	1 (0.4)	0.064
Blood urea increased	1 (0.4)	2 (0.7)	
Metabolism and nutrition disorders			
Patients with ≥1 event	127 (47.9)	116 (42.0)	
Anorexia	106 (40.0)	92 (33.3)	
Metabolic acidosis	1 (0.4)	1 (0.4)	
Musculoskeletal and connective tissue disorders			
Patients with ≥1 event	84 (31.7)	106 (38.4)	
Myalgia	23 (8.7)	42 (15.2)	0.024
Arthralgia	19 (7.2)	36 (13.0)	0.032
Nervous system disorders			
Patients with ≥1 event	86 (32.5)	106 (38.4)	
Headache	28 (10.6)	30 (10.9)	
Neurotoxicity	2 (0.8)	10 (3.6)	0.037
Psychiatric disorders			
Patients with >= 1 event	58 (21.9)	63 (22.8)	
Insomnia	35 (13.2)	35 (12.7)	
Renal and urinary disorders			
Renal failure	2 (0.8)	0 (0.0)	
Respiratory, thoracic, and mediastinal disorders			
Patients with ≥1 event	177 (66.8)	173 (62.7)	
Dyspnea	83 (31.3)	97 (35.1)	
Cough	72 (27.2)	65 (23.6)	
Hemoptysis	32 (12.1)	28 (10.1)	
Skin and subcutaneous tissue disorders			
Patients with ≥1 event	107 (40.4)	134 (48.6)	0.058
Alopecia	19 (7.2)	108 (39.1)	<0.001
Rash	37 (14.0)	19 (6.9)	0.007
Erythema	3 (1.1)	8 (2.9)	

Abbreviations: MedDRA = Medical Dictionary for Regulatory Authorities; n = number of patients with the specified treatment-emergent adverse event; N = number of randomized and treated patients.

Table App.5.2. Summary of Study Drug-Related Treatment-Emergent Adverse Events by System Organ Class Occurring in at Least 10% of Patients in Study JMEI

MedDRA Preferred Term System Organ Class	Alimta (N=265) n (%)	Docetaxel (N=276) n (%)	p-Value
All patients with ≥1 event	207 (78.1)	237 (85.9)	0.025
Blood and lymphatic system disorders			
Patients with ≥1 event	69 (26.0)	163 (59.1)	<0.001
Neutropenia	27 (10.2)	121 (43.8)	<0.001
Leukopenia	32 (12.1)	93 (33.7)	<0.001
Anemia	48 (18.1)	58 (21.0)	
Febrile neutropenia	5 (1.9)	37 (13.4)	<0.001
Thrombocytopenia	23 (8.7)	3 (1.1)	<0.001
Gastrointestinal disorders			
Patients with ≥1 event	121 (45.7)	120 (43.5)	
Nausea	80 (30.2)	41 (14.9)	<0.001
Diarrhea	34 (12.8)	65 (23.6)	0.001
Vomiting	43 (16.2)	32 (11.6)	
Stomatitis	19 (7.2)	30 (10.9)	
Constipation	15 (5.7)	11 (4.0)	
Abdominal pain	6 (2.3)	8 (2.9)	
General disorders and administration site conditions			
Patients with ≥1 event	114 (43.0)	117 (42.4)	
Fatigue	65 (24.5)	66 (23.9)	
Pyrexia	22 (8.3)	23 (8.3)	
Asthenia	17 (6.4)	27 (9.8)	
Mucosal inflammation	16 (6.0)	19 (6.9)	
Edema	4 (1.5)	10 (3.6)	
Chest pain	2 (0.8)	2 (0.7)	
Hepatobiliary disorders			
Hepatic failure	1 (0.4)	0 (0.0)	
Immune system disorders			
Hypersensitivity	2 (0.8)	4 (1.4)	
Infections and infestations			
Sepsis	1 (0.4)	3 (1.1)	
Investigations			
Alanine aminotransferase increased	20 (7.5)	4 (1.4)	<0.001
Aspartate aminotransferase increased	18 (6.8)	2 (0.7)	<0.001
Weight decreased	3 (1.1)	5 (1.8)	
Creatinine renal clearance decreased	6 (2.3)	1 (0.4)	0.064
Blood creatinine increased	5 (1.9)	0 (0.0)	0.028
Metabolism and nutrition disorders			
Patients with ≥1 event	60 (22.6)	67 (24.3)	
Anorexia	54 (20.4)	57 (20.7)	
Musculoskeletal and connective tissue disorders			
Patients with ≥1 event	18 (6.8)	50 (18.1)	<0.001

(continued)

Table App.5.2. Study Drug-Related Treatment-Emergent Adverse Events by System Organ Class Occurring in at Least 10% of Patients in Study JMEI (concluded)

MedDRA Preferred Term System Organ Class	Alimta (N=265) n (%)	Docetaxel (N=276) n (%)	p-Value
Nervous system disorders			
Patients with ≥1 event	31 (11.7)	63 (22.8)	<0.001
Neurotoxicity	2 (0.8)	10 (3.6)	0.037
Headache	6 (2.3)	4 (1.4)	
Renal and urinary disorders			
Renal failure	1 (0.4)	0 (0.0)	
Respiratory, thoracic and mediastinal disorders			
Dyspnea	3 (1.1)	10 (3.6)	0.089
Cough	2 (0.8)	1 (0.4)	
Skin and subcutaneous tissue disorders			
Patients with ≥1 event	74 (27.9)	121 (43.8)	<0.001
Alopecia	14 (5.3)	106 (38.4)	<0.001
Rash	32 (12.1)	15 (5.4)	0.009
Erythema	2 (0.8)	8 (2.9)	

Abbreviations: MedDRA = Medical Dictionary for Regulatory Authorities; n = number of patients with the specified treatment-emergent adverse event; N = number of randomized and treated patients.

Appendix 6: Publications

Study	Publication
JMEI	Hanna et al. 2002
JMBR	Smit et al. 2003
JMAL	Clarke et al. 2002
JMAN	Rusthoven et al. 1999
JMAY	Manegold et al. 2000
JMBZ	Shepherd et al. 2001
JMEK	Scagliotti et al. 2003

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ORIGINAL REPORT

Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients With Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy

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ABSTRACT

Purpose
To compare the efficacy and toxicity of pemetrexed versus docetaxel in patients with advanced non–small-cell lung cancer (NSCLC) previously treated with chemotherapy.

Patients and Methods
Eligible patients had a performance status 0 to 2, previous treatment with one prior chemotherapy regimen for advanced NSCLC, and adequate organ function. Patients received pemetrexed 500 mg/m^2 intravenously (IV) day 1 with vitamin B_{12}, folic acid, and dexamethasone or docetaxel 75 mg/m^2 IV day 1 with dexamethasone every 21 days. The primary end point was overall survival.

Results
Five hundred seventy-one patients were randomly assigned. Overall response rates were 9.1% and 8.8% (analysis of variance $P = .105$) for pemetrexed and docetaxel, respectively. Median progression-free survival was 2.9 months for each arm, and median survival time was 8.3 versus 7.9 months (P = not significant) for pemetrexed and docetaxel, respectively. The 1-year survival rate for each arm was 29.7%. Patients receiving docetaxel were more likely to have grade 3 or 4 neutropenia (40.2% *v* 5.3%, $P < .001$), febrile neutropenia (12.7% *v* 1.9%; $P < .001$), neutropenia with infections (3.3% *v* 0.0%; $P = .004$), hospitalizations for neutropenic fever (13.4% *v* 1.5%; $P < .001$), hospitalizations due to other drug related adverse events (10.5% *v* 6.4%; $P = .092$), use of granulocyte colony-stimulating factor support (19.2% *v* 2.6%, $P < .001$) and all grade alopecia (37.7% *v* 6.4%; $P < .001$) compared with patients receiving pemetrexed.

Conclusion
Treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects compared with docetaxel in the second-line treatment of patients with advanced NSCLC and should be considered a standard treatment option for second-line NSCLC when available

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INTRODUCTION

Lung cancer is the most common cancer in the world today (12.3% of all new cases), with an estimated 1.2 million new cases and 1.1 million deaths (17.8% of all cancer deaths) worldwide in 2000.[1] Non–small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer. For chemotherapy-naïve patients with a good performance status (PS) and stage IIIb (with pleural effusion) or IV disease, platinum-based chemotherapy offers a modest survival advantage over best supportive care (BSC) alone.[2-4]

Docetaxel (Taxotere; Aventis Pharmaceuticals, Bridgewater, NJ) is currently the only US Food and Drug Administration and European Agency for the Evaluation of Medical Products–approved chemotherapy agent for the second-line treatment of advanced NSCLC. The approval was based on phase III studies by Shepherd et al[5] and Fossella et al.[6] For patients with a good PS at the

time of disease progression following first-line chemotherapy, docetaxel, despite a low response rate, is associated with a 10% to 20% prolongation of 1-year survival and an improved quality of life when compared with ifosfamide, vinorelbine, or BSC alone.[5,6] In view of these modest results, new agents with single-agent activity are greatly needed for this patient population.

Pemetrexed (Alimta, Eli Lilly and Company, Indianapolis, IN) is a novel, multitargeted antifolate chemotherapy agent that is active in multiple tumor types including NSCLC.[7-10] Its primary mechanism of action is to inhibit the enzyme thymidylate synthase, resulting in decreased thymidine necessary for pyrimidine synthesis. Pemetrexed also inhibits dihydrofolate reductase and glycinamide ribonucleotide formyl transferase, the latter of which is a folate-dependent enzyme involved in purine synthesis. Phase II studies of pemetrexed in previously untreated patients with NSCLC have demonstrated single agent response rates of 17% to 23%.[7,8] A phase II study of pemetrexed in patients with advanced NSCLC, who had progressed during or within 3 months of completing first-line chemotherapy, demonstrated a response rate of 8.9% and median survival time of 5.7 months.[9]

Folate and vitamin B_{12} nutritional status affects the toxicity of pemetrexed, including rates of neutropenic fever. Treatment with pemetrexed without vitamin supplementation results in a significantly higher incidence of hematologic and nonhematologic toxicity.[10-12] Therefore, supplementation with folic acid at 350-1,000 μg orally daily and vitamin B_{12} 1,000 μg IM every 9 weeks is essential to control the toxicity of pemetrexed. Bunn et al reported that in a multistudy single-agent database of 246 patients treated with pemetrexed, 5.0% versus 0% had drug-related deaths, 32.0% versus 2.6% had grade 4 neutropenia, and 37.0% versus 6.4% had any grade 4 hematologic or grade 3 or 4 nonhematologic toxicity, without and with vitamin supplementation, respectively.[12] Based on the similar efficacy observed between pemetrexed and docetaxel in separate trials and the expected lower toxicity rates with pemetrexed, a multinational phase III study comparing these two agents in the second-line treatment of NSCLC was undertaken.

PATIENTS AND METHODS

Patients with histologic or cytologic confirmation of NSCLC with stage III or IV disease not amenable to curative therapy were assessed for eligibility. Eligible patients met the following criteria: treatment with only one prior chemotherapy regimen for advanced disease (one additional prior regimen was allowed for neoadjuvant, adjuvant, or neoadjuvant plus adjuvant therapy); measurable or evaluable disease; an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2; and adequate bone marrow, renal, and hepatic function. Patients with prior docetaxel or pemetrexed treatment, Common Toxicity Criteria (CTC) $\geq$ grade 3 peripheral neuropathy, an inability to interrupt nonsteroidal anti-inflammatory drugs, uncontrolled pleural effusions, symptomatic or uncontrolled brain metastases, or significant weight loss ($\geq$ 10% body weight in the preceding 6 weeks) were ineligible. The protocol was approved through institutional ethics review boards, and all patients provided written informed consent before treatment.

Treatment Plan

Eligible patients were randomly assigned to receive either pemetrexed or docetaxel. Patient randomization was stratified for PS (0 or 1 *v* 2), prior platinum or paclitaxel use, number of prior chemotherapy regimens (1 or 2), time since last chemotherapy (<3 *v* ≥ 3 months), best response to last chemotherapy (objective tumor response/stable disease versus progressive disease/unknown), stage (III *v* IV), baseline plasma homocysteine level (<12 μmol/L *v* ≥ 12 μmol/L), and center. Patients received either 500 mg/m^2 pemetrexed as a 10-minute intravenous infusion or 75 mg/m^2 docetaxel as a 1-hour intravenous infusion on day 1 of a 21-day cycle. Cycles were repeated until disease progression, unacceptable toxicity, or until the patient or the investigator requested therapy discontinuation. Patients on the pemetrexed arm were instructed to take folic acid 350-1,000 μg (or an equivalent) orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. A 1,000 μg vitamin B_{12} injection was administered intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and was repeated approximately every 9 weeks until after discontinuation. Folic acid and vitamin B_{12} were given because of their ability to reduce toxicities without affecting the efficacy of pemetrexed.[11] Patients on the pemetrexed arm were instructed to take dexamethasone (4 mg orally twice daily the day before, the day of, and the day after pemetrexed) as a prophylactic measure against skin rash. Patients on the docetaxel arm were instructed to take dexamethasone (8 mg orally twice daily the day before, the day of, and the day after docetaxel), but were not required to take vitamin supplementation. A maximum of two dose reductions were allowed based on nadir counts or clinically significant nonhematologic toxicities and dose delays up to 42 days from day 1 of the current cycle were permitted for recovery from adverse events. Granulocyte colony-stimulating factor support was allowed to treat a neutropenic event or as prophylaxis in a patient who had experienced a neutropenic event with a previous cycle.

The baseline assessment included a history and physical examination, complete blood count, comprehensive blood chemistries, calculated creatinine clearance, vitamin metabolite panel, chest x-ray and computed tomorgraphy scan of the chest and the upper abdomen. Bone scans and brain imaging were performed only if clinically indicated. The Lung Cancer Symptom Scale (LCSS) was administered at baseline and weekly during the study. The observer LCSS was administered at baseline and at the end of each cycle.[13] Toxicity evaluations were based on the National Cancer Institute CTC, version 2. Hematologic laboratory values and folic acid compliance (pemetrexed arm only) were evaluated weekly. Chemistry laboratory values were evaluated following days one and eight of each cycle. Tumor measurements were assessed after every two cycles.

Statistical Analysis

The primary objective of the study was to compare overall survival between the two treatment groups on an intent-to-treat basis. Secondary objectives were to compare toxicities (including use of concomitant supportive measures), objective response rates

(RR), progression-free survival (PFS), time to progressive disease (TPD), time to treatment failure (TTF), time to response, duration of response, and quality-of-life measurements (using the LCSS) between the treatment groups.

Unless otherwise noted, all tests of hypotheses were conducted at the $\alpha = 0.05$ level, with a 95% CI. Cox proportional hazard models were used to compare the overall survival time and other time-to-event end points between the treatment arms; Kaplan-Meier estimates were used to assess the median time-to-event parameters, except for time-to-response using analysis of variance. The study was designed to have an 81% chance of demonstrating noninferiority for survival time (defined as pemetrexed arm $\leq$ 10% worse than docetaxel arm) for pemetrexed when compared to docetaxel using the true hazard ratio (HR) to be 0.83. This translated to an upper bound of the 95% CI less than 1.11 for the HR of pemetrexed over docetaxel. In addition, the hypothesis that pemetrexed retained $\geq$ 50% of the survival benefit of docetaxel over BSC using data from the randomized comparative trial of docetaxel versus BSC by Shepherd et al[5] was prospectively planned (percent retention method).[14] In the trial reported by Shepherd et al, the HR of docetaxel over BSC was estimated to be 0.56 (95% CI, 0.35 to 0.88). Setting the percentage of historical benefit at 50% and maintaining an approximate one-sided 2.5% type I error, an upper 95% CI bound of less than 1.21 for the HR of pemetrexed over docetaxel was required to establish the noninferiority of pemetrexed.

Tumor response was compared using the Fisher's exact test with 95% CI calculated using the method of Leemis and Trivedi.[15] A Cox proportional multiple regression (CMR) model was developed with an interactive stepwise regression to identify the potential factors as predictors of survival independent of therapy. A final model was fitted on the survival, including therapy in the model to estimate the treatment effect adjusting for these factors. The incidence of CTC toxicities, adverse events, concomitant medications used, and hospitalizations were analyzed using Fisher's exact test. Distribution of changes from baseline in the average symptom burden index (ASBI) of the patient LCSS, and individual symptoms of the observer LCSS, were compared with the Mental-Haenszel χ^2 test.[16]

The overall survival time was defined as the time from the date of randomization to date of death due to any cause. Patients who were alive on the date of last follow-up were censored on that date. PFS was the time from randomization until documented progression or death from any cause and was censored at the date of the last follow-up visit for patients who were still alive and who had not progressed. TPD was defined as the time from the date of randomization to the first date of documented disease progression and was censored at the date of death for patients who died without documented disease progression or the date of the last follow-up visit for patients who were still alive and who had not progressed. TTF was defined as the time from randomization to the date of progression of disease, discontinuation of treatment, or death due to any cause and was censored at the date of the last follow-up visit for patients who did not discontinue, who were still alive, and who did not have disease progression. Tumor response was assessed using the Southwest Oncology Group criteria[17] and required confirmation at least 4 weeks after initial response (Complete response [CR] defined as complete disappearance of all measurable and evaluable disease; partial response [PR] defined as $\geq$ 50% decrease in the sum of products of perpendicular diameters of all measurable lesions; progressive disease [PD] defined as 50% increase in the sum of products of all measurable lesions, or worsening of evaluable disease, or appearance of any new lesions; and stable disease [SD] defined as not qualifying for CR, PR, or PD). Duration of tumor response was defined as the time from the date of the first objective status assessment of CR or PR until the first date of documented disease progression or death due to any cause and was censored at the date of the last follow-up visit for tumor responders who were still alive and who had not progressed. Duration of clinical benefit (CR/PR/SD) was defined as the time from the date of randomization to the first date of documented disease progression or death due to any cause for patients who had a best overall tumor response better than progressive disease and was censored at the date of the last follow-up visit for those patients who were still alive and had not progressed.

For each patient, LCSS scores were rated as improved, stable, or worsened based on comparison with baseline. The average symptom burden index (ASBI) was the average of the six symptom-specific questions regarding anorexia, fatigue, cough, dyspnea, hemoptysis, and pain.[13] Meaningful change for the ASBI was defined as at least half of the SD of the baseline ASBI for all patients that was maintained for at least 4 consecutive weeks.[18] Meaningful change for observer LCSS scales was defined as at least a one-point change on the five-point scale that was maintained for at least two cycles. Changes in LCSS scores that could not be confirmed were classified as unknown.

RESULTS

From March 2001 through February 2002, 571 patients were randomly assigned to receive either pemetrexed or docetaxel. Two hundred sixty-five of 283 patients randomly assigned to pemetrexed received at least one cycle of therapy (18 patients received no treatment due to: failure to meet inclusion criteria [n = 7], death from disease [n = 5], other adverse events [n = 3], personal conflict [n = 2], or protocol violation [n = 1]). Two hundred seventy-six of 288 patients randomly assigned to docetaxel received at least one cycle of therapy (12 patients received no treatment due to failure to meet inclusion criteria [n = 2], death from disease or other cause [n = 2], personal conflict [n = 5], loss to follow-up [n = 3].) At the time of analysis, 409 (71.6%) of 571 patients had died. The median follow-up for all patients was 7.5 months, and the clinical data were collected up to January 30, 2003. The baseline patient and disease characteristics are listed in Table 1.

The two arms were well balanced for all demographic and stratification factors. All 571 randomly assigned patients were assessable for survival, and 538 of 541 patients (n = 265 for pemetrexed, 276 for docetaxel) who received therapy were assessable for response. One pemetrexed and two docetaxel patients were randomly assigned and received at least one cycle of therapy but did not meet the protocol required criteria for response evaluation.

Treatment Administered

The median number of cycles of chemotherapy administered was four in each group, with a range of one to 20 and

Table 1. Baseline Patient and Disease Characteristics

Characteristic	% of Patients: Pemetrexed Group (n = 283)	Docetaxel Group (n = 288)
Sex		
Male	68.6	75.3
Female	31.4	24.7
Age, years		
Median	59	57
Range	22-81	28-87
Performance status		
0 or 1	88.6	87.6
2	11.4	12.4
Stage IV	74.9	74.7
Prior platinum	92.6	89.9
CR/PR to prior platinum	34.7	37.5
Prior paclitaxel	25.8	27.8
CR/PR to prior paclitaxel	39.7	35.0
Best response, any prior chemotherapy		
CR/PR	35.7	36.5
SD	37.5	32.3
PD/unknown or not evaluable	26.9	31.3
Time since last chemotherapy		
< 3 months	50.4	48.1
Histology		
Adenocarcinoma	54.4	49.3
Squamous cell carcinoma	27.6	32.3
Homocysteine levels		
< 12 μmol/L	7.4	68.9
Prior radiation	44.2	45.5

Abbreviations: CR, complete response, PR, partial response, SD, stable disease, PD, progressive disease

one to14 for patients receiving pemetrexed and docetaxel, respectively. Patients received 96.6% and 94.4% of the planned dose-intensity of pemetrexed and docetaxel, respectively (P = not significant).

Efficacy

There was no significant difference in overall RR (9.1% *v* 8.8%) or SD rates (45.8% *v* 46.4%) between the pemetrexed and docetaxel arms, respectively. The RR to second-line treatment in patients with a CR or PR, SD, and PD to first-line therapy was 11.1%, 10.2%, and 4.6%, respectively, and the SD rate to second-line treatment in patients with a CR or PR, SD, and PD to first-line therapy was 47.0%, 50.0%, and 40.3% respectively.

Paclitaxel sensitivity and resistance in first-line treatment did not predict for a difference in response between pemetrexed and docetaxel in second-line treatment (P = not significant). Patients who achieved a CR or PR with first-line paclitaxel (n = 54) had a 7.1% versus 3.9% RR to pemetrexed and docetaxel, respectively (SD rates were 32.1% *v* 30.8%). Patients with SD following first-line paclitaxel (n = 55) had an RR of 3.8% versus 6.9% for pemetrexed and docetaxel, respectively (SD rates were 50.0% *v* 51.7%) and patients with PD (or unknown response) with first-line paclitaxel (n = 44) had an RR of 5.3% versus 4.0% for pemetrexed and docetaxel, respectively (SD rates 42.1% *v* 48.0%).

There were no significant differences in PFS (Fig 1, Table 2), TPD and TTF (Table 2). There was also no significant difference in median time to response, median duration of response, and median duration of clinical benefit (Table 2). On an intent-to-treat basis, the median survival time for pemetrexed was 8.3 months versus 7.9 for docetaxel (HR, 0.99; 95% CI, 0.82 to 1.2; noninferiority P = .226; Fig 2). Using the percent retention method, the estimate of the percentage of survival benefit (of docetaxel over BSC) retained by pemetrexed was 102% with the lower 95% CI bound of 52% and was statistically significant (P = .047). The 1-year overall survival rate for each arm was 29.7%.

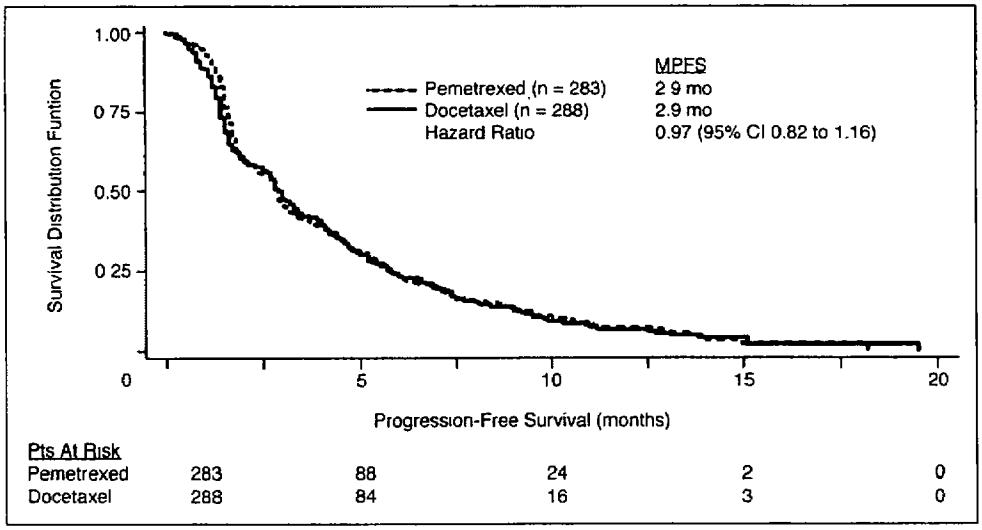

Fig 1. Median progression-free survival (MPFS). Pts, patients Mo, months.

Table 2. Summary of Time-To Event-Variables (ITT)

Variable	Pemetrexed Group* (n = 283)	Docetaxel Group (n = 288)	HR	95% CI	P
Progression-free survival			0.97	0.82 to 1.16	.759‡
Median, months†	2.9	2.9			
Range, months	0-18.2	0-19.5			
Patients censored, %	6.4	10.4			
Time-to-progression			0.97	0.80 to 1.17	.721‡
Median, months†	3.4	3.5			
Range, months	0.5-18.2	0.3-19.5			
Patients censored, %	24.7	27.8			
Time-to-treatment failure			0.84	0.71 to 0.997	.046‡
Median, months†	2.3	2.1			
Range, months†	0.0-18.2	0.0-13.1			
Patients censored, %	1.4	1.7			
Duration of response			0.77	0.40 to 1.47	.427‡
Median, months†	4.6	5.3			
Range, months†	2.1-15.3	1.7-11.7			
Patients censored, %	25.0	16.7			
Duration of clinical benefit			0.91	0.71 to 1.16	.450‡
Median, months†	5.4	5.2			
Range, months†	1.2-18.2	1.5-14.6			
Patients censored, %	10.3	13.9			
Time-to-response			NA	NA	.105§
Median, months	1.7	2.9			
Range, months	1.2-4.3	1.4-7.8			

Abbreviations: ITT, intent-to-treat; HR, hazard ratio, NA, not assessable
*Pemetrexed (n = 282) in time-to-treatment failure analysis
†Median time-to-event value calculated using Kaplan-Meier method
‡Comparison of hazard ratio between treatment arms using the Cox Proportional Hazard model
§Analysis of variance *P* value.

Approximately 41.9% of all randomly assigned patients (46.6% and 37.2% of patients on the pemetrexed and docetaxel arms, respectively) received additional anticancer drug therapy after going off-study. Approximately 31.8% of patients randomly assigned to the pemetrexed arm eventually received docetaxel off-protocol. The median survival was 9.5 months for this group and 11.2 months for patients on the docetaxel treatment arm that received any other poststudy chemotherapy. Only 1.8% of all patients received gefitinib (Iressa; AstraZeneca UK Limited, Cheshire, UK) poststudy.

Multiple Regression Analysis

CMR analysis was performed on 532 patients to identify additional factors that affected survival and to estimate

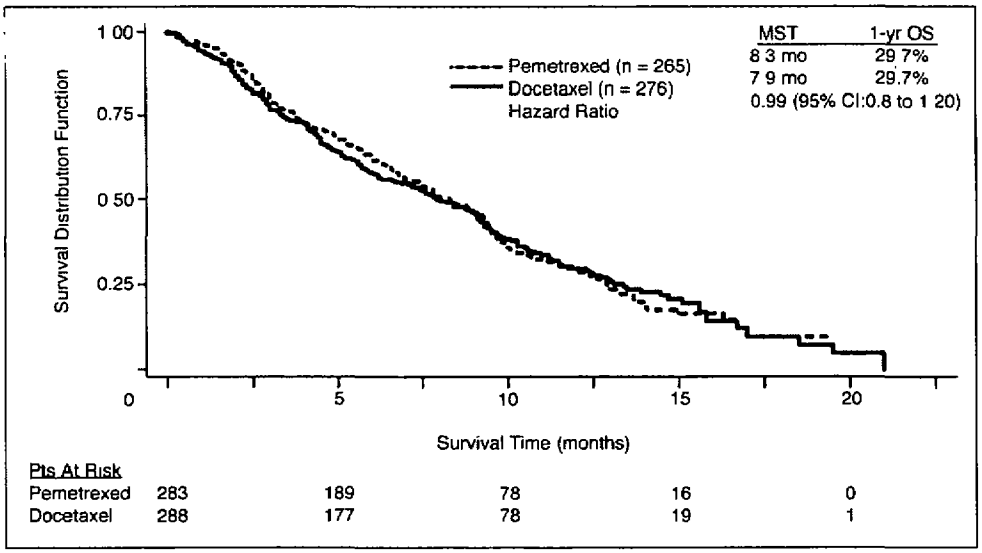

Fig 2. Median survival time (MST) Mo, months, yr, year, Pts, patients

Table 3. Cox Model Subgroup Analysis of Variables Associated With Improved Survival

Variable	Pemetrexed Survival (months)	Docetaxel Survival (months)	P*
Performance status			
0 or 1	9.4	9.1	.996
2	3.6	2.2	.264
Stage			
III	9.3	10.3	.948
IV	7.9	7.2	.896
Time since last chemotherapy			
< 3 months	7.0	6.2	.670
≥ 3 months	9.3	9.2	.588
Effect of treatment adjusted for prognostic factors	—	—	.051†

*Comparison between treatment arms using Cox Proportional Hazard model.
†Effect of treatment adjusted for prognostic factors *P* value is based on non-inferiority model

the treatment effect adjusting for these factors. The CMR analysis showed that pemetrexed and docetaxel achieved similar survival after adjusting for all baseline factors. The factors significantly associated with increased survival were: PS 0 or 1 (HR, 0.25; 95% CI, 0.19 to 0.34; $P < .001$), stage III disease (HR, 0.77; 95% CI, 0.60 to 0.97; $P = .026$), and longer time since last chemotherapy (HR, 0.74; 95% CI, 0.60-0.97; $P = .004$). Similar survival was seen between treatment groups after adjusting for each of these factors (HR, 0.93; 95% CI, 0.76-1.13; noninferiority $P = .051$; Table 3).

Quality of Life Analysis

Overall, 474 patients (pemetrexed, n = 227; docetaxel, n = 247) were assessable for the ASBI analysis of the patient LCSS. There was no significant difference in the distribution of numbers of patients reporting changes in the ASBI between the two arms of the study (Table 4). Overall, 472 patients (pemetrexed, n = 239; docetaxel, n = 233) were evaluable for observer LCSS analysis. Patients on both arms were rated with similar rates of improvement or stabilization of anorexia (55.6% *v* 60.9%), fatigue (54.8% *v* 56.7%), cough (63.6% *v* 64.4%), dyspnea (63.6% *v* 59.9%), hemoptysis (70.3% *v* 73.2%) and pain (64.0% *v* 62.1%).

Toxicity

All treated patients (n = 541) were assessable for toxicity. Hematological toxicity and hospitalizations, growth factor and transfusion needs are summarized in Tables 5 and 6 and nonhematologic toxicity is summarized in Table 7. Treatment-related deaths were attributed to docetaxel and pemetrexed in 5 and 3 patients, respectively. Patients receiving docetaxel experienced significantly higher rates of neutropenia, neutropenic fever, infections and hospitalization due to neutropenic events compared to patients receiving pemetrexed. In addition, more patients on the docetaxel arm required hospitalization due to other drug-related adverse events (excluding neutropenic complications) compared to those on the pemetrexed arm (10.5% versus 6.4%, $P = .092$). In addition, the use of granulocyte colony-stimulating factors (G-CSFs) was substantially increased for patients receiving docetaxel when compared to pemetrexed. Only 4 patients in the docetaxel arm and 1 patient in the pemetrexed arm received G-CSF as prophylaxis without a prior event of neutropenia. The remaining patients used G-CSF during treatment of neutropenia (n = 49 in the docetaxel arm; n = 5 in the pemetrexed arm) or as prophylaxis for subsequent cycles following an episode of neutropenia. There were no statistically significant differences in the

Table 4. Rates of Change in Average Symptom Burden Index of the Patient Lung Cancer Symptom Scale

	% of Pemetrexed (n = 227) Patients	% of Docetaxel (n = 247) Patients	P*
Improved	21.2	21.5	
Worsened	33.0	27.9	.1447
Stable	29.5	24.7	
Unknown	16.3	25.9	

NOTE The Average Symptom Burden Index is the average of the six symptom-specific questions from the patient Lung Cancer Symptom Scale regarding anorexia, fatigue, cough, dyspnea, hemoptysis, and pain
*Mantel-Haenszel χ^2 test was used to evaluate any treatment differences over all categories (improved, worsened, stable, unknown).

Table 5. Grade 3 and 4 Hematologic Toxicities

	% of Pemetrexed Patients (n = 265)	% of Docetaxel Patients (n = 276)	P*
Neutropenia	5.3	40.2	< .001
Febrile Neutropenia	1.9	12.7	< .001
Neutropenia with infection	0.0	3.3	.004
Anemia	4.2	4.3	.99
Thrombocytopenia	1.9	0.4	.116

NOTE Toxicities graded using the National Cancer Institute Common Toxicity Criteria version 2.
*Fisher's exact test

Table 6. Hospitalizations and Supportive Care

	% of Pemetrexed Patients (n = 265)	% of Docetaxel Patients (n = 276)	P*
≥ 1 hospitalization for neutropenic fever†	1.5	13.4	< .001
≥ 1 hospitalization for any other drug-related adverse event	6.4	10.5	.092
G-CSF/GM-CSF	2.6	19.2	< .001
Erythropoietin	6.8	10.1	.169
RBC transfusions	16.6	11.6	.1078

Abbreviations. G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.
*Fisher's exact test.
†Pemetrexed treated patients were hospitalized for neutropenic fever a total of 29 days; docetaxel treated patients were hospitalized for neutropenic fever a total of 195 days

incidences of thrombocytopenia, anemia, RBC transfusions, or use of erythropoietin between the treatment groups. There was a significantly higher rate of alopecia for patients receiving docetaxel and a slightly greater incidence of rise in ALT for patients receiving pemetrexed.

DISCUSSION

This is the largest phase III study ever reported for the second-line treatment of advanced NSCLC. In our study, response and clinical benefit rates (CR/PR/SD) were similar in patients receiving either pemetrexed or docetaxel. Patients who had a clinical benefit with first-line chemotherapy were more likely to have clinical benefit with second-line therapy on this trial. Patients with stage III disease (*v* stage IV disease), PS 0 or 1 (*v* 2), or were ≥ 3 months (*v* < 3 months) since last their chemotherapy benefited more with second-line chemotherapy on this trial. All efficacy end points, including overall survival time (median 8.3 versus 7.9 months) and 1-year percent survival (29.7%), were clinically comparable between treatment arms.

The patients receiving docetaxel in the current study performed as well as (or in some categories better than) the patients receiving docetaxel on the phase III studies reported by Shepherd et al[5] and Fossella et al.[6] The RR to docetaxel at 75 mg/m^2 on all three studies was 6.7% to 8.8% and the SD rate was 36% to 46%. The median survival time for docetaxel was 5.7 months in the Fossella et al study, 7.5 months in the Shepherd et al study, and 7.9 months in this study.

The design and patient characteristics of this trial have similarities, but also important distinctions from the trials previously reported by Shepherd et al and Fossella et al. Each study evaluated patients who had previously received chemotherapy for advanced NSCLC, required an ECOG PS 0 to 2, and excluded patients with symptomatic brain metastases. However, only the current study limited patients to one prior chemotherapy regimen for advanced disease (25% to 35% of patients on the other trials had received > one prior regimen for metastatic disease), did not require prior platinum (although 95% of patients had received platinum) and excluded patients with uncontrolled pleural effusions and significant weight loss. The study by

Table 7. Nonhematologic Toxicities

	Pemetrexed (n = 265)		Docetaxel (n = 276)		
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	P*
Fatigue	34.0	5.3	35.9	5.4	.99
Nausea	30.9	2.6	16.7	1.8	.57
Vomiting	16.2	1.5	12.0	1.1	.72
Pulmonary	0.8	0.0	2.1	1.4	NA†
Neurosensory	4.9	0.0	15.9	1.1	NA†
Stomatitis	14.7	1.1	17.4	1.1	.99
Alopecia	6.4	1.1	37.7	3.6	< .001
Diarrhea	12.8	0.4	24.3	2.5	.069
Rash	14.0	0.8	6.2	0.7	1.00
Weight loss	1.1	0.0	1.8	0.0	NA
Edema	4.5	0.0	8.3	0.0	NA
ALT	7.9	1.9	1.4	0.0	.028

Abbreviation. NA, not applicable
*Fisher's exact test used, comparison is between grade 3 and 4 toxicities except for alopecia
†*P* value not calculated due to small number of patients (< 4 when arms combined) experiencing grade 3 or 4 toxicity.

Shepherd et al did not allow prior paclitaxel, while 42% of patients (on the 75 mg/m^2 arm of docetaxel) had received paclitaxel on the Fossella et al study as did 25% in this study. Prior treatment with paclitaxel did not seem to reduce efficacy to any of the agents under study in either of the trials. PS 2 patients made up approximately 24% and 18% of those treated with docetaxel in the Shepherd et al and Fossella et al studies. Approximately 12% on each arm in this study had a PS of 2. Otherwise, the patient characteristics were similar on all three studies (sex, age, stage, % with PD to first-line therapy). Patients on this study and the Fossella et al study did not routinely receive G-CSF as prophylaxis, unless the patient had already experienced a neutropenic event with a previous cycle, but rather only as treatment for toxicity. Therefore, the high rates of use of G-CSF on the docetaxel arm of the current study cannot be attributed to the routine use of G-CSF for prophylaxis.

Although there was clinically equivalent efficacy demonstrated between the two agents in this study, there were several clinically and statistically significant differences in their toxicity profiles. There were higher rates of neutropenia (with and without complications) and more frequent use of G-CSF for patients on the docetaxel arm when compared to the pemetrexed arm. The rate of grade 3 or 4 neutropenia due to docetaxel in our study was 40.2%, which is significantly lower than the rates of neutropenia reported with the 75 mg/m^2 docetaxel arms of the studies by Shepherd et al (67.3%) and Fossella et al (> 54%). The rate of neutropenic fever due to docetaxel in our study was 12.7%, which is also comparable to that observed in the combined docetaxel arms in the Shepherd et al (11.5%) and Fossella et al studies (10%). When considering only the 75 mg/m^2 arms of those studies, however, the rate of neutropenic fever was lower in the Shepherd et al study (1.8%) and Fossella et al study (8%) when compared with our study, despite a significantly higher percentage of patients at risk. Pemetrexed treated patients experienced significantly fewer hospitalizations for neutropenic fever. Rates of infection with docetaxel were also comparable between the three studies (approximately 3% in the combined docetaxel arms). The higher rate of neutropenic complications with docetaxel in this study is not related to the duration of treatment given (median 3 to 4 cycles on each study), patient characteristics—the Shepherd et al study had more PS 2 patients, and they were more heavily pretreated with chemotherapy in that 25% were receiving docetaxel as third-line or greater—or use of prophylactic G-CSF without a preceding neutropenic event. In addition, the rates of other hematologic toxicities (anemia and thrombocytopenia) were comparable among the three studies.

In this study, patients treated with pemetrexed had a significantly lower rate of alopecia ($P < .001$) and a trend toward lower rates of grade 3 or 4 diarrhea ($P = .069$) compared with patients receiving docetaxel. An increase in ALT was the only toxicity that was higher in the pemetrexed arm ($P = .028$). Overall, the rates of improvement or stabilization of baseline symptoms were similar between the two arms ($P = .145$).

In conclusion, treatment with pemetrexed demonstrated clinically equivalent efficacy with a significantly improved safety profile compared with those receiving docetaxel in the second-line setting for advanced NSCLC in this study. Based on these results, treatment with pemetrexed should be considered a standard treatment option for second-line NSCLC.

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Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Owns stock (not including shares held through a public mutual fund): Paolo Paoletti, Eli Lilly; Frances A. Shepherd, Eli Lilly. Acted as a consultant within the last 2 years: Nasser Hanna, Eli Lilly, Aventis; Ulrich Gatzemeier, Eli Lilly; Paul A. Bunn Jr., Eli Lilly; Miklos Pless, Eli Lilly; Christian Manegold, Eli Lilly; Frank V. Fossella, Eli Lilly, Aventis; Frances A. Sheperd, Eli Lilly, Aventis. Performed contract work within the last 2 years: Paul A. Bunn Jr., Eli Lilly; Frances A. Sheperd, Eli Lilly. Received more than $2,000 a year from a company for either of the last 2 years: Nasser Hanna, Eli Lilly, Aventis; Ulrich Gatzemeier, Eli Lilly; Paul A. Bunn Jr., Eli Lilly; Christian Manegold, Eli Lilly; Frank V. Fossella, Eli Lilly, Aventis; Frances A. Sheperd, Eli Lilly, Aventis.

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ALIMTA® (pemetrexed disodium) as second-line treatment of non-small-cell lung cancer: a phase II study

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Background: The purpose of this study was to evaluate ALIMTA® (pemetrexed disodium, LY231514), a multi-targeted antifolate with first-line activity against non-small-cell lung cancer (NSCLC), in a second-line setting.

Patients and methods: Patients with NSCLC were eligible for this phase II study if they had progressive disease within 3 months after first-line chemotherapy or progression while being treated with first-line chemotherapy. In 81 patients studied, two cohorts of patients were assigned based on whether the first-line therapy had included a platinum regimen. ALIMTA was administered at 500 mg/m^2 by 10-min intravenous infusion once every 21 days.

Results: The response rate in the 79 evaluable patients with poor prognostic features was 8.9% [95% confidence interval (CI) 2.6% to 15.1%]. The response rate in the platinum-pretreated group was 4.5% and 14.1% in the non-platinum-pretreated group. The median duration of response was 6.8 months (95% CI 3.4–7.8 months, 0% censoring). The median survival time was 5.7 months (95% CI 4.0–8.3 months, 7.6% censoring). The probability of survival for at least 6 months was estimated to be 48%. The median time to disease progression was 2 months (95% CI 1.4–2.8 months, 0% censoring). The principal toxicity was myelosuppression, which was reversible.

Conclusions: ALIMTA is active in a second-line setting in non-platinum-pretreated NSCLC patients progressing within 3 months of first-line chemotherapy. This study demonstrates that it is possible to evaluate new drugs against NSCLC in a second-line setting.

Key words: non-small-cell lung cancer, pemetrexed, second-line chemotherapy

Introduction

The incorporation of chemotherapy into the treatment of advanced non-small-cell lung cancer (NSCLC) has become more frequent during the last decade. The primary reason for this has been the demonstration of efficacy of chemotherapeutics in prolonging survival [1] and improvement in the quality of life (QoL) of patients treated with chemotherapy versus the best supportive care [2]. Additionally, a number of new and active agents have been introduced during the last 5 years [3]. The inclusion of these newer agents into combination regimens has resulted in higher response rates, extended progression-free survival and improved QoL [4–6].

Despite these advances, therapeutic results are still far from optimal, and additional new therapies are needed, particularly drugs with a mechanism of action distinct from those currently in use. The emerging practice of using taxanes in the first-line treatment of NSCLC [7] also argues for the development of non-taxanes for use in second-line, although docetaxel may have some activity in this setting [8].

Many antifolates have been evaluated in the treatment of NSCLC, but have not yet gained a role in standard clinical practice [9–12]. Because ALIMTA® (pemetrexed disodium, LY231514; Eli Lilly & Company, Indianapolis, IN, USA), a novel multi-targeted antifolate, has multiple intracellular targets, it may have an advantage over older antifolates and may be more promising in this disease. In initial phase II studies testing the antitumor activity of ALIMTA in previously untreated patients with NSCLC, response rates of 17% and 23% were observed [13, 14]. The inclusion of new drugs into the currently available chemical weaponry against advanced NSCLC will probably depend on more than their activity in previously untreated patients. However, because many NSCLC patients now receive second-line treatment following failure of a front-line regimen, new drugs with greater efficacy in previously treated patients are needed.

Patients and methods

Patients

Patients with performance status 0–1 (WHO) and age ≥18 years, with histological or cytological proof of metastatic or locally advanced NSCLC were

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eligible if they had progressive disease while on first-line chemotherapy, or within 3 months after the last administration. Documentation of disease progression by computed tomography scan or chest X-ray was required. Other requirements for eligibility included bi-dimensionally measurable disease, estimated life expectancy ≥8 weeks, adequate organ function including absolute granulocyte count $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, hemoglobin ≥9 g/dl, bilirubin <1.5 × upper limit of normal, alanine aminotransferase and aspartate aminotransferase <3 × upper limit of normal, and calculated creatinine clearance ≥45 ml/min. Patients were excluded for the following reasons: brain metastasis, active infection, pregnancy, breast-feeding, serious systemic disorders or clinically detectable effusions. All patients signed informed consents according to local ethical medical committee regulations.

Treatment

ALIMTA was supplied as a lyophilized powder in 100 and 500 mg vials. By adding normal saline, a solution was prepared and drug was administered as a 10-min intravenous infusion at a dose of 500 mg/m^2 every 21 days. Dexamethasone 4 mg (or equivalent) was taken twice per day orally on the day before, the day of, and the day after each dose of ALIMTA. Dose adjustments were based on nadir blood counts or the occurrence of grade 3/4 non-hematological toxicities (National Cancer Institute common toxicity criteria) during the preceding cycle. Treatment was delayed for a maximum of 2 weeks to allow granulocytes to recover to $\geq 1.5 \times 10^9$/l and to allow platelets to recover to $\geq 100 \times 10^9$/l. No concomitant chemotherapy, immunotherapy, hormonal therapy or the routine use of hematopoietic growth factors was allowed. The administration of non-steroidal anti-inflammatory drugs was not permitted beginning 2 days before study and not until 2 days after each infusion. Radiotherapy was allowed only for the treatment of painful lesions. Leucovorin administration was recommended for any patient who experienced grade 4 neutropenia (lasting 5 days or more), grade 4 thrombocytopenia, or grade 3/4 mucositis.

Measurement of study end points

The primary objective of this study was to determine tumor response rate to ALIMTA therapy in patients with advanced NSCLC, who had received prior treatment for metastatic cancer. Standard South Western Oncology Group response criteria were used to define antitumor effects, and assessments occurred in alternate therapy cycles using a consistent method appropriate for the defined target lesion.

Secondary objectives included the measurement of the following time-to-event variables: duration of response for responding patients, time to progression, time to treatment failure, and survival time. Duration of response was measured from the first assessment of complete or partial response until progression or death. Time to treatment failure, time to progression, and survival times were measured beginning with the first dose of study drug. An additional secondary objective was to assess any changes in QoL scored with the European Organization for Research and Treatment of Cancer QLQ-C30 and LC 12 forms before each cycle of therapy. A final QoL score was obtained before each patient's formal discontinuation from the study.

Statistics

Group A in this study included patients who had disease progression or recurrence following treatment with a platinum-containing regimen. Group B included patients who had disease progression or recurrence following treatment with a non-platinum-containing regimen. For each group, up to a total of 35 qualified patients were to be enrolled in a two-stage design [15]. Twenty patients were enrolled in the first stage in each group. If no responses within a group were observed, the accrual to this group would be stopped. If at least one patient responded to ALIMTA, another 15 patients were to be enrolled to this group into the second stage of the study for a total of 35 patients. If fewer than five patients exhibited a response to ALIMTA by the end of the second stage the conclusion could be drawn that the regimen was not worthy of further study in patients with this condition. This design tests the null hypothesis that the true response rate is 5% versus the alternative hypothesis that the true response rate is at least 20% at a significance level of 0.03 with a power of 86%.

Results

Patients

Between November 1997 and April 1999, 82 patients previously treated for NSCLC signed informed consent documents to enter the study. One of these did not receive treatment due to a personal decision. Two patients were treated but were considered unevaluable for efficacy analysis. One patient did not have a bi-dimensionally measurable lesion and one had primary pancreatic cancer with lung metastases. Efficacy analysis and potential factors influencing efficacy were studied from the 79 patients considered evaluable; 44 had progressive disease during or shortly after platinum-containing therapy (group A), and 35 had progressive disease during or shortly after a non-platinum-containing regimen (group B). Safety analysis was assessed on 81 patients who received treatment. Patient characteristics are described in Table 1. Treatment was given on an outpatient basis. The total number of cycles given was 249; the median number of cycles was two (range one to eight cycles).

Toxicity

Three patients required dose reductions in a total of four cycles. One patient experienced thrombocytopenia that required an initial 50% dose reduction and a further 50% dose reduction in the following cycle. One patient experienced a rash. One patient experienced mucositis and an abnormal laboratory test, which led to a dose reduction. There were 16 cycle delays (6%) for toxicity. Anemia, thrombocytopenia and rash each led to the delay of two cycles. In addition, the following resulted in a single cycle delay: flu syndrome, abnormal liver function tests, asthenia, dyspnea, conjunctivitis, cholecystitis, pneumonia, rhinitis, infection and mucositis. Overall, toxicity was mild with grade 4 granulocytopenia seen in 15 patients (19%), and grade 4 thrombocytopenia in four patients (5%). Clinical toxicity occurred infrequently with grade 3 rash, infection, nausea, vomiting, fatigue and pulmonary toxicity in four (1.6%), one (0.4%), one (0.4%), two (0.8%), four (1.6%) and one (0.4%) cycles, respectively. Three patients died of septic complications while experiencing grade 4 neutropenia. One patient died of pneumonia, which was not felt to be drug-related. More detailed information is given in Tables 2 and 3. In seven patients, drug toxicity was the possible reason for discontinuation of treatment (four deaths, three adverse events).

Response and survival

An independent, central review of response data indicated that there were six partial responses and one complete response. Thus, the overall response rate was 8.9% [95% confidence interval (CI) 2.6% to 15.1%] in the 79 evaluable patients. Two additional

Table 1. Patient characteristics

	Total	Group A (%)	Group B (%)
No. of treated patients	81	45	36
No. of evaluable patients	79	44	35
Age (years)			
Median	61	58	68
Range	32–80	32–78	40–80
No. of courses of ALIMTA	249	141	108
Median	2	2	2
Range	1–8	1–8	1–7
Prior radiotherapy	20	11 (22)	9 (25)
Prior surgery	23	12 (27)	11 (31)
WHO performance status			
0	20	11 (25)	9 (26)
1	59	33 (75)	26 (74)
Stage			
IIIB	14	6 (14)	8 (23)
IV	65	38 (86)	27 (77)
No. of courses first-line	292	151	141
Mean	3.7	3.4	4.0
Range	1–13	1–12	1–13
First-line chemotherapy			
Cisplatin	29	29	–
Carboplatin	15	15	–
Gemcitabine	28	10	18
Vinorelbine	25	3	22
Mitomycin	19	6	13
Paclitaxel	10	6	4
Docetaxel	8	6	2
Etoposide	6	6	0
Ifosfamide	6	6	0
Raltitrexed	4	4	0
Irinotecan	5	3	2
Vinblastine	2	2	0
Teniposide	1	1	0
Temozolamide	1	0	1
Interval since last administration of first-line			
≤1 month	52	26	26
1–2 months	16	10	6
>2 months	11	7	4
Best response to first-line			
Complete response	0	0	0
Partial response	20	9 (20)	11 (31)
Stable disease	31	18 (41)	13 (37)
Progressive disease	28	17 (39)	11 (31)

–, Patients not pretreated.

Table 2. Hematological and laboratory toxicity maximum grade per patient ($n = 81$)

	Grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Hemoglobin	27 (33)	32 (40)	10 (12)	1 (1)
White blood cells	18 (22)	13 (16)	24 (30)	7 (9)
Neutrophils	10 (12)	15 (19)	13 (16)	15 (19)
Platelets	19 (24)	4 (5)	8 (10)	4 (5)
ALT/AST	39 (50)/43 (55)	16 (21)/11 (14)	5 (6)/3 (4)	0/0
Alkaline phosphatase	33 (42)	2 (3)	1 (1)	0
Creatinine	6 (8)	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3. Non-hematological toxicity maximum grade per patient ($n = 81$)

	Grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Cutaneous	15 (19)	17 (21)	4 (5)	0
Infection	4 (5)	6 (7)	0	3 (4)
Fever	7 (9)	12 (15)	0	0
Diarrhea	5 (6)	5 (6)	0	0
Nausea	25 (31)	16 (20)	1 (1)	0
Vomiting	15 (19)	11 (14)	2 (3)	0
Neuromotor (fatigue)	15 (19)	11 (14)	4 (5)	0
Stomatitis	14 (17)	3 (4)	0	0

unconfirmed partial responses were reported by the treating physicians. Of the remaining patients, 25 (31.6%) achieved stable disease, 30 (38.0%) had progressive disease and 17 (21.5%) had no response assessment. Five of the responding patients in this study had not previously received treatment with platinum, compared with two responders in the platinum-pretreated group. All but one patient responding to second-line ALIMTA had an objective tumor response to first-line treatment. Response by patient group is described in detail in Table 4. Treatment was continued to a maximum of eight cycles. At the time of discontinuation, 47 patients had experienced progressive disease. Time off first-line treatment and type of chemotherapy used in the first-line did not have a discernable influence on the probability of response.

Table 4. Response

	All (%)	Group A (%)	Group B (%)
Evaluable	79	44	35
Complete response	1 (1.3)	0	1 (2.9)
Partial response	6 (7.6)	2 (4.5)	4 (11.4)
Stable disease	25 (32)	16 (36)	9 (26)
Progressive disease	30 (38)	18 (41)	12 (34)
No assessment	17 (22)	8 (18)	9 (26)

The median duration of response was 6.8 months (95% CI 3.4–7.8 months, 0% censoring). The probability of a tumor response lasting 6 months or longer was estimated to be 57% for responding patients. The median survival time was 5.7 months (95% CI 4.0–8.3 months, 7.6% censoring). The probability of a patient surviving at least 6 months was estimated to be 48%. The median time to progression was 2 months (95% CI 1.4–2.8 months, 0% censoring). The median time to treatment failure was 1.6 months (95% CI 1.4–2.5 months, 0% censoring). Time to event evaluation by patient group is described in detail in Table 5.

In two patients, ALIMTA was restarted on a compassionate-need basis. One patient experienced a further response to treatment. The other patient experienced severe skin toxicity during the second cycle of retreatment. The third cycle of treatment was therefore given after administration of type H_1 and H_2 histamine receptor blockers, as well as dexamethasone. Using this protective approach, no further skin toxicity was seen in this patient.

Quality of life

A total of 76 qualified patients completed at least one QoL questionnaire. The median number of questionnaires completed by the 76 patients was three (range one to seven), which coincides with the median of two cycles of therapy. On-study compliance was 74.1% for eight cycles of therapy. At the end of cycle 5, only 11 patients completed questionnaires. Any results at this point or

Table 5. Survival

	All ($n = 79$)	Group A ($n = 44$)	Group B ($n = 35$)
Median survival (months)	5.7	6.4	4.0
Six-month survival	48%	55%	40%
Nine-month survival	29%	32%	26%
One-year survival	23%	25%	20%
Median duration of response (months)	2	1.6	6.8
Median progression-free interval (months)	2.0	2.3	1.6
Progression-free at 6 months	18%	23%	11%
Progression-free at 9 months	5%	7%	3%

beyond were highly influenced by individual patient response. Therefore, only results from the first four cycles of therapy, when at least 30% of patients had completed questionnaires, were considered more representative of the larger population.

For the first four cycles of therapy, the changes in median score from baseline were 0 in all scales/items, except for a small improvement (i.e. 4.2 points) in emotional functioning and an improvement (i.e. 33.3 points) in hair loss after cycle 3. Owing to the decreasing number of observations over time and the lack of a control, interpretation of the QoL results was limited. Observations at later cycles may represent a selection bias of those patients with stable disease or with tumor responses. However, based on the available data, it appears that QoL of patients during their time on study was unchanged.

Discussion

It is unclear what the threshold of activity of a new drug in second-line treatment of NSCLC should be in order to consider the drug promising. Based on the predefined statistical analysis it may be concluded that ALIMTA is not worthy of further evaluation in platinum-pretreated patients. However, this study was designed before the landmark studies of docetaxel in second-line treatment of NSCLC were published. In these studies [8, 16] incorporating a less well-defined group of patients, the overall response rate was 7%. Moreover, even this low response rate was associated with improvement of QoL over best supportive care alone [16]. In the study reported here, the overall response rate was 8.9%. Further, the 1-year overall survival of 23% in patients treated with ALIMTA is comparable to that achieved with second-line docetaxel. Therefore, we feel the results from this study indicate that ALIMTA has activity as a single agent in the treatment of NSCLC confirming reports from phase II trials in previously untreated patients [13, 14].

Both hematological and non-hematological toxicities were moderate. As expected, myelotoxicity was the most significant adverse event. It is important to note that the addition of vitamin B_{12} and folic acid in ongoing trials has significantly reduced the myelotoxicity of ALIMTA and has allowed patients to receive more cycles of therapy [17]. It is reasonable to expect this intervention to have a similar impact in second-line NSCLC patients receiving ALIMTA.

Combination chemotherapies involving platinum-containing agents have resulted in improved survival in the front-line treatment of metastatic NSCLC [1]. Several new agents (taxanes, gemcitabine, vinorelbine, irinotecan) introduced in the last 5 years have led to further improvement. First-line chemotherapy commonly fails due to acquired chemoresistance, but ALIMTA may carry an advantage through its mechanism of action. ALIMTA potently inhibits thymidylate synthase, a highly expressed drug resistance-related enzyme, as well as a number of secondary enzyme targets [18]. This mechanism of action may explain why ALIMTA has activity in tumors refractory to standard regimens.

Unfortunately there is a high rate of failure of first-line therapies and effective salvage regimens are in demand. With the relative success and reported milder toxicity of new agents, the use of second-line chemotherapy has become an accepted reality. Guidelines to apply this in daily practice are not available. Because first-line regimens are increasingly active, the bar for testing new drugs in previously untreated patients has been raised accordingly. New standards for evaluating novel NSCLC agents are therefore needed. A recent review of second-line treatment in NSCLC [19] examined over 60 studies. Insufficient information in most reports made it impossible to weigh the relative importance of those factors possibly having an impact on second-line treatment or new drug testing. In the current study, entry was restricted to patients with demonstrated disease progression within a short interval following first-line treatment. This disease progression factor, along with the nature of front-line therapy, is likely to be of paramount importance in refining treatment decisions for second-line NSCLC. Six of the seven responses achieved in this study were seen in patients who had previously responded to first-line treatment. No significant correlation was noted between response to ALIMTA and types of agents used in first-line therapy, although five patients were in the group who had not received prior platinum. Likewise, disease stabilization was achieved in patients who either responded or had stable disease during first-line therapy. Only a small number of patients with progressive disease during first-line therapy had stable disease during treatment with ALIMTA.

In conclusion, ALIMTA has shown activity in two studies in chemonaive NSCLC patients. In addition, this antifolate has now demonstrated activity as a second-line agent, at least in patients who have not been pretreated with (cis)platinum-containing

chemotherapy, with moderate toxicity. Because the mechanism of action allows the agent to be non-cross-resistant with the currently used cytotoxic agents, ALIMTA may be a useful second-line NSCLC agent. A phase III study comparing ALIMTA with docetaxel as second-line therapy for NSCLC has been planned on the basis of the results reported here and will finish accrual in the summer of 2002.

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Original article

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Phase II trial of pemetrexed disodium (ALIMTA®, LY231514) in chemotherapy-naïve patients with advanced non-small-cell lung cancer

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Background: To evaluate the efficacy and safety of pemetrexed therapy for chemotherapy-naïve patients with surgically incurable non-small-cell lung cancer (NSCLC).

Patients and methods: Eligible patients received pemetrexed 600 mg/m^2 every 3 weeks. Restaging was performed after every two cycles of therapy and toxicity was assessed at each cycle of pemetrexed. In the absence of disease progression or undue toxicity, treatment was continued for a maximum of 12 cycles.

Results: Fifty-nine patients (median age 59 years; range 39–74 years) received a median of four cycles of pemetrexed. Nineteen patients (32%) had a ECOG performance status (PS) of two and 39 patients (66%) had stage IV disease. The most common histological sub-types were adenocarcinoma (20 patients, 34%) and large cell (18 patients, 31%). Sixteen patients (27%) had received prior radiotherapy. Nine patients achieved a partial response for an overall response rate of 15.8% (95% confidence interval CI 7% to 28%). The median duration of response was 4.9 months, and the median survival was 7.2 months. The principal toxicities were myelosuppression and rash. While grade 3 or 4 neutropenia was seen in 25 patients (42%), only two patients (3%) developed grade 3 infection. Eighteen patients (31%) developed grade 3 or 4 cutaneous toxicity, which improved with prophylactic oral dexamethasone administered for 3 days beginning the day before pemetrexed treatment. Asymptomatic elevations in hepatic biochemistry (especially alanine transaminase and aspartate transaminase) were seen in 47 patients (80%); however, these did not interfere with the dose or schedule of pemetrexed and returned to normal levels throughout the study.

Conclusions: This is the largest study confirming the encouraging single-agent activity of pemetrexed in chemotherapy-naïve patients with NSCLC. In addition, this study demonstrates that a dose of 600 mg/m^2 can be delivered safely; however, treatment should be restricted to patients with a PS of 0 or 1. The results of combination studies are awaited with interest.

Key words: non-small-cell lung cancer, pemetrexed, phase II

Introduction

Lung cancer remains the single most common cancer problem in the Western world. The most recent World Health Organisation data for causes of death worldwide estimated that lung cancer would be responsible for 1.2 million deaths in 2000 [1]. Seventy-five percent of cases of lung cancer are non-small-cell lung cancer (NSCLC), for which surgery remains the principal curative option. However, the curative potential of surgery is limited because the majority of patients have inoperable disease at presentation. In addition, approximately 50% of patients who undergo an operation with curative intent subsequently relapse, resulting in a large group of patients who could benefit from effective palliative therapies [2]. The treatment options in NSCLC have changed significantly in the last 5 years with the introduction of a number of new agents that appear to be more active and less toxic than older therapies (reviewed in Clarke and Boyer [3]). These compounds include the taxoids, paclitaxel and docetaxel, gemcitabine, vinorelbine and irinotecan. Reported phase II response rates for these agents as monotherapy in patients with untreated NSCLC range between 20% and 30%, with combinations producing response rates of up to 50%. However, a recent

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randomised phase III study in patients with previously untreated NSCLC, performed by investigators from the Eastern Cooperative Oncology Group (ECOG), demonstrated response rates of only between 15% and 23% for combinations of a platinum derivative and each of paclitaxel, gemcitabine and docetaxel [4]. There is thus a need for new agents, especially with different mechanisms of action, to improve cure rates and palliation for patients with NSCLC.

Pemetrexed (ALIMTA®, LY231514) is a novel folate-based anticancer compound with a broad spectrum of activity against human tumour cell lines and xenograft models. Pemetrexed predominantly inhibits thymidylate synthase (TS), but is also active against other folate enzymes involved in the *de novo* synthesis of purines and pyrimidines, including dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT) [5]. Like many folate-based compounds, pemetrexed is a substrate for folylpolyglutamyl synthetase (FPGS), and the resulting polyglutamated forms demonstrate up to 100-fold greater potency than the parent compound against TS and GARFT, but not DHFR [6]. Further evidence that pemetrexed inhibits multiple enzyme targets is demonstrated by the failure of co-administered thymidine to completely reverse pemetrexed-induced cytotoxicity in tumour cell lines. However, the combination of thymidine and a purine source, such as hypoxanthine, results in almost 100% reversal of cytotoxicity. In addition, there is evidence for incomplete cross-resistance between pemetrexed and raltitrexed (Tomudex), a specific folate-based inhibitor of TS [7].

Polyglutamation of pemetrexed also results in prolonged intracellular drug retention, thereby permitting intermittent schedules of administration. Multiple phase I schedules of pemetrexed have been evaluated, including once a week for 4 weeks re-peated every 6 weeks, once a day for 5 days repeated every 3 weeks and a single dose repeated every 3 weeks (reviewed by Rinaldi [8]). The preferred schedule was a 10-min intravenous infusion administered every 3 weeks [9]. The maximum tolerated dose (MTD) using this schedule was 700 mg/m^2, and the dose-limiting toxicity (DLT) was myelosuppression, although non-haematological toxicities such as rash, nausea, mucositis and fatigue were also reported. A dose of 600 mg/m^2 was recommended for phase II studies. The aim of this phase II trial was to investigate the activity and toxicity of pemetrexed in patients with chemotherapy-naïve, locally advanced, recurrent or metastatic NSCLC.

Patients and methods

Patient selection

All patients in this study had histologically or cytologically confirmed, bidimensionally measurable, stage III or IV NSCLC. Patients could not have received prior chemotherapy. Radiation therapy >6 weeks prior to study enrolment was allowed if the irradiated site was not the only site of measurable disease. Patients were at least 18 years of age, had a ECOG performance status (PS) ≤2 and a life expectancy of at least 12 weeks. Minimum bone marrow function requirements were white blood cell count ≥3.5 × 10^9/l, platelets ≥100 × 10^9/l, haemoglobin ≥9 g/dl and absolute granulocyte count (AGC) >2.0 × 10^9/l. Minimum liver function requirements were bilirubin <1.5-fold the upper limit of normal (ULN), prothrombin time or activated partial thromboplastin time <1.5× control, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <3-fold ULN (may be elevated to 5-fold ULN in patients with known hepatic metastases). Patients with childbearing potential were required to use adequate contraceptive precautions. Patients were ineligible if they were pregnant or breast-feeding, or had any of the following: an active infection or other serious concomitant disorder; cerebral metastases requiring steroid treatment; a calculated creatinine clearance rate of <45 ml/min or presence of clinically detectable third space fluid collection. Patients were also ineligible if they had evidence of prior/concurrent malignancy other than *in situ* carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or other malignancy treated ≥5 years previously without evidence of recurrence. All patients were required to provide written evidence of informed consent, and the protocol was approved by the ethics committee of each participating institution.

Pre-treatment investigations, performed within 3 weeks of commencing treatment, included full history and examination, assessment of weight and PS, and baseline radiology. In addition, the following evaluations were required no more than 2 weeks prior to treatment: laboratory tests including full blood count (FBC), coagulation profile, biochemistry (electrolytes, urea and creatinine, liver function tests, calcium, uric acid and phosphate); electrocardiograph; calculated creatinine clearance and measurement of vital signs. During treatment, FBC was taken once a week and biochemistry, urinalysis, vital signs and toxicity evaluation were taken once every 3 weeks.

Treatment

Pemetrexed was supplied as a lyophilised powder in 100 mg vials and reconstituted in 0.9% saline to form a clear solution containing 5–50 mg/ml. The drug was administered as a continuous infusion over 10 min at a dose of 600 mg/m^2 and courses were repeated every 3 weeks to a maximum of 12 cycles. Patients were retreated on schedule if the AGC was >1.5 × 10^9/l and platelets >100 × 10^9/l, and if the calculated creatinine clearance was >45 ml/min. Dose reduction of 25% occurred if the nadir granulocyte count was <0.5 × 10^9/l and the nadir platelet count ≥50 × 10^9/l, or if grade 2 mucositis occurred, after the previous course of pemetrexed. A 50% dose reduction occurred if the nadir granulocyte count was ≥0.5 × 10^9/l, in association with a nadir platelet count of 25–49 × 10^9/l, or if grade 3 or 4 mucositis occurred after the previous course of pemetrexed. A 75% dose reduction was undertaken if the granulocyte nadir was <0.5 × 10^9/l and the nadir platelet count was 25–49 × 10^9/l, or if the nadir platelet count was <25 × 10^9/l, regardless of the nadir granulocyte count. Once a dose reduction had occurred, it was not permitted to re-escalate for subsequent courses. If a patient could not be retreated within 42 days from the last course of pemetrexed, they were excluded from further treatment. If Common Toxicity Criteria (CTC) grade 2 or greater cutaneous toxicity occurred, the patient was to receive prophylactic oral dexamethasone in subsequent cycles at a dose of 4 mg bd from the day prior to treatment for a total of 3 days. If a patient experienced protracted neutropenia (i.e. grade 4 for >7 days) it was planned that leucovorin rescue be administered. In addition, if short-acting non-steroidal anti-inflammatory drugs (NSAIDs) were being taken, it was required that these medications be stopped for 3 days, commencing the day before treatment. If long-acting NSAIDs were being taken, it was required that these be stopped for 7 days commencing 5 days before treatment with pemetrexed.

Assessment of study endpoints and statistical analysis

The initial study plan was to enrol up to 35 eligible patients from three Australian and two South African centres in a two-stage sequential fashion. Thirteen patients were to be enrolled in the first stage and if at least one patient responded to pemetrexed, another 22 patients were to be enrolled. If no patient of the first 13 responded the study was to be stopped. Subsequent to enrolment of the first 35 patients, an additional cohort of patients was included to more accurately define the confidence intervals of response. All patients were considered eligible for response if they fulfilled the eligibility criteria for study entry and received at least one cycle of pemetrexed. Response was assessed after every two cycles of treatment using standard South West Oncology Group criteria. Response duration was defined as the time from treatment initiation to the appearance of objective evidence of disease progression. Stable disease was measured from commencement of treatment until disease progression. Overall survival was measured from the date of initial treatment to the date of death and was estimated by the Kaplan–Meier method. All patients receiving at least one cycle of pemetrexed were assessable for toxicity and these were graded according to CTC.

Results

From April 1996 to July 1998, 59 patients received treatment with pemetrexed. The patient demographic data are summarised in Table 1.

Table 1. Demographic data for non-small-cell lung cancer patients treated with pemetrexed

Patient criteria	No. of patients (%)
Patient number	59
Median age (range)	59 (39–74)
Sex	
Male	39 (66)
Female	20 (34)
Stage	
IIIA	6 (10)
IIIB	14 (24)
IV	39 (66)
ECOG Performance status	
0	12 (20)
1	28 (48)
2	19 (32)
Histology	
Squamous	10 (17)
Adenocarcinoma	20 (34)
Large cell	18 (31)
Mixed	2 (3)
Unclassified	9 (15)
Prior therapy	
Surgery including biopsy	56 (97)
Radiotherapy	16 (28)

Toxicity

The 59 patients received a median of four cycles of therapy (range 1–12 cycles). Six patients received a single cycle of pemetrexed before discontinuing treatment. In four of these, all with a pre-treatment PS of 2, treatment was stopped due to rapid disease progression. In the other two patients, treatment was discontinued on the basis of an adverse event. These consisted of a cerebrovascular accident and grade 4 diarrhoea, with the latter thought to be treatment related. Five other patients discontinued treatment following an adverse event after a range of 2–11 cycles of pemetrexed. In only one of these, a febrile episode, was the chemotherapy possibly implicated. The median dose of pemetrexed delivered was 600 mg/m^2. In 13 patients (22%) dose reduction was required due to toxicity (rash, one patient; stomatitis or mucous membrane disorder, six patients; haematological toxicity, four patients; diarrhoea, nausea, fever, asthenia, one patient each). Dose delay occurred in 19 patients, 11 for patients' convenience and eight for toxicity (one patient each for decreased creatinine clearance, pharyngitis, severe constipation, pneumonia, vomiting, rash, stomatitis and infection). All patients were assessable for toxicity. The principal toxicities experienced by patients in this study are listed in Tables 2 and 3. Grade 3/4 neutropenia occurred in 25 patients (42%), but was not frequently complicated by febrile neutropenia, with grade 3 infection occurring in only two patients (3%) and grade 4 infection not seen. Only three patients (5%) experienced grade 3/4 thrombocytopenia, one of whom required platelet transfusion.

The liver function abnormalities observed were all clinically asymptomatic and principally manifest by elevations in serum ALT with parallel, but less significant, changes in AST. Eight (14%) and three patients (5%) had grade 3 elevations in ALT and AST, respectively. Abnormalities in serum alkaline phosphatase [two patients grade 3 (5%)] and γ-glutamyl transferase were less significant and only occasionally was the serum bilirubin elevated. The abnormalities in hepatic biochemistry were self-limited and settled both with continued treatment and on cessation of therapy, and did not necessitate dose reduction and/or delay.

Eighteen patients (31%) experienced grade 3/4 cutaneous toxicity. In two additional patients there was evidence of asymptomatic diffuse hyperpigmentation of the upper body that resolved on cessation of treatment. In only two cases did the skin toxicity affect ongoing patient treatment, with one delay for rash and one dose reduction by 50%; this toxicity improved with prophylactic treatment with dexamethasone. All skin changes completely resolved on cessation of therapy.

Grades 3/4 nausea and vomiting occurred in eight (14%) and five (9%) patients, respectively, and were easily managed

Table 2. Laboratory toxicities following treatment with pemetrexed (worst grade per patient)

Toxicity	Grade (%)				
	0	1	2	3	4
Leucopenia	13 (22)	7 (12)	19 (32)	16 (27)	4 (7)
Neutropenia	20 (34)	7 (12)	7 (12)	16 (27)	9 (15)
Anaemia	7 (12)	18 (31)	28 (48)	4 (7)	3 (3)
Thrombocytopenia	40 (68)	13 (22)	3 (5)	0 (0)	3 (5)
Lymphopenia	2 (3)	3 (5)	9 (15)	26 (44)	19 (32)
Alkaline phosphatase	22 (37)	31 (53)	6 (10)	0 (0)	0 (0)
ALT/AST	12 (20)	22 (37)	13 (22)	12 (20)	0 (0)
Bilirubin	45 (76)	1 (2)	10 (17)	1 (2)	2 (3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

Table 3. Non-laboratory toxicities following treatment with pemetrexed (worst grade per patient)

Toxicity	Grade (%)				
	0	1	2	3	4
Cutaneous	10 (17)	15 (25)	16 (27)	11 (19)	7 (12)
Nausea	14 (24)	14 (24)	23 (39)	8 (14)	0 (0)
Vomiting	32 (54)	8 (14)	14 (24)	3 (5)	2 (3)
Diarrhoea	40 (68)	7 (12)	10 (17)	0 (0)	2 (3)
Fever	47 (80)	3 (5)	8 (14)	1 (2)	0 (0)
Alopecia	48 (81)	10 (17)	1 (2)	0 (0)	0 (0)
Infection	45 (76)	4 (7)	8 (14)	2 (3)	0 (0)
Fatigue	26 (44)	10 (17)	20 (34)	3 (5)	0 (0)
Mucositis	33 (56)	10 (17)	13 (22)	3 (5)	0 (0)

with simple anti-emetics such as metoclopramide. In addition, grades 3/4 stomatitis and diarrhoea occurred in only three (5%) and two (3%) patients, respectively.

Response

Of the 59 patients treated with pemetrexed, 57 were assessable for response. Two patients were subsequently deemed ineligible, one following the appearance of a colonic tumour of identical histology to a previously biopsied pulmonary lesion, and another who on review did not fulfil the entry criteria. Nine patients achieved a partial response [response rate (RR) of 15.8%; 95% confidence interval (CI) 7% to 28%], while in another 27 patients (47%) there was stable disease. One of 18 patients (5%) with a PS of 2 developed a response to pemetrexed compared, with eight of 40 with a PS of 0 or 1 (18%). Three of the patients achieving a response had stage III (one with stage IIIA, two with stage IIIB) disease while the other six had stage IV disease. The median duration of response was 4.9 months, the median time to disease progression 4.4 months and the median survival 7.2 months. The probability of surviving 12 months was 32%.

Discussion

This study confirms the single-agent activity of pemetrexed in chemotherapy-naïve patients with advanced NSCLC. The RR of 16% (95% CI 7% to 28%) overlaps with that recently reported by Rusthoven et al. [10] (RR 23.3%; 95% CI 9.9% to 42.3%), from a Canadian trial of pemetrexed in chemotherapy-naïve patients with incurable NSCLC involving 33 patients. It was initially of identical design to the current study; however, the dose was reduced to 500 mg/m^2 after the first three patients had been treated because of toxicity experienced in the lung study and in a colorectal trial of pemetrexed being performed in the same unit [10, 11]. The patient population was similar to the current study with a predominance of patients with adenocarcinoma (55%) and stage IV disease (76%), although only one patient (3%) in the Canadian trial had a PS of 2 compared with 19 patients (32%) in the current study, and this could explain the difference in RRs [10].

These results are also similar to the single-agent response rates reported for other new agents being used in NSCLC, including gemcitabine, vinorelbine, paclitaxel, docetaxel and irinotecan. The lack of response in the PS 2 patients is also consistent with data from studies of these other drugs which demonstrate that, apart from gemcitabine, RRs in PS 2 patients rarely exceed 10%. In fact, in many recent studies in NSCLC, including the latter stages of the ECOG trial, the eligibility criteria have been restricted to patients with a PS of 0 and 1 [4].

Unlike the Canadian study, the planned dose of pemetrexed 600 mg/m^2 was able to be delivered in the current trial without unacceptable toxicity. The incidence of grades 3/4 neutropenia was 39% in the Canadian study compared with 41% in the current study, and infection was uncommon in both studies [10]. Cutaneous toxicity was less frequent in the current study, with 31% of patients experiencing grades 3/4 cutaneous toxicity compared with 39% in the Canadian study, although 10% of patients in the current study developed grade 4 cutaneous toxicity, which did not occur at the lower dose. However, the routine adoption of prophylactic oral dexamethasone given at a dose of 4 mg twice daily, the day before, day of and day after treatment, appeared to substantially improve patient tolerance of cutaneous toxicity. The incidence of nausea and vomiting were comparable in the two studies and were not a significant clinical problem. In addition, in neither study was there a significant incidence of stomatitis or diarrhoea, which are major clinical problems with other folate-based drugs such as methotrexate and raltitrexed, especially when combined with neutropenia.

Asymptomatic abnormalities of hepatic transaminases were seen in 80% of patients treated and in 14% there were eleva-

tions of to up to 20-fold of normal values. As has been reported with other folate-based drugs such as CB3717 and raltitrexed, it was possible to maintain dose intensity and schedule of pemetrexed without adversely affecting transaminase levels [12, 13]. On the contrary, there was a fall in transaminase levels despite continued treatment with pemetrexed. There was no evidence of progressive hepatic impairment and other indices of hepatic function, such as the prothrombin time and serum albumin level, remained normal. It is important to appreciate this clinical scenario as there is a risk of erroneously attributing the liver function abnormalities to progressive hepatic malignancy or inappropriately stopping or delaying treatment.

In more recent studies involving pemetrexed, routine administration of folic acid and vitamin B_{12} supplements was received by all patients, commencing 1 week prior to chemotherapy. This treatment has been utilised to improve the 'functional folate status' of patients prior to receiving pemetrexed. Patients with a poor functional folate status, reflected by elevated baseline plasma homocysteine concentrations, have been shown to experience worse toxicity with pemetrexed, especially grades 3 and 4 myelosuppression, mucositis and diarrhoea [14]. The addition of vitamin supplementation has been demonstrated to significantly decrease the incidence of these toxicities and also drug-related deaths [15].

In summary, pemetrexed appears to have significant single-agent activity in patients with NSCLC. There is a potential for non-cross-resistance between this agent and many of the other commonly used anticancer drugs, and in particular, pemetrexed should not be subject to resistance from the various multidrug resistance mechanisms. Evidence for non-cross resistance of pemetrexed in NSCLC has been suggested by the encouraging preliminary results of a multi-centre study performed in patients who had received prior chemotherapy [16]. Combination studies with other active agents, such as paclitaxel, docetaxel, irinotecan, vinorelbine, cisplatin and gemcitabine, are being pursued as is the activity of pemetrexed when used as second-line therapy in patients with NSCLC. The final results of two trials combining cisplatin and pemetrexed have recently been published and reported response rates of 39–45% and median survivals of 8.9–10.8 months for patients with chemotherapy-naïve stage IIIB or IV NSCLC [17, 18]. These data further confirm the promise of pemetrexed in the treatment of NSCLC.

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Multitargeted Antifolate LY231514 as First-Line Chemotherapy for Patients With Advanced Non–Small-Cell Lung Cancer: A Phase II Study

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Purpose: To evaluate the efficacy and safety of the multitargeted antifolate LY231514 (MTA) in patients receiving initial chemotherapy for unresectable, advanced non–small-cell lung cancer (NSCLC).

Patients and Methods: Patients with measurable, advanced NSCLC who had not received previous chemotherapy for advanced disease were considered for this study. Eligible patients who gave written informed consent initially received MTA 600 mg/m² intravenously (IV) for 10 minutes every 3 weeks. After three patients received treatment at this dose, the dose was reduced to 500 mg/m² IV at the same infusion time and frequency because of toxicity seen in this study and another Canadian MTA trial in colorectal cancer. Patients received up to four cycles after complete or partial remission or six cycles after stable disease was documented.

Results: Thirty-three patients were accrued onto the study. All were assessable for toxicity, and 30 patients were assessable for response. All but one patient had an Eastern Cooperative Oncology Group performance status score of 0 or 1, 18 patients (55%) had adenocarcinoma, and nine patients (27%) had squamous cell carcinoma. Twenty-five patients (76%) had stage IV disease, and the remainder had stage IIIB disease at trial entry. Seven patients experienced a confirmed partial response and no complete responses were seen; thus, the overall response rate was 23.3% (95% confidence interval, 9.9% to 42.3%). The median duration of response was 3.1 months (range, 2.3 to 13.5 months) after a median follow-up period of 7.9 months. Four (67%) of six patients with stage IIIB disease and three (12.5%) of 24 with stage IV disease responded to treatment. Four patients (13.3%) experienced febrile neutropenia and 13 (39%) experienced grade 3 or 4 neutropenia, whereas only one patient (3%) developed grade 4 thrombocytopenia. Nonhematologic toxicity was generally mild or moderate, but 39% of patients developed a grade 3 skin rash. Most other toxicities comprised grade 1 or 2 stomatitis, diarrhea, lethargy, and anorexia. Ten patients stopped protocol therapy because of toxicity.

Conclusion: MTA seems to have clinically meaningful activity as a single agent against advanced NSCLC. Toxicity is generally mild and tolerable. Further study of this agent in combination with cisplatin and other active drugs is warranted in this disease.

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THYMIDYLATE SYNTHASE (TS) is the primary target of the fluoropyrimidines fluorouracil (5-FU) and fluorodeoxyuridine, long-established active agents in the treatment of gastrointestinal cancers, breast cancer, and other malignancies.[1,2] Biomodulation of 5-FU by leucovorin,[2] interferon,[3] or methotrexate[4] has resulted in greater inhibition of TS and, consequently, improved response rates[5] and survival,[6] particularly among patients with colorectal cancer. However, the fluorinated pyrimidines, such as 5-FU, are indirect inhibitors of TS, requiring metabolic activation, and are linked to other effects, such as alteration of RNA metabolism.[1] Such non-TS–inhibiting effects may lead to a low therapeutic index due to increased toxicity or loss of efficacy. In addition, inhibition of TS results in an increase in intracellular deoxyuridine monophosphate that can compete with pyrimidine analogs for binding to TS.[8]

Direct and more specific inhibitors of TS have been developed that interact with the folate-binding site of TS.[9-11] These folate analogs have been designed to improve the specificity for TS inhibition; furthermore, deoxyuridine monophosphate would enhance rather than competitively reverse their binding to TS. Multitargeted antifolate LY231514 (MTA) was designed as a folate-based TS inhibitor with a glutamate side chain in this new class of folate antimetabolites.[12,13] Although MTA itself only moderately inhibits TS, polyglutamation of the parent drug and its metabolites readily occurs, and the polyglutamated form of MTA is 100-fold more potent than MTA itself. In addition, other folate-requiring enzymes may act as targets for this drug, including dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, aminoimidazole carboxamide

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ribonucleotide formyltransferase, and C1 tetrahydrofolate synthase.[14,15]

MTA has demonstrated activity in a wide range of tumor types. The drug is highly active against CCRF-CEM human leukemia cells in vitro; the activity is partially reversible with the addition of thymidine.[12-14] The 50% inhibitory concentration in CCRF-CEM cells was 7 ng/mL.[13] It is also cytotoxic in human tumor colony-forming unit assays against human colon, renal, small-cell lung and non–small-cell lung cancers, hepatomas, and carcinoid tumors.[16] MTA can inhibit tumor growth in mice transplanted with human colon xenografts resistant to methotrexate.[17] In beagle dogs treated with a weekly and/or single-dose intravenous (IV) schedule, major toxicities included anorexia, emesis, diarrhea, mucositis, weight loss, neutropenia, lymphopenia, and mild anemia. Plasma concentrations increased linearly with increasing doses, with the terminal half-life occurring at about 2.3 hours.[18] Early studies have suggested that dietary supplementation with folic acid may improve the therapeutic index by reducing toxicity in mice.

A phase I trial of single-agent MTA was recently completed in which patients were treated by 10-minute IV infusion every 3 weeks. Starting at 50 mg/m^2, doses were escalated to 700 mg/m^2, at which point three of six patients developed grade 4 neutropenia and grade 3 or 4 thrombocytopenia. In patients who received 500 to 600 mg/m^2 MTA, serum peak concentrations were 70 to 200 μg/mL, values well above the 50% inhibitory concentration in CCRF-CEM cells (data for peak concentrations provided by J. Walling, personal communication, October 1998). Twenty patients were treated at the 600-mg/m^2 dose level, and 25% of them developed grade 4 neutropenia, 10% developed grade 3 or 4 thrombocytopenia, and 50% developed grade 2 pruritic skin rash. Four partial responses (four [11%] of 37 patients) were seen in patients with pancreatic and colorectal cancer.[19]

With these data, the recommended starting dose for phase II studies using this schedule was 600 mg/m^2. Two phase II studies have been conducted through the National Cancer Institute of Canada Clinical Trials Group, one in colorectal cancer and one in non–small-cell lung cancer (NSCLC). The results of the latter study are reported here.

PATIENTS AND METHODS

Patient Selection

Eligible patients were accrued between September 1995 and February 1997. These patients had histologically or cytologically confirmed inoperable, locally advanced, or metastatic NSCLC with evidence of bidimensionally measurable disease. Prior radiation therapy was permitted if acute side effects had resolved. Previous systemic therapy given for advanced disease was not permitted, but prior adjuvant therapy was allowed if the last dose was given ≥ 12 months earlier. Other eligibility criteria included (1) age ≥ 16 years, (2) Eastern Cooperative Oncology Group performance status of 0 to 2, (3) serum creatinine level within normal limits, (4) good hepatic function (ie, serum bilirubin ≤ 1.5 times the upper normal limit and AST ≤ two times the upper normal limit or ≤ five times the upper normal limit if liver metastases were present), (5) adequate bone marrow function and reserve (absolute granulocyte count > 1.5 × 10^9/L and platelet count ≥ 150 × 10^9/L), (6) absence of clinically detectable third-space fluid collections, (7) absence of clinical evidence of brain metastases, and (8) no concurrent treatment with other experimental drugs, anticancer therapy, or folinic/folic acid supplements.

Drug Administration

MTA was supplied as a lyophilized powder in 100-mg vials and was reconstituted by adding 10 mL of 0.9% sodium chloride. The appropriate dose was then withdrawn, diluted in normal saline, and administered intravenously over 10 minutes every 3 weeks. Retreatment at the initial dose and on schedule was determined by the lack of hematologic (≤ grade 1 on day of treatment and granulocytopenia ≥ 0.5 × 10^9/L and thrombocytopenia ≥ 50 × 10^9/L at nadir) and nonhematologic (grade ≤ 2) toxicity. Patients with grade ≤ 2 nonhematologic toxicity were treated symptomatically without delays, except for cases of grade 2 skin rash, in which case treatment was delayed until rash improved to grade ≤ 1. Patients with severe (grade 3 or 4) nonhematologic toxicity received a 25% dose reduction during subsequent cycles once toxicity had subsided. Those with nadir granulocytopenia less than 0.5 but less than severe thrombocytopenia (≥ 50 × 10^9/L) also received a 25% dose reduction for the next cycle. The use of nonsteroidal anti-inflammatory drugs and salicylates was permitted but not on or around the day of treatment. (This precaution was taken because of previous kinetic data suggesting increased drug levels during coadministration of anti-inflammatory agents.) Supportive-care agents, such as colony-stimulating factors, were permitted but could not be substituted for dose reductions required according to protocol. No dose escalations were permitted.

Measurements of Study End Points

All patients were assessable for toxicity from the time of their first treatment. Patients who had received at least one cycle of MTA and had follow-up measurements performed to assess change in tumor size were assessable for response. Response was assessed on day 1 of each cycle by clinical tumor measurements and documentation of the tumor size of measurable and nonmeasurable disease, using positive radiographic tests. If results were initially negative, tests were repeated only if clinically indicated. All sites with measurable lesions were followed for response. Measurements of undimensional lesions (ie, single largest dimensions) and bidimensional lesions (the products of the largest diameter and its largest perpendicular) were summed at each assessment and the best response on study was recorded.

A complete response required the disappearance of all clinical and radiologic evidence of tumor for at least 4 weeks. A partial response required a ≥ 50% decrease in the sum of the products of the diameters of all measurable lesions, also for at least 4 weeks. Stable disease designated a steady-state of disease, which was a response less than a partial response or progression less than progressive disease, both for at least 6 weeks from the start of therapy. In addition, there could be no new lesions or increases in the size of any nonmeasurable lesions for

complete or partial remissions or for stable disease. Progressive disease indicated an unequivocal increase of at least 25% in the sum of the products of the diameters of all measurable lesions compared with baseline or the appearance of new lesions. Nonmeasurable disease was not considered in the response assessment, except that new lesions would constitute progressive disease; all nonmeasurable lesions had to disappear for a designation of complete response to be made.

Response duration was defined from the time that criteria for response were met until disease progression was objectively documented, with disease progression measured from the time that response was established. Stable disease was measured from the start of therapy until disease progression. All reported responses were verified by independent radiology review.

RESULTS

Thirty-three patients were accrued onto this study. All patients were assessable for toxicity, and 30 patients were assessable for response. The three unassessable patients came off study before the second treatment because of toxicity. One hundred thirty-two cycles were administered; 13 cycles were given to the three patients at the initial 600-mg/m^2 dose (median, six cycles; range, one to six cycles), and 75 cycles were given to patients who started at the 500-mg/m^2 dose (median, four cycles; range, one to eight cycles). Of the 30 patients who started at the 500-mg/m^2 dose, 15 received one cycle at this dose, four received two cycles, and 11 received three or more cycles. Fourteen patients required a dose reduction to 375 mg/m^2 for one or more cycles. Four patients required a further dose reduction to 281 mg/m^2. Characteristics of the 33 patients are listed in Table 1. The majority were male, presented with excellent performance status, and received only radiotherapy as prior treatment. A majority (18 of 33) had adenocarcinoma as a histologic diagnosis, and 26 of 33 patients had more than one site of involvement at study entry. At the time this article was written, the median follow-up was 7.9 months (range, 3.3 to 16.8 months). (For patients who died, the last follow-up date was the date of death.)

Antitumor Activity

Of the 30 patients assessable for response, none had a complete response and seven patients had a confirmed partial response; thus, the overall response rate was 23.3% (95% confidence interval, 9.9% to 42.3%). When all eligible patients are included, the response rate is 21.2%. The median time to progression for all patients was 3.8 months (range, 0.5 to 15.8 months). The median survival time of all patients was 9.2 months (Fig 1), and the 1-year survival rate was 25.3% (95% confidence interval, 9.7% to 40.9%). A higher response was seen among stage IIIB patients (four [67%] of six) compared with those who entered the study with stage IV disease (three [12.5%] of 24).

Table 1. Patient Characteristics

		No. of Patients
Age, years		
Median	63	
Range	42-74	
Sex		
Female		7
Male		26
Performance status*		
0		13
1		19
2		1
Histology		
Adenocarcinoma		18
Squamous		9
Undifferential		6
Prior therapy		
Radiation therapy		11
Sites of disease		
Lung		27
Lymph nodes		24
Liver		8
Bone		7
Adrenal		7
Pleural effusion		5
Subcutaneous		1
Spleen		1
Stage at study entry		
IIIB		8
IV		25
No. of organ sites involved		
1		7
2		11
3		10
≥ 4		5

*Eastern Coopoerative Oncology Group performance status.

Toxicity

After the first three patients were accrued, a decision was made to reduce the starting dose to 500 mg/m^2 based on the combined toxicity of 12 patients entered onto this study and a Canadian study of the same initial dose and schedule in patients with advanced colorectal cancer (Cripps et al, manuscript submitted for publication). Of the first three patients in the present trial, one patient experienced grade 3 dyspnea, mucositis, and high fever with radiographic suspicion of pneumonia. The patient recovered but refused further therapy. The other two patients completed six cycles of therapy at the initial dose. Two of the three patients experienced grade 3 neutropenia, and none experienced higher than grade 2 renal or hepatic toxicity. The hematologic toxicity experienced by the 30 patients who started at the 500-mg/m^2 dose level was similar to that of the other three patients. Hematologic toxicity, as median nadir counts and by worst grade experienced for all patients, is listed in Table 2. Overall, only two patients experienced a grade 4

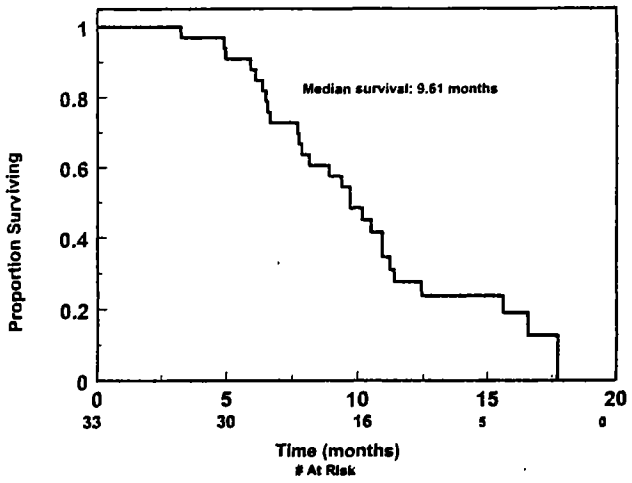

Fig 1. Overall survival of all patients.

adverse event; one experienced a cerebrovascular accident, and the other patient developed a deep vein thrombosis and pulmonary thromboembolus associated with severe shortness of breath. Neither of these events was considered related to the MTA therapy. Other than these cases, the most severe and prevalent nonhematologic toxicities are listed in Table 3. Severe (grade 3) nonhematologic toxicity presented most commonly as a skin rash (39%), lethargy (27%), anorexia (12%), nausea (12%), vomiting (9%), and diarrhea (9%), most of which was attributable to the study drug. The skin rash was generalized in half of affected patients and symptomatic with primarily pruritus in 23 of 26 patients. Subsequent retrospective analysis in this and the colorectal phase II study of the same agent showed that patients who received dexamethasone in their first cycle had a lower frequency and severity of skin rash (without dexamethasone, 93% of cycles with skin rash, 47.5% grade 3; with dexamethasone, 56% of cycles with skin rash, 12% grade 3). Four patients (12% of all patients) on the study developed febrile neutropenia, with one documented severe systemic infection considered related to protocol therapy.

Nonhematologic biochemical changes were mild. Only three patients developed transient grade 3 elevations of their liver function tests (bilirubin and AST), and only one patient developed grade 2 elevation of serum creatinine (Table 4).

Table 3. Nonhematologic Toxicity (n = 33)

Toxicity	Grade (no. of patients) 1	2	3	4	Total No. of Patients	% of Patients	% Drug-Related Only
Skin rash	3	10	13	0	26	79	79
Lethargy	5	15	9	0	29	88	76
Anorexia	8	10	4	0	22	67	58
Diarrhea	9	2	3	0	14	42	33
Nausea	13	9	4	0	26	79	76
Arthralgia	1	4	3	0	8	24	0
Stomatitis	5	4	2	0	11	33	33
Vomiting	8	5	3	0	16	49	46
Tearing	6	3	2	0	11	33	30
Edema	5	5	3	0	13	39	21
Febrile neutropenia			4		4	12	12
Infection	3	3	4	0	10	30	6

DISCUSSION

Initial results from preclinical animal studies and phase I trials suggested clinical activity for MTA primarily against colorectal and pancreatic cancer.[19,20] The level of activity seen in the present study in NSCLC was higher than initially anticipated, and independent reviewers confirmed all responses. This promising level of clinical activity was seen in patients with lung and lymph node involvement as well as in those with visceral and bone involvement, although the proportion of patients who responded was much higher in the group of stage IIIB patients. In another phase II study of MTA in patients with NSCLC by Clarke et al,[21] all patients were initially treated with 600 mg/m^2 MTA. Response rates were comparable to those in this study; among 12 patients assessable for response, the overall response rate was 33% (all partial responses). Toxicity profiles were similar between the two studies; in addition, toxicity seen in the phase I studies was similar to that reported for other drugs in this class.[19,20,22] Neutropenia was the predominant hematologic toxicity, resulting in dose reduction in 12% of patients, but it did not lead to treatment delays; only one patient (3%) experienced dose-reducing (grade 4) thrombocytopenia.

Most symptomatic, nonhematologic toxicity was managed with appropriate supportive care; for ≥ grade 3 toxicity, the next cycle was delayed until symptoms resolved to ≥ grade 1 severity and subsequent doses were reduced by 25%. Nausea and emesis were infrequent and not severe,

Table 2. Hematologic Toxicity (n = 33)

	Nadir (× 10^9/L) Median	Range	Toxicity Grade 0	1	2	3	4
Hemoglobin, g/L	111	73-149	6	14	10	3	0
WBC	2.5	0.4-8.1	6	5	9	11	2
Granulocytes	1.1	0.0-4.0	7	3	10	9	4
Platelets	152	20-278	17	14	1	0	1

Table 4. Biochemical Changes (n = 31)

Test	Toxicity Grade 0	1	2	3	4
Serum creatinine	29	1	1	0	0
Bilirubin	26	0	4	1	0
AST	5	17	7	2	0
Alkaline phosphatase	14	16	1	0	0

and physician discretion was permitted for prophylaxis based on the low emetogenic potential projected from phase I studies. Skin rashes were frequent; 30% of patients had treatment delayed with no subsequent dose reduction, whereas patients with generalized, symptomatic rash (39%) were given a 25% dose reduction. Both groups were treated prophylactically with dexamethasone for 3 days starting the day before each subsequent dose. With this intervention, skin toxicity decreased in subsequent cycles. Later in the study, it was noted that prophylactic dexamethasone given in cycle 1 seemed to have a beneficial effect in reducing the expected frequency and severity of skin rash. Future trials should likely incorporate this premedication at the first dose. Thirty percent of patients came off protocol therapy because of toxicity, most often gastrointestinal. This highlights the considerable interpatient variability of the toxicity experienced. Nonhematologic biochemical alteration of renal and hepatic function was relatively mild and of no clinical consequence. In three patients (9%), grade 3 elevation of bilirubin or AST levels resulted in dose reduction.

The decision to reduce the starting dose from 600 mg/m^2 to 500 mg/m^2 early in this study was based largely on the toxicity seen in a larger cohort of patients in a Canadian phase II study of colorectal cancer that is using the same dose and schedule. The toxicity seen in all other phase II trials of lung, breast, and gastrointestinal tumors at the 600-mg/m^2 dose and schedule has been similar to that seen in our study. Factors that may be associated with the more severe toxicity seen in the Canadian colorectal trial cohort have not yet been identified. The clinical activity in our trial is similar to that seen in the study of Clarke et al,[21] in which all patients started at a dose of 600 mg/m^2. Furthermore, it is interesting that all responding patients were treated at an initial dose of 500 mg/m^2.

MTA clearly has relevant clinical activity in patients with advanced NSCLC and toxicity that is tolerable with conventional dose and schedule adjustments. In addition to its effect on multiple enzymes in the folate-dependent pathways, MTA can synchronize treated cells at the G_1/S interface initially, followed by synchronous entry of treated cells into S phase II 4 hours after initial drug exposure in vitro.[23] A recent study suggests that MTA may enhance the cytotoxic effect of other drugs, such as gemcitabine, when target cancer cells are exposed to MTA 12 to 24 hours earlier.[24] A phase I combination trial of these two agents is in progress. As a result, further studies are planned to test the efficacy of MTA in combination with other agents with proven efficacy against NSCLC, such as the taxanes and platinum compounds. Our group is presently conducting a phase II combination study of MTA and cisplatin in advanced NSCLC. Ultimately, it is hoped that MTA may contribute to an improvement in the survival and quality of life of some patients with this disease.

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Original article

Front-line treatment of advanced non-small-cell lung cancer with MTA (LY231514, Pemetrexed disodium, ALIMTA™) and cisplatin: A multicenter phase II trial

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Summary

Background: To evaluate the activity of MTA plus cisplatin in chemotherapy-naïve patients with non-small cell lung cancer (NSCLC).

Patients and methods: Thirty-six chemotherapy-naïve patients with NSCLC received 500 mg/m^2 MTA plus 75 mg/m^2 cisplatin every 21 days, with 4 mg dexamethasone orally twice daily on the day before, of, and after MTA administration.

Results: Median age was 58 years. WHO performance status was 0–2. Eighteen patients each had stage IIIB and IV disease. Seventeen patients each had squamous-cell and adenocarcinoma; two had undifferentiated disease. Fourteen patients (39%; 95% confidence interval: 23%–57%) showed partial response; seventeen (47%) had stable disease. Median survival was 10.9 months. Twenty-one patients (59%) experienced grade 3 or 4 granulocytopenia without fever or infection. Five (14%) and six (17%) patients experienced grade 3 anemia and grade 3 or 4 thrombocytopenia, respectively. Nonhematological toxicities included grade 3 nausea in two patients (6%), and grade 3 and 4 diarrhea in one patient (3%) each. One patient each experienced grade 4 ALT and grade 3 bilirubin and AST elevations.

Conclusions: MTA plus cisplatin is well tolerated and active against NSCLC. Further studies of this combination are warranted.

Key words: cisplatin, MTA, non-small-cell lung cancer (NSCLC), phase II

Introduction

Lung cancer is the most common type of cancer in men, and has increased in incidence in women over the last decade. Approximately 75% of lung cancers are non-small-cell lung cancers (NSCLC), and it is the major cause of cancer-related death in both North America and Europe [1]. NSCLC treatment varies according to the patient's tumor stage at the time of diagnosis, with many patients receiving multimodality treatment consisting of various combinations of surgery, radiotherapy, and chemotherapy. The role of chemotherapy recently has been increasing in all tumor stages [2].

In stages I through III NSCLC, combination-chemotherapy is being clinically tested as an integral part of multimodality treatment regimens, either as adjuvant or neoadjuvant chemotherapy, or in patients who are inoperable, as simultaneous or sequential radio–chemotherapy. In stage IV NSCLC, chemotherapy combinations containing cisplatin are an important part of palliative therapy, since it has been demonstrated that such combination chemotherapy improves survival, provides symptom relief, and improves quality of life when compared to best supportive care alone [3–5]. Despite major progress in treatment over the last 10 years, considerable improvements are still needed. The newest anticancer drugs, some with unique mechanisms of action, i.e., new antimetabolites, new antitubulins, topoisomerase-I inhibitors, etc., offer hope that a more effective and tolerable chemotherapy can be found which can meet higher demands and be adaptable to a variety of clinical situations [6–8].

Historically, antifolates have not been widely used in the treatment of NSCLC. While a number of them, including nolatrexed, raltitrexed, trimetrexate, and edatrexate, have recently been evaluated in this tumor [9–14], none has yet gained a role in standard clinical practice.

MTA (LY231514, Pemetrexed disodium, ALIMTA™) is a novel multitargeted antifolate which inhibits several enzymes of the folate pathways, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. This feature distinguishes it from the older antifolates. MTA is polyglutamated intracellularly, which results in prolonged retention in cells and sustained cytotoxic effects [15].

Single-agent dose-finding studies with MTA determined that a dose and schedule of 600 mg/m^2 administered intravenously over 10 minutes every 21 days provided both safety and convenience for patients [16]. Initial phase II evaluation showed in two separate studies that MTA had single-agent activity in patients with NSCLC, with reported response rates of 23% and 17%

[17, 18]. A review of MTA in NSCLC that includes a discussion of these two studies has recently been published [19].

Of the combination phase I trials initiated with MTA, the study defining the doses at which MTA and cisplatin could safely be administered in combination was of particular interest in NSCLC, given the important role of cisplatin in the treatment of this tumor. In this study, patients with solid tumors received MTA intravenously over 10 minutes and cisplatin over 2 hours once every 21 days. The MTD was determined to be 600 mg/m^2 MTA and 100 mg/m^2 cisplatin, with dose-limiting toxicities of reversible neutropenia and leukopenia, and delayed fatigue. The dose selected for further evaluation in the phase II setting was 500 mg/m^2 MTA and 75 mg/m^2 cisplatin [20].

The current study was designed to explore the antitumor activity of MTA and cisplatin combination therapy when given to chemotherapy-naïve patients with locally advanced or metastatic NSCLC.

Patients and methods

Patient population

Patients were eligible if they met the following criteria: Histologic or cytologic diagnosis of stage IIIB or IV NSCLC with stage IIIB or IV bidimensionally measurable lesions; age ≥ 19 years; no prior chemotherapy; prior radiation therapy to less than 25% of the bone marrow; performance status ≤ 1 on the WHO scale; adequate bone marrow reserve (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, and hemoglobin ≥ 9 g/dl); adequate renal function (calculated creatinine clearance of ≥ 45 ml/min using the modified Cockcroft and Gault formula); adequate hepatic function (bilirubin ≤ 1.5 times the upper limit of normal, and aspartate and alanine transaminases ≤ 3.0 times the upper limit of normal). Patients were ineligible if they had an active infection, clinical evidence of CNS metastases or third-space fluid collections, albumin < 2.5 g/dl, or were unable to interrupt aspirin or other NSAID administration on or around the day of MTA administration. The local ethical committees of each participating center approved the protocol. Written informed consent was obtained from all patients before treatment.

Patient evaluation

Pretreatment evaluation included a complete medical history and physical exam, a complete blood cell (CBC) count, a standard biochemical profile, urinalysis for protein, blood, and microscopic, calculated creatinine clearance using the modified Cockcroft and Gault formula, an electrocardiogram, chest X-rays, and a radiologic imaging study for tumor measurement. (Ultrasound was not permitted as a method of tumor measurement.) During treatment, a CBC count was performed weekly; in the case of grade 3 or 4 neutropenia or thrombocytopenia, a CBC count was performed every other day to document the duration of this toxicity. A biochemistry panel was performed on day 8 of each cycle; a biochemistry panel, urinalysis, and calculated creatinine clearance was performed prior to each cycle. The duration of any grade 3 or 4 chemistry toxicity was documented by retesting every other day. A medical history and physical exam were performed prior to each cycle to document overall impact of disease and treatment-related toxicity, graded using the NCI common toxicity criteria (CTC) scale.

Treatment plan

All patients received 500 mg/m^2 MTA (Eli Lilly and Company, Indianapolis, Indiana) as an intravenous infusion over 10 minutes, followed 30 minutes later by 75 mg/m^2 cisplatin; treatment was administered preferably on an outpatient basis every 21 days. Cisplatin administration and pre- and post-hydration were performed according to local policy. Patients were also medicated with dexamethasone 4 mg orally twice per day on the day before, the day of, and the day after MTA administration. Dose adjustment criteria were based primarily on hematologic parameters, with adjustments also allowed for neurosensory toxicity greater than grade 1 or other nonhematological toxicity greater than grade 2. Doses of both drugs were reduced in subsequent cycles by 15% if chemotherapy-induced grade 4 neutropenia lasting greater than five days accompanied by grade 1 or 2 thrombocytopenia occurred or if grade 3 neutropenia and thrombocytopenia occurred simultaneously. Doses of both drugs were reduced by 25% if grade 4 neutropenia was accompanied by grade 3 thrombocytopenia, and doses of both drugs were reduced by 50% in any case of grade 4 thrombocytopenia. Any patient who required more than two dose reductions for hematological toxicity was discontinued from the study. Dose delays were required if a patient's calculated creatinine clearance (using the modified Cockcroft and Gault formula) dropped to below 45 ml/min in the presence of grade 3 or 4 neutropenia or thrombocytopenia. Drug administration was not resumed until the patient's calculated creatinine clearance had risen to 45 ml/min or higher. Reduced dose levels were maintained for all subsequent doses of treatment.

Measurement of study endpoints

The primary objective of the study was to determine the tumor response rate for patients with stage IIIB or IV NSCLC who received treatment with MTA in combination with cisplatin. Standard SWOG response criteria were used to define the antitumor effects; responses were assessed in alternate therapy cycles with CT scan or chest X-ray [21]. Responses had to be confirmed; in case of CR and PR a second assessment had to be scheduled for four weeks after the first documentation of response. All patients who received at least one dose of both MTA and cisplatin were assessable for response.

Secondary objectives included the measurement of time to event variables such as duration of response for responding patients, time to progressive disease, and survival time. According to SWOG-criteria the duration of response was calculated from the time of first objective assessment of CR/PR to the first time of progression or death due to any cause. The time to progressive disease was calculated from the time of study entry to the first observation of disease progression. Overall survival was measured from the time of study entry to the time of death due to any cause, and was estimated by the method of Kaplan and Meier [22].

Sample size and statistical considerations

It was planned to have up to 35 qualified patients to be enrolled in a two stage sequential study [37]. Thirteen of the patients were to be enrolled into the first stage of the study. If fewer than two patients had responded to MTA and cisplatin therapy, the accrual would have been stopped. Our plan further stipulated that if at least 2 patients responded to MTA–cisplatin, another 22 patients were to be enrolled into the second stage of the study. If fewer than 7 patients had exhibited a response to MTA–cisplatin by the end of the second accrual stage, by which time 35 patients were enrolled in the study, the conclusion would have been drawn that this regimen was not worthy of further study. If, on the other hand, at least seven patients responded after the second accrual stage, the conclusion would have be drawn that the treatment was promising.

The procedure described above tested the null-hypotheses (H_0) that the true response rate is $\leq 20\%$ *versus* the alternative hypotheses (H_A) that the true response rate is at least 40%. The significance level (i.e.,

Table 1. Patient characteristics

	Number of patients (%)
Total	36
Age (years)	
Median	
58	
Range	
26–73	
Sex	
Male	29 (81)
Female	7 (19)
Performance Status (WHO)	
0	8 (22)
1	27 (75)
2[a]	1 (3)
Stage at entry	
IIIB	18 (50)
IV	18 (50)
Histology	
Squamous	17 (47)
Adeno	17 (47)
NSCLC	2 (6)
Prior treatment	
None	29 (80)
Surgery	6 (17)
Radiotherapy	1 (3)
Number of involved sites	
1	12 (33)
2	12 (33)
3	9 (25)
4	3 (8)

[a] This patient was enrolled in violation of the protocol entry criteria, which required a performance status less than 2.

the probability of rejecting the H_0 when it is true) is 0.04. The power (i.e., the probability of rejecting H_0 when the alternative hypotheses is true) is 81%.

The average sample size for the test procedure described is 30 patients whenever the true response rate is 20% and is 30 patients when the true response rate is 40%.

Results

Patient demographics

From November 1997 to March 1998, 36 chemotherapy-naïve patients with NSCLC were enrolled. Patient characteristics are listed in Table 1. Ninety-seven percent of the patients had a WHO performance status of 0–1, and patients were distributed equally between stage IIIB and stage IV disease at baseline. Seventeen patients (47%) each had adenocarcinoma and squamous-cell carcinoma, with two patients (6%) having undifferentiated histology. The majority of patients had received no prior treatment for their cancer, with six (17%) having had prior surgery and one (3%) having received prior radiotherapy.

Response to treatment

Thirty-six patients were assessable for response. Fourteen patients achieved a PR (39%; 95% confidence interval [95% CI]: 23%–57%), while 17 patients (47%) had stable disease as their best response. Of the 14 partial responses, six were in patients with stage IIIB disease, and eight were in patients with stage IV disease. The median duration of response for responding patients was 10.4 months (range 0.3–15.4 months; 95% CI: 6.3–12.2 months), with 75% of patients having a response duration of greater than 6 months, and 50% having a response duration of greater than 9 months. The median time to progressive disease was 6.3 months (range 1.0–16.9 months; 95% CI: 2.9–14.1 months; 22% censoring). Fifty-six percent of patients remained progression free at six months, with thirty-six percent and thirty-three percent remaining progression free at nine months and one year, respectively. The median survival was 10.9 months (range 1.0–17.7 months; 95% CI: 6.8–16.9 months; 36% censoring), and 6-month, 9-month, and 1-year survival probabilities were 81%, 56%, and 50%, respectively.

Table 2 Hematologic toxicity of the combination of MTA and cisplatin in all patients ($n = 36$)

Toxicity	Maximum CTC toxicity grade			
	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Granulocytes	1 (3)	6 (17)	10 (28)	11 (31)
Hemoglobin	9 (25)	19 (53)	5 (14)	– (–)
Platelets	12 (33)	5 (14)	5 (14)	1 (3)
WBC	9 (25)	13 (36)	9 (25)	2 (6)

Compliance with treatment

A total of 148 cycles of treatment were administered with a median number of four cycles per patient (range 1–11 cycles). Thirty-eight cycles (26%) were delayed (two cycles were shortened due to scheduling conflicts). Common reasons for delay were scheduling conflicts unrelated to disease or treatment (22 cycles, 15%), decreasing creatinine clearance (5 cycles, 3%), weight loss (3 cycles, 2%), and leukopenia (2 cycles, 1%). The administered median dose for MTA and cisplatin was 500.5 mg/m^2/cycle (range 375–512 mg/m^2/cycle) and 75 mg/m^2/cycle (range 56–77 mg/m^2/cycle).

Hematologic and nonhematologic toxicity

Hematologic toxicity was evaluated in all patients and in all cycles (Table 2). Grade 3 or 4 granulocytopenia was experienced by 10 patients (28%) and 11 patients (31%), respectively. No cases of febrile neutropenia or infection resulted. Grade 3 anemia was experienced by five patients (14%) and grade 3 or 4 thrombocytopenia was experienced by five (14%) and one patient (3%), respectively. While 12 patients (33%) required red cell transfusions and 1 patient required platelet support, no patient experienced hemorrhage.

Table 3. Nonhematologic toxicity of the combination of MTA and cisplatin in all patients (n = 36).

Toxicity	Maximum CTC toxicity grade			
	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Nausea/vomiting	21 (58)	8 (22)	2 (6)	– (–)
Diarrhea	5 (14)	3 (8)	1 (3)	1 (3)
Fever	1 (3)	2 (6)	– (–)	– (–)
Infection	1 (3)	1 (3)	– (–)	– (–)
Cutaneous	8 (22)	5 (14)	– (–)	– (–)
Neuro motor	5 (14)	15 (42)	2 (6)	– (–)
Hair	10 (28)	3 (8)	– (–)	– (–)
Pulmonary	– (–)	– (–)	1 (3)	– (–)
Stomatitis	10 (28)	2 (6)	1 (3)	– (–)
Weight loss	8 (22)	3 (8)	– (–)	– (–)

Table 4. Biochemical changes (n = 36).

Toxicity	Maximum CTC toxicity grade			
	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Serum creatinine	11 (31)	2 (6)	– (–)	– (–)
Bilirubin	– (–)	5 (14)	1 (3)	– (–)
AST	5 (14)	1 (3)	1 (3)	– (–)
ALT	11 (31)	– (–)	– (–)	1 (3)
Alkaline phosphatase	9 (25)	– (–)	– (–)	– (–)

Severe nonhematological toxicity was rare (Table 3). Grade 3 nausea was experienced by two patients (6%), and grade 3 or 4 diarrhea was experienced by one patient (3%) each. In contrast to earlier studies with MTA [17, 18], disabling fatigue (classified as neuromotor toxicity using the CTC grading system) was not seen in this patient population, with 15 patients experiencing grade 2 fatigue and two patients experiencing grade 3 fatigue.

Nonhematologic biochemical changes were mild (Table 4). Grade 3 elevations in bilirubin and AST occurred in one patient each, and a single patient experienced grade 4 elevation of ALT. Two patients developed grade 2 elevation of serum creatinine, but decreasing creatinine clearance resulted in treatment delays in only 3% of cycles.

Discussion

Preclinical and phase I studies with MTA have demonstrated antitumor activity in colorectal cancer, pancreatic cancer, NSCLC, and malignant pleural mesothelioma [16, 20]. Results from at least two phase II studies have been published which show the activity of single agent MTA in advanced NSCLC [17-18]. In the first, all patients were treated with MTA 600 mg/m^2. Among 42 patients assessable for response, the overall response rate was 17% (all partial remissions). In the second, a starting dose of 600 mg/m^2 was reduced to 500 mg/m^2 after the first three patients experienced a high degree of toxicity, including skin rash and fatigue. It was consequently determined that prophylactic administration of dexamethasone for three days beginning the day before MTA administration decreased both the frequency and severity of this toxicity. A partial response was obtained in 23% of the patients in this study.

MTA has demonstrated interesting preclinical activity in combination with a variety of anticancer agents, and is a promising candidate for combination therapy in the clinical setting. Teicher and coworkers showed that the combination of MTA and cisplatin produced additive to greater than additive cell kill in EMT-6 tumor-bearing mice, and greater than additive tumor growth delay in mice implanted with the H460 non-small-cell lung cancer carcinoma [23]. Our study is the first phase II study of MTA plus cisplatin completed in advanced NSCLC [24].

The dosage and schedule selected for this study were based upon the experiences reported by Thoedtmann and colleagues in the phase I setting [20]. In this study, two schedules were applied: a day 1, every three weeks schedule; and a day 1 and 2, every three weeks schedule. In the day 1 schedule, MTA was given first over a 10-minute period, followed by cisplatin as a 2-hour infusion. The MTD identified was 600 mg/m^2 MTA combined with 100 mg/m^2 cisplatin. The dose-limiting toxicity was neutropenia. The dose recommended for phase II studies using this schedule was 500 mg/m^2 MTA combined with 75 mg/m^2 cisplatin. Because of a concern that the pre-hydration required for cisplatin could potentially affect MTA pharmacokinetics, a schedule that incorporated a 24-hour delay between the administration of MTA and cisplatin was tested. In this day 1 and 2 schedule, patients received MTA (600 mg/m^2) on day 1 and cisplatin (75 mg/m^2) on day 2. The dose-limiting toxicity was myelosuppression and neutropenic sepsis. On this schedule, two patients died from treatment-related complications and skin toxicity appeared to be more common. Because data showed that prehydration for cisplatin did not affect MTA pharmacokinetics, and because the day 1 and 2 schedule was not as convenient for patients, this schedule was not recommended for further clinical investigation.

Our phase II study demonstrated that the day 1, every three weeks schedule with 500 mg/m^2 MTA combined with 75 mg/m^2 cisplatin was effective in advanced NSCLC. Fourteen of the thirty-six patients included (39%) showed an objective partial remission, with slightly greater than half of all responses being in patients with stage IV disease (response confirmation four weeks following first response documentation). This response rate is almost twice as high as the rate shown by single agent MTA alone, and is comparable to the response rates shown by other new drugs (e.g., gemcitabine, paclitaxel, navelbine) when tested in combination with cisplatin in randomized and non-randomized studies [25–36] in advanced NSCLC.

In general, the MTA plus cisplatin combination was

well tolerated. The most prevalent hematologic toxicities were leukopenia and granulocytopenia. Eight patients had grade 3 and 3 had grade 4 leukopenia. Five patients had grade 3 granulocytopenia and eight had grade 4 granulocytopenia. However, no clinical problems such as infection or febrile neutropenia arose as a result of these toxicities. Nonhematological toxicity was mild to moderate. Twenty-two patients had some degree of fatigue, but only two patients experienced grade 3 toxicity (5.6%). This is in contrast to earlier experience in phase I and phase II studies, but may be the result of the consistent use of concomitant oral corticosteroids in this study [16, 17, 20]. Although some degree of nausea and vomiting were reported by 31 patients, only 2 patients experienced grade 3 toxicity. Neurotoxicity was extremely rare, with only three reports of grade 2 tinnitus, which did not require treatment.

MTA is a new drug with a unique mechanism of action among those agents widely used in the treatment of NSCLC. While antifolates have not typically been used in the treatment of this tumor, MTA differs substantially from older antifolates in that it has potent activity against multiple enzymatic targets. This may confer a therapeutic advantage by allowing MTA to retain activity in the face of resistance mechanisms such as overexpression or mutation of the primary target, and may explain, in part, why MTA has shown consistent activity in NSCLC.

On the basis of our experience, it can be concluded that the combination of MTA plus cisplatin is active and well tolerated in advanced NSCLC. However, in order to ensure good tolerability, prophylactic dexamethasone treatment is recommended prior to MTA administration. The outpatient feasibility and convenience provided by the short infusion time of MTA and the treatment schedule of once every three weeks further complement the tolerability of this regimen. The response rate of more than 40% and the promising median and one-year survival rates are strong arguments for clinically testing this combination and this treatment schedule further in NSCLC.

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Phase II Study of Pemetrexed Disodium, a Multitargeted Antifolate, and Cisplatin as First-Line Therapy in Patients with Advanced Nonsmall Cell Lung Carcinoma

A Study of the National Cancer Institute of Canada Clinical Trials Group

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BACKGROUND. Pemetrexed disodium (Alimta [Eli Lilly and Company, Indianapolis, IN], LY231514, multitargeted antifolate) is a new multitargeted antifolate agent that inhibits multiple enzymes in the folate pathway. Phase II trials showed single-agent response rates of 16% and 23% in untreated patients with nonsmall cell lung carcinoma (NSCLC). This study was undertaken to determine the response to pemetrexed disodium given in combination with cisplatin.

METHODS. Previously untreated patients were eligible if they had Stage IIIB or IV NSCLC, performance status 0, 1, or 2, adequate hematology and biochemistry and bidimensionally measurable lesions. Patients with brain metastases or neuropathy higher than Grade 2 were excluded. Pemetrexed disodium 500 mg/m^2 was given over 10 minutes, and cisplatin 75 mg/m^2 with hydration and mannitol diuresis was administered on Day 1 of each 21-day cycle. Dexamethasone 4 mg was taken orally once every 12 hours starting 24 hours before treatment and continuing for 6 doses after treatment. Four patients had detailed pemetrexed disodium pharmacokinetic analysis performed.

RESULTS. Between May 1998 and June 1999, 31 patients were treated on the study. There were 20 males and 11 females; median age was 60 years (range, 35–75 years); there were 5 Stage IIIB, 26 Stage IV, 26 performance status 0 or 1, and 5 performance status 2. In 29 patients evaluable for response, there were 13 partial responses (PRs; overall response rate [ORR], 95%; confidence interval [CI]: 26–64%) of median duration 6.1 months (1.6–7.8 months). Three of four evaluable patients with performance status 2 achieved PR, and 11 of 24 evaluable Stage IV patients responded (ORR, 45.8% in Stage IV). Eighteen patients died. The median survival rate was 8.9 months (range, 1–15+ months). A total of 160 courses were delivered (median, 6 for both cisplatin and pemetrexed disodium). Grade 3 and 4 anemia was observed in 5 and 1 patients, respectively, and Grade 3 and 4 granulocytopenia in 7 and 4 patients, respectively. Grade 3 nausea and emesis occurred in only 2 patients, Grade 3/4 diarrhea in 3 patients, and 2 patients had Grade 3 motor neuropathy. Nine patients had Grade 2 infections, and there was one case of febrile neutropenia. Pharmacokinetic results showed C_{max}, clearance and V_{ss} values to be similar to data from single-agent pemetrexed disodium given in the same dose.

CONCLUSIONS. The combination of pemetrexed disodium and cisplatin is active against advanced NSCLC and is a well-tolerated convenient outpatient regimen. It deserves further study to compare it with other standard regimens for NSCLC. *Cancer* **2001;92:595–600.** © *2001 American Cancer Society.*

KEYWORDS: lung carcinoma, chemotherapy, nonsmall cell lung carcinoma, pemetrexed disodium, antifolate agents, cisplatin.

The multitargeted antifolate pemetrexed disodium (Alimta, LY231514, multitargeted antifolate) is a new chemotherapeutic agent that has been shown to inhibit several enzymes in the folate pathway including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT).[1] In preclinical studies, pemetrexed disodium showed activity against a wide range of tumor types including lung carcinoma, mesothelioma and breast, colon, and bladder carcinomas.[2-4] Based on the preclinical activity observed in vitro and in murine models, Phase II trials of single-agent pemetrexed disodium were initiated in patients with advanced nonsmall cell lung carcinoma (NSCLC). In a Canadian study in which pemetrexed disodium, 500 or 600 mg/m^2, was administered over 10 minutes every 3 weeks, 7 of 30 patients achieved partial response (23.3%, 95% confidence interval [CI], 9.9–42.3%).[5] In a similar study undertaken in Australia and South Africa, the overall response rate to single-agent pemetrexed disodium was 16%.[6]

The encouraging single-agent response rates and favorable toxicity profile observed in the Phase II trials led to the development of combination chemotherapy studies of pemetrexed disodium with cisplatin. A Phase I trial showed that pemetrexed disodium 500 mg/m^2 could be administered safely with cisplatin 75 mg/m^2 every 3 weeks, and 1 of 6 patients with NSCLC responded.[7] Based on these results, two Phase II studies of pemetrexed disodium in combination with cisplatin were initiated, one in Germany and one in the National Cancer Institute of Canada, Clinical Trials Group. We report here the results of our Phase II trial.

MATERIALS AND METHODS

Patient Selection

Previously untreated patients were eligible for the study if they had Stage IIIB or IV NSCLC with evidence of at least one bidimensionally measurable lesion. Prior radiation therapy was permitted if acute side effects had resolved and radiation had not been given to the sole site of disease. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 were eligible, and they were required to have a life expectancy of at least 12 weeks. They had to have adequate hematology (absolute granulocyte count, $\geq 1.5 \times 10^9$/L and platelets $\geq 150 \times 10^9$/L). The serum creatinine had to be within the normal limit set by the institution and the bilirubin level less than or equal to 1.5 times the upper normal limit. Hepatic enzymes had to be less than or equal to 2 times the upper normal limit or less than or equal to 5 times the upper normal limit if documented liver metastases were present. All patients gave informed consent. Patients were excluded from the study if they had brain metastases, if they had received prior chemotherapy, or if they were taking anti-inflammatory drugs or salicylates that could not be stopped for the day of treatment. The study protocol was approved by a Human Experimentation Review Committee at each of the participating institutions.

Drug Administration

Pemetrexed disodium was supplied as a lyophilized powder in 20-, 100-, and 500-mg vials and was reconstituted by adding 10 mL of 0.9% sodium chloride. The appropriate dose of 500 mg/m^2 was infused intravenously over 10 minutes. Cisplatin 75 mg/m^2 was infused over 60 minutes with mannitol diuresis according to local institutional standard protocols. Because premedication with steroid had been shown in Phase II single-agent pemetrexed disodium studies to prevent skin rash, all patients received dexamethasone 4 mg orally once every 12 hours starting 24 hours before treatment and continuing for 6 doses after treatment. Antinausea medications were administered according to standard institutional protocols. Colony stimulating factors were not used routinely. In most institutions, treatment was administered in the outpatient setting.

In the absence of disease progression or unacceptable toxicity, treatment was administered every 3 weeks, and chemotherapy was continued for a maximum of 6 cycles of pemetrexed disodium and cisplatin. At the discretion of the investigator, patients could receive two further courses of pemetrexed disodium alone without cisplatin.

Measurements of Study Endpoints

All patients were assessable for toxicity from the time of their first treatment. Patients who had received at least one cycle of pemetrexed disodium and cisplatin and who had follow-up measurements performed to document changes in tumor size were considered assessable for response. All sites of measurable disease were followed for response. Chest X-ray and physical examination were performed before each treatment cycle, and computed tomography (CT) scans were repeated after every two cycles. Scans that were negative initially were repeated only if clinically indicated.

Standard response criteria were used, and complete and partial responses had to be confirmed at least 4 weeks after their first documentation. External radiology review was performed to validate all responses. Response duration was defined from the time that criteria were met until documentation of disease progression. Survival rate was calculated from the date of first treatment until death or date of last follow-up, and all patients were included in the survival analysis.

Pharmacokinetics

Because the Phase I combination trial of pemetrexed disodium and cisplatin suggested that coadministration of cisplatin might increase the clearance of pemetrexed disodium,[7] assessment of pemetrexed disodium pharmacokinetics was incorporated by protocol amendment for the final four patients enrolled on the trial to gain more information. Pharmacokinetic analysis was performed by noncompartmental methods using the WinNonlin computer program. Area under the plasma concentration versus time curve (AUC_{0-t}) and area under the first moment curve ($AUMC_{0-t}$) were calculated by the linear trapezoidal method and extrapolated to infinite time using the predicted concentration ($\hat{C}$) at the last measurable sampling time (T) and the apparent terminal elimination rate constant (γ_z) values as

$$AUC_{0-\infty} = AUC_{0-t} + \frac{\hat{C}}{\lambda_z} \quad (1)$$

$$AUMC_{0-\infty} = AUMC_{0-t} + \frac{\hat{C}}{\lambda_z} \cdot \left(\tau + \frac{1}{\lambda_z}\right) \quad (2)$$

Mean residence time (MRT), total plasma clearance (CL), and volume of distribution at steady state (V_{ss}) were calculated as:

$$MRT = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}} - \frac{\tau}{2} \quad (3)$$

$$CL_p = \frac{Dose}{AUC_{0-\infty}} \quad (4)$$

$$V_{ss} = CL_p \cdot MRT \quad (5)$$

where τ is the duration of infusion (10 minutes).

Drug Analysis Method

Human plasma samples were assayed for pemetrexed disodium using sensitive, selective, and validated methods.[8] Analysis was performed by liquid chromatography coupled with tandem mass spectrometry using an electrospray interface (LC/ESI/MS/MS). The methods for analysis of pemetrexed disodium were validated over the concentration ranges of 10.0 to 2000.0 ng/mL and 1.0 μg/mL to 2000.0 μg/mL in human plasma.

RESULTS

Between May 1998 and June 1999, 32 patients entered the study. One patient did not receive chemotherapy because of rapid tumor progression after registration but before treatment, and this patient has not been included in the analysis. The baseline patient characteristics of the remaining 31 patients are shown in Table 1. The median age was 60 years (range, 35–75 years), and there were 20 male and 11 female patients. Most patients had a good performance status, but five patients had ECOG performance status 2. Twenty-six patients had Stage IV tumors.

TABLE 1
Patient Characteristics

Characteristic	No. of patients
Median age (yrs) (range)	60 (35–75)
Gender	
Male	11
Female	20
Performance status	
0	2
1	24
2	5
Histology	
Adenocarcinoma	18
Squamous	6
Undifferentiated	6
Not specified	1
Prior radiation	8
Stage at study entry	
IIIB	5
IV	26

Response and Survival

Of the 31 patients entered, 29 were evaluable for response. One patient died 4 days after receiving his first course of pemetrexed disodium and cisplatin. He was found at home 3 days after treatment with decreased consciousness and respiratory distress and was admitted to hospital where a large myocardial infarction and pulmonary embolus were diagnosed. One patient was not assessable for response because of lack of follow-up radiology. Of the remaining 29 patients, 13 patients achieved partial remission for an overall response rate of 45% (95% CI, 26–64%). The median duration of response was 6.1 months (range, 1.6–7.8 months).

Three of the four evaluable ECOG performance status 2 patients achieved response, and 11 of the 24 evaluable Stage IV patients responded (45.8%). Eighteen patients died. At the time of this report, the median survival rate of the entire group of 31 patients was 8.9 months (range, 1–15+ months), and the 1 year survival rate was 49%.

Toxicity

A total of 160 chemotherapy cycles were delivered to 31 patients. The median number of cycles delivered was six for both cisplatin and pemetrexed disodium. The planned dose intensity for cisplatin was 25 mg/m^2 per week, and the actual delivered dose intensity was 24.5 mg/m^2 per week (range, 16.5–25.9 mg/m^2). The

TABLE 2
Hematologic and Associated Toxicity[a]

Toxicity	No. of patients	Nadir		Toxicity grade			
		Median	Range	1	2	3	4
Hemoglobin (g/L)	30	103	48–127	12	7	5	1
Leukocytes ($\times 10^9$/L)	30	2.8	0.4–7.9	8	11	5	2
Granulocytes ($\times 10^9$/L)	30	1.3	0.1–4.9	5	6	7	4
Platelets ($\times 10^9$/L)	30	140	8–297	16	0	0	1
Infection	31			1	9	0	0
Febrile neutropenia	31			0	0	1	0
Hemorrhage	31			4	2	1	0

[a] Worst toxicity by patient and numbers of patients with each toxic effect.

TABLE 3
Nonhematologic Toxicity[a] (n = 31)

Toxicity	Grade (no. of patients)				% of patients
	1	2	3	4	
Fatigue	6	14	8	0	87.1
Anorexia	5	12	1	0	58.1
Nausea	8	16	1	0	80.6
Vomiting	8	9	1	0	58.1
Diarrhea	3	7	2	1	41.9
Stomatitis	4	8	1	0	35.5
Skin rash	5	4	0	0	25.8
Tearing	6	5	0	0	38.7
Edema	7	6	0	0	16.1
Neuropathy (sensory)	6	1	0	0	12.9
Neuropathy (motor)	0	0	2	0	3.2

[a] Worst toxicity by patient.

planned dose intensity of pemetrexed disodium was 166.7 mg/m^2 per week, and the actual dose intensity was 160 mg/m^2 per week (range, 110.0–172.1 mg/m^2).

Hematologic toxicity is summarized in Table 2. Grade 3 or 4 granulocytopenia was observed in 33% of patients, but there was only 1 episode of febrile neutropenia. Thrombocytopenia was rare, and a platelet count below 25 $\times$ 10^9/L was observed in only 1 patient who subsequently was found to have bone marrow replacement by adenocarcinoma.

Nonhematologic toxicity is displayed in Table 3. Grade 3 nausea and vomiting were observed in only one patient each, and three patients experienced Grade 3 or 4 diarrhea. Despite premedication with dexamethasone, nine patients developed rash, but this was of Grade 2 severity in only four patients. Two patients developed Grade 3 neuromotor toxicity.

Pharmacokinetics

Plasma pemetrexed disodium concentration-time profiles for the four patients tested are presented in Figure 1. Individual plasma pemetrexed disodium concentrations decreased quickly over the first 24–48 hours after termination of the 10-minute intravenous infusion. Plasma concentrations were below the detection limit of the assay beyond 48 hours after start of infusion. Plasma concentration-time profiles appeared to be consistent with previously reported results.[9]

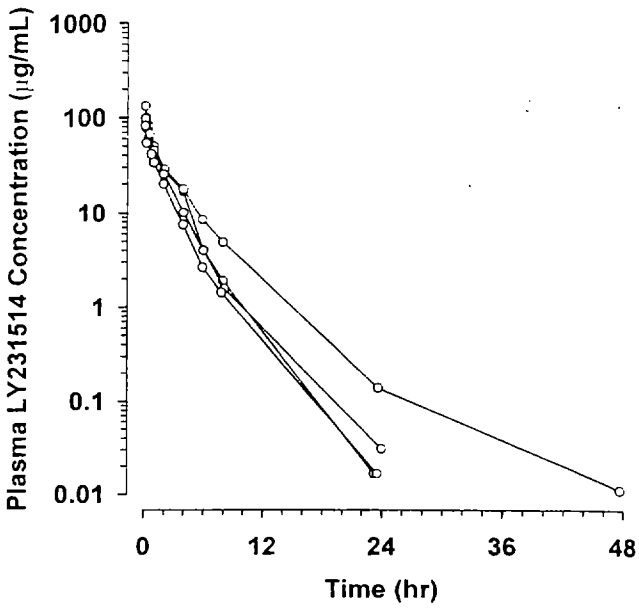

FIGURE 1. Individual plasma concentration-time profiles.

Mean (%CV, coefficient of variation) pharmacokinetic parameter estimates are presented in Table 4. Because there were few patients in both studies, comparisons between studies should be interpreted with caution. Nevertheless, pharmacokinetic parameters were generally consistent with previously reported results after single-agent administration.[9]

DISCUSSION

A large meta-analysis using updated data on 9387 patients from 52 randomized clinical trials showed conclusively that treatment with chemotherapy adds significantly to survival for virtually all stages of NSCLC.[10] In studies of advanced disease that compared supportive care to supportive care plus chemotherapy, the use of cisplatin-based treatment showed a benefit of chemotherapy with a hazard ratio of 0.73 ($P < 0.0001$) and a reduction in the risk of death of 27%, which was equivalent to an absolute improvement in survival of 10% at 1 year, or an increased median survival rate of 1.5 months.

The last decade has seen the introduction of several new chemotherapeutic agents such as gemcitabine, the taxanes paclitaxel and docetaxel, and vinorel-

TABLE 4
Mean (% CV) Alimta (LY231514, MTA) Pharmacokinetic Parameters

Parameter	No. of patients	C_{max} (μg/mL)	CL (mL/min/m^2)	V_{ss} (L/m^2)	$t_{1/2}$ (hr)
Single-agent administration[9] (%)	20	137 (33)	39.9 (24)	7.1 (21)	4.5
Current study (%)	4	110 (23)	48.5 (28)	7.0 (21)	2.9
Previous study[7] (%)	4	0.1 (21)	67.2 (31)	13.0 (32)	3.6

CV: coefficient of variation; CL: plasma clearance

bine that have activity against NSCLC and that produce single-agent response rates of greater than or equal to 20% in previously untreated patients with advanced tumors. Response rates for the new agents in combination with cisplatin or carboplatin usually have ranged from 30–40% or higher, and randomized trials comparing chemotherapy combinations using these new agents uniformly have reported median survival times of approximately 8–10 months and 1-year survival rates in the range of 30% to 40%.[11]

This multicenter study suggests that the combination of pemetrexed disodium and cisplatin has activity that is similar to that observed when cisplatin is combined with gemcitabine, the taxanes, or vinorelbine.[11] The overall response rate of 44.8% is encouraging, particularly because the response rate observed in patients with Stage IV disease was 45.8%. Furthermore, three of four evaluable patients who had an ECOG performance status of 2 achieved partial remission. Although these are few patients, this is in distinct contrast with the recent report by Johnson et al.[12] who found a very low overall response rate of only 13% (range, 6–17%) and median survival time of only 3.9 months (range, 1.9–7.9 months) in patients with performance status 2 who were participating in a large ECOG randomized trial. These results coupled with the high rates of Grade 3, 4, and 5 toxicity in such patients led to a protocol amendment to exclude performance status 2 patients from the rest of their study.

Our results are almost identical to those of Manegold et al. who also evaluated pemetrexed disodium 500 mg/m^2 with cisplatin 75 mg/m^2 in 36 patients with advanced NSCLC.[13] Their response rate was 38.8%, and the median duration of response was 6 months. Their study, however, had a higher proportion of patients with Stage III tumors (50%) and squamous cell pathology (50%).

Overall, the combination of pemetrexed disodium and cisplatin was very well tolerated in our study. Despite premedication with dexamethasone, rash was still observed in 9 of 31 patients. However, the rash was of only Grade 1 or 2 severity and did not result in discontinuation or delay of treatment for any patient. In the single-agent study reported by Rusthoven et al.[5] skin rash was reported in 79% of patients, and this led to treatment delay, dose reduction, or discontinuation of chemotherapy in 30% of patients when dexamethasone premedication was not used routinely.

The tolerability of the regimen is further supported by the observation that the planned dose intensities and actual dose intensities of both drugs were almost identical, and that 80.6% of patients received greater than 90% of their planned dose intensity. In fact, 17 patients received 6 or more cycles of treatment, which clearly reflects both efficacy and tolerability.

Because much of the toxicity of combination chemotherapy for NSCLC is contributed by cisplatin, there has been recent interest in developing noncisplatin chemotherapy regimens to treat this malignancy. In in vitro clonogenic assays, pemetrexed disodium and gemcitabine were shown to be synergistic when the tumor cells were exposed to gemcitabine before pemetrexed disodium.[14] In the human tumor xenograft model, pemetrexed disodium showed greater than additive antitumor effects when administered with paclitaxel and docetaxel, and synergistic effects when given with the topoisemerase I inhibitor, irinotecan.[14] Furthermore, pemetrexed disodium and the other antitumor agents could all be given at full dose without increased toxicity resulting from the combination. A Phase I study also has shown that pemetrexed disodium may be combined with gemcitabine.[15] Studies of pemetrexed disodium in combination with gemcitabine will be of particular interest in patients with NSCLC because gemcitabine is one of the most active agents for the treatment of this malignancy[16] and has a very favorable toxicity profile, even in elderly patients.[17] A Phase II study of this nonplatinum combination in advanced NSCLC is ongoing.

Minor differences in pharmacokinetic parameters were observed between this study and that of the Phase I pemetrexed disodium plus cisplatin combination.[7] Total plasma clearance in this study was 28% lower, and V_{ss} was approximately 46% lower than that reported previously. In the previous study in which pemetrexed disodium was administered with cisplatin, pemetrexed disodium pharmacokinetics were not

altered by the saline prehydration regimen. The data from this study also show pemetrexed disodium clearance and V_{ss} values to be similar to those of a comparable dose given as a single agent in another trial,[9] suggesting that cisplatin administration with its concomitant mannitol diuresis does not substantially affect pemetrexed disodium clearance. The terminal elimination half-life was generally consistent between all three studies. The differences in mean pharmacokinetic parameters between studies may not be clinically significant, and dosage adjustments as a result of these minor differences in clearance do not appear to be justified.

The combination of pemetrexed disodium and cisplatin is active against NSCLC and is a well tolerated convenient outpatient regimen. It deserves further study to compare it to other standard regimens for NSCLC and should be evaluated in combination with nonplatinum chemotherapy agents.

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Phase II Randomized Study of Pemetrexed plus Carboplatin or Oxaliplatin, as Front-line Chemotherapy In Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Cancer

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Pemetrexed, a novel multitargeted antifolate, in single-agent phase II studies has shown clinical activity against non-small-cell lung cancer (NSCLC) as first or second-line therapy and, in preclinical models, when combined with carboplatin and oxaliplatin has shown synergistic activity. Both these combinations have already been studied in the phase I setting. In a multicenter, phase II randomized study, eighty chemotherapy-naive patients (pts), with locally advanced or metastatic NSCLC received either (Arm A) pemetrexed (500 mg/m^2) + carboplatin (AUC6) IV infusion (39 pts), or (Arm B) pemetrexed (500 mg/m^2) + oxaliplatin (120 mg/m^2) IV infusion (41 pts), on day 1 of 21-day cycle, for up to 6 cycles of therapy. Vitamins and dexamethasone were provided per pemetrexed therapy. The primary objective determined the response rate for the two regimens; secondary endpoints included time to event measures and toxicity. Main pt characteristics are: 60 males, 20 females, median age 60 years (range 36-79), ECOG PS 0–1/2 99%/1%, stage IIIB/IV 36%/64%. Cycles delivered were 382 (Arm A=191, median 6, range 1-7; Arm B=191, median 6, range 1-8). Confirmed response rate in Arm A was 33%, with stable disease reported in 44% of pts, and in Arm B, 29% and 46%, respectively. Main grade 3/4 hematological toxicities in Arm A included neutropenia (26%), febrile neutropenia (3%), thrombocytopenia (18%) and anemia (8%). In Arm B neutropenia (2%) was the only grade 4 hematologic toxicity recorded, with grade 3 neutropenia (5%), thrombocytopenia (2%), and anemia (2%) being reported. Main non-hematologic toxicities included grade 3 fatigue (8%) and stomatitis (3%) in Arm A, with grade 3 vomiting (7%), neuropathy (2%), diarrhea (2%), and hypersensitivity reactions (2%) in Arm B. Nine months after the last patient was randomized, both TTPD and survival are immature. These data will be mature at the meeting. Response rates are similar and toxicity profiles lower compared to those of other platinum doublets. These two tested regimens may provide a better therapeutic index than other regimens for the palliative treatment of advanced NSCLC.