Oncologic Drugs Advisory Committee
July 27, 2004
Briefing Material

Application #	**NDA 21-677**
Drug Name	**AlimtaÒ (pemetrexed)**
Medical Reviewer	**Martin H. Cohen, M.D.**
Medical Team Leader	**John R. Johnson,M.D.**
Documents reviewed	**EDR \\CDSESUB1\N21677\ N_000\2003-11-03**

Table of Contents

Table of Tables

Table of Figures

Clinical Review for NDA 21-677

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA decision on approval is deferred pending discussion of the Oncologic Diseases Advisory Committee.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Deferred

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The safety and efficacy review is based on data provided in EDR \\CDSESUB1\N21677\ N-000\2003-11-03. The pivotal phase 3 trial was titled "A Phase 3 Trial of ALIMTA versus Docetaxel in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Who Were Previously Treated with Chemotherapy". Results of four supporting phase 2 NSCLC trials, two first-line and 2 second-line were also provided.

B. Efficacy

The sponsor claimed that survival of LY231514 treated patients was non-inferior to survival of docetaxel treated patients. FDA statistical analysis indicated that non-inferiority was not demonstrated. Even if non-inferiority was demonstrated, however, it would not be credible because of post-study chemotherapy. Thirty fewer docetaxel treated patients received post-study chemotherapy compared to LY231514 treated patients (randomized and treated population [RT]) Comparable findings were obtained with the ITT population. While 32% of LY231514 treated patients received post-study docetaxel it was observed that patients receiving any post-study chemotherapy drug(s) survived longer than those who did not. The majority of patients on both arms who did not receive post-study chemotherapy were performance status 0 or 1 at their last study visit and, conceivably, could have received additional treatment.

Response rate, time to progression and symptom improvement was comparable for the two study arms.

C. Safety

Safety testing was adequate. LY231514 produced significantly less neutropenia and less febrile neutropenia than did docetaxel. Myalgias, arthralgias and neurotoxicity were also significantly higher in the docetaxel arm. There were fewer hospitalizations and less need for granulocyte colony stimulating factors with LY231514 treatment but LY231514 patients spent more days in the hospital. LY231514 patients required more red blood cell transfusions. The incidence of fatigue, weight loss, nausea, vomiting and constipation were statistically significantly higher in the LY231514 arm. Other clinically significant AEs that were different between the treatment arms included increased alanine and aspartate aminotransferases (LY231514 higher incidence), skin rash (LY231514 higher incidence) and decreased creatinine clearance (LY231514 higher incidence.

There is also an issue regarding vitamin supplementation in LY231514 treated patients but ot in docetaxel treated patients. Twenty-nine percent of the latter patients had elevated homocysteinne (Hcys) levels. Hyperhomocysteinemia is risk factor for atherosclerotic disease in the coronary, cerebral, and peripheral arterial circulations. It also appears to be a risk factor for venous thromboembolism and for neuronal cell damage. Low dietary intake of vitamins B6, B12 and folic acid is the most prevalent cause of hyperhomocysteinemia. Vitamin B12 and folic acid supplementation have been shown to reliably reduce elevated Hcys levels and to reduce hematological and non-hematological toxicity of LY231514 treatment. Hcys was, in fact, better than baseline albumin (another predictor of toxicity) at predicting LY231514 toxicity. There is no reason to suspect that vitamin supplementation, if administered, would not have also reduced toxicity in hyperhomocysteinemic docetaxel treated patients

D. Dosing

The recommended dose of Alimta is 500 mg/m2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. Patients receiving Alimta also received dexamethasone, for skin rash prophylaxis, and vitamin supplementation including a low-dose daily oral folic acid preparation (350 to 1000 μg folic acid) and vitamin B12 1000 μg i.m. during the week preceding the first dose of Alimta and every 3 cycles thereafter.

Patients receiving docetaxel also received dexamethasone to reduce the severity of fluid retention and hypersensitivity reactions.

E. Special Populations

1. **Pediatrics** LY231514 safety and efficacy have not been established in children.

2. **Elderly** - A statistically significant age by treatment interaction was observed for diarrhea (p=0.0496). Among patients $\geq$ 65, docetaxel-treated patients experienced a significantly higher frequency of diarrhea compared with

LY231514-treated patients (34% versus 13%, p=0.003). There was no difference in the incidence of diarrhea between the treatment arms among the younger patients.

3. **Renal or Hepatic Impairment** - In clinical studies, patients with creatinine clearance (Ccr) $\geq$ 45 mL/min using the standard Cockcroft and Gault formula or GFR measured by Tc99m-DPTA serum clearance method required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients.

   LY231514 is not extensively metabolized by the liver. Dose adjustments should be made based on CTC levels of hepatic impairment. Patients eligible for the study had to have a bilirubin less than or equal to the upper limit of normal (ULN), aspartate transaminase (AST) and alanine transaminase (ALT) $\leq$1.5 x ULN and alkaline phosphatase $\leq$5 x ULN.

4. **Gender** - There was no statistically significant gender by treatment interaction

5. **Ethnicity** - Approximately 70% of study patients were Caucasian. East and Southeast Asians comprised approximately 17% of the study population. Patients of African descent comprised 3% of the population. There was no significant difference in efficacy or safety results among these ethnic populations.

6. **Pregnancy** - Category D **-** LY231514 may cause fetal harm when administered to a pregnant woman.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: ALIMTA®

Proprietary Name: Pemetrexed for injection

Applicant: Eli Lilly and Company

Drug Class: Antifolate

Indication:

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

Proposed: Alimta as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy

Dosage and Administration:

Current Label: The dose of Alimta is 500 mg/m2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

Proposed Label: Same

B. State of Armamentarium for Indication(s)

Prior to the 1980s available chemotherapy drugs demonstrated limited activity against NSCLC. In the 1980s, several agents were introduced, including cisplatin, mitomycin C, ifosfamide, vindesine, vinblastine, carboplatin, and etoposide. Response rates of these drugs as single agents ranged from 10% to 20%, with combinations resulting in response rates of 20% to 40%. Response rates to combinations of these drugs range from approximately 20% to 38%, with median survival times of 5 months to 10.8 months.

Vinorelbine is approved for first- line treatment of advanced NSCLC in several countries, including US, France, Italy, Spain, Germany, and UK, both as a single agent and in combination with cisplatin. As a single agent, it has shown response rates of 20% or higher. The combination of vinorelbine and cisplatin has, in some studies, resulted in improved response rates and survival advantages compared to either agent alone, with 1-year survival rates of 33% to 35% compared to 12% for cisplatin and 30% for vinorelbine. One study of vinorelbine plus cisplatin versus vinorelbine alone showed a higher response rate for the combination (43% versus 16%), but no advantage in median survival time (33 weeks for vinorelbine plus cisplatin versus 32 weeks for vinorelbine alone.

Gemcitabine and paclitaxel were both approved in 1998 in the US for use in combination with cisplatin for the first- line treatment of advanced NSCLC. In five Phase 2 trials of the gemcitabine/cisplatin combination, response rates ranged from 38% to 54% and median survival from 8.4 months to 14.3months. In a Phase 3 study of paclitaxel combined with cisplatin, without and with filgrastim, response rates

were 27% and 32%, and median survival times were 9.5 and 10.5 months, respectively.

Historically, NSCLC has not responded well to second- line chemotherapy. In December 1999, however, docetaxel was approved in US for use in patients with locally advanced or metastatic NSCLC after failure of prior platinum-containing chemotherapy.

C. Important Milestones in Product Development

Single Agent NSCLC Phase 2 Study Results are summarized in **Table 1**.

Table 1: Alimta Phase 2 Experience

Study	JMACa	JMADb	JMANc	JMAOd	JMAGe	JMALf	JMBRg
Site	US	US	Canada	Canada	UK	Aus/ S Africa	Europe/ Aus
Tumor	colorectal	pancreas	NSCLC	colorectal	breast	NSCLC	NSCLC
Pts	1st line	1st line	1st line	1st line	Mixed	1st line	2nd line
No. Pts	41	35	30	29	36	42	80
Cycles							
Median	4	2	3	3	4	4	2
Range	1-12	1- 12	1- 8	1- 8	1- 9	1- 9	1- 7
CR	1	1	0	0	1	0	1
PR	5	1	7	5	10	7	8
Overall RR (%)	15.4	5.7	23	17	31	17	11.2
(95% CI, %)	(4.1- 26.7)	(0.7- 19.1)	(9.9- 42.3)	(8- 39.7)	(16- 46)	(7- 31)	NA

a John et al. 1998 b Miller et al. 1998 c Rusthoven et al. 1999 d Cripps et al. 1997 e Smith et al. 1997 f Clarke et al. 1998 g unpublished data Abbreviation: NA = not available

One study (H3E- MC- JMBR), begun in 1997, looked at LY231514 in second- line treatment of NSCLC patients, some of whom had received a platinum-containing regimen. This study used a starting dose of 600 mg/m2 once every 21 days. However, due to unexpected toxicity (Grade 3 mucositis and Grade 4 vomiting and myalgia) the starting dose for all subsequent LY231514 trials, including Study JMBR, was reduced to 500 mg/m2. 80 patients were evaluable. The response rate was 11%.

Study JMAN, a multi- institutional completed in Canada, included chemo-naive patients. Seven partial responses were observed in 30 evaluable patients [23.3% (95% CI 9.9% to 42.3%)]. All responding patients were treated at the 500 mg/m2 dose level.

Study JMAL, in previously untreated NSCLC, carried out jointly between Australia and South Africa, enrolled 53 patients, with 42 evaluable for response at the time of the most recently published results. All patients received LY231514 600 mg/m2 every 3 weeks in this study. The partial response rate was 17% (7/42).

Study JMBR, a second- line NSCLC trial, was conducted in several European countries and in Australia (unpublished data). Patients had to have had failure of prior chemotherapy, as defined by disease progression during, or within 3 months after, the prior chemotherapy. Of the 80 evaluable patients, 42 had received platinum- containing prior regimens. All patients received a LY231514 starting dose of 500 mg/m2. The overall response rate was 11.2%. Overall median survival time is 5.8 months, with 21.3% of patients censored.

In 646 Phase 2 patients who have been treated on the once every 3 weeks schedule with Alimta 600 mg/m2 the most frequent, serious toxicity has been hematologic. CTC Grade 3 and 4 hematologic toxicity included neutropenia (23% and 24%, respectively) and thrombocytopenia (7% and 5%, respectively). The frequency of serious infection was low (CTC Grade 4 infection 2%). Likewise, despite thrombocytopenia serious episodes of bleeding have been rare (< 1%). While 6% of patients experienced CTC Grade 3 (3% with Grade 4) skin rash, prophylactic dexamethasone is reported to ameliorate or prevent the rash in subsequent cycles. Other Grade 3 and 4 non-hematologic toxicities included stomatitis, diarrhea, vomiting, and infection. As seen in clinical studies of other antifolates, transient Grade 3 and 4 elevations of liver transaminases are common but not dose limiting. There have been no cases of persistent transaminase elevation.

Toxicity at 600 mg/m2 has been compared to that at 500 mg/m2. For hematologic parameters there appears to be no difference between the incidence of Grade 3 and 4 toxicity or Grade 4 toxicity alone. For non-hematologic parameters there is also no difference except for rash, fatigue, and stomatitis, which appear to be less severe at 600 mg/m2. Of note, patients who were administered Alimta 500 mg/m2 in previous trials received concomitant dexamethasone after the onset of toxicity, whereas patients at the 600 mg/m2 dose level were given dexamethasone prophylactically. The reduced toxicity profile at the 600 mg/m2 dose level is thus likely a result of prophylactic corticosteroid administration, and is not considered a dose response effect of Alimta treatment.

Folic Acid and Vitamin B12 Supplementation

It is well established that toxicity induced by antifolate antimetabolites can be reversed and/ or prevented by treatment with folic acid or its reduced forms. An initial multivariate analysis was conducted in late 1997 to assess the relationship of metabolites of folic acid and vitamins B12 and B6, drug exposure, and other pre-specified baseline patient characteristics to toxicity following therapy with

LY231514. Data were examined from 139 Phase 2 patients with various solid tumors who had been treated with LY231514 600 mg/m2 I.V. over 10 minutes once every 21 days. These patients had homocysteine (Hcys), cystathionine, and methylmalonic acid levels measured at baseline and once each cycle thereafter. This study demonstrated that toxicity resulting from LY231514 therapy appeared to be higher in patients with elevated pre- therapy Hcys levels, that elevated baseline Hcys levels ($\geq$10 µM) highly correlate with severe hematological and non-hematological toxicity and that Hcys was better than baseline albumin (another predictor of toxicity) at predicting LY231514 toxicity.

A second study also demonstrated that baseline Hcys was a highly statistically significant predictor of febrile neutropenia ($p < 0.0001$), Grade 4 neutropenia ($p= 0.0191$), Grade 4 thrombocytopenia ($p< 0.0001$), and Grade 3 or 4 diarrhea ($p< 0.0001$).

Hcys level has also been shown to be a sensitive indicator of folate and vitamin B12 status. Study results indicate that folic acid and vitamin B12 supplementation permits dose escalation by ameliorating LY231514 associated toxicity.

As of December 1999, all patients in LY231514 trials receive folic acid and vitamin B12 supplementation. There have been no deaths from LY231514 toxicity in the approximately 250 patients who have received folic acid and vitamin B12 with LY231514. In contrast, of 1,169 earlier patients who did not receive folic acid and vitamin B12, 3.9% died from causes at least possibly related to LY231514. Before vitamin supplementation was added to all LY231514 treatment regimens, 37% of patients experienced Grade 4 hematologic or Grade 3 or 4 non-hematologic toxicity. An analysis of 78 patients who have received vitamins along with LY231514 has shown that only 6.4% experienced such toxicity.

D. Other Relevant Information

None

E. Important Issues with Pharmacologically Related Agents

All antifolates tend to accumulate in third-space fluid collections and to be erratically released from these fluid collections. This may lead to severe toxicity. For patients with clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) consideration should be given to draining the effusion prior to dosing.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

No chemistry review was conducted for this NDA as there was no new data submitted

B. Animal Pharmacology and Toxicology

No animal pharmacology and toxicology review was conducted for this NDA as there was no new data submitted.

C. Biopharmaceutics

No animal pharmacology and toxicology review was conducted for this NDA as there was no new data submitted.

D. Statistics

See statistics section of review.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

From the product label. No new information is submitted.

The pharmacokinetics of LY231514 administered as a single-agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. LY231514 has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that LY231514 is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment. LY231514 is not metabolized to an appreciable extent. LY231514 is primarily eliminated in the urine with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. LY231514 total systemic clearance is 91.8 mL/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min [calculated using the standard Cockcroft and Gault formula or measured glomerular filtration rate using the Tc99m-DPTA serum clearance method]). Between patient variability in clearance is moderate at 19.3%. LY231514 total systemic exposure

(AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of LY231514 are consistent over multiple treatment cycles.

Drug Interactions

Chemotherapeutic Agents — Cisplatin and carboplatin do not affect the pharmacokinetics of LY231514. Similarly, the pharmacokinetics of total platinum are unaltered by LY231514.

Vitamins — Coadministration of oral folic acid or intramuscular vitamin B_{12} does not affect the pharmacokinetics of LY231514.

Drugs Metabolized by Cytochrome P450 Enzymes — Results from in vitro studies with human liver microsomes predict that LY231514 would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Aspirin — Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of LY231514.

Special Populations
Analyses to evaluate the effects of special populations on the pharmacokinetics of LY231514 included 287 patients with a variety of advanced tumor types from 10 single-agent Phase 2 studies, 70 patients from the Phase 3 malignant pleural mesothelioma registration trial, and 47 patients from a Phase 1 renal study.

Geriatric — No effect of age on the pharmacokinetics of LY231514 was observed over a range of 26 to 80 years.

Pediatric — Pediatric patients were not included in clinical trials.

Gender — The pharmacokinetics of LY231514 were not different between male and female patients.

Race — The pharmacokinetics of LY231514 were similar in Caucasians and patients of African descent. Insufficient data are available to compare pharmacokinetics for other ethnic groups.

Hepatic Insufficiency — No effect of AST (SGOT), ALT (SGPT), or total bilirubin on the pharmacokinetics of LY231514 was observed. However, specific studies of hepatically impaired patients have not been conducted.

Renal Insufficiency — Pharmacokinetic analyses included 127 patients with reduced renal function. Total plasma clearance and renal clearance of LY231514 decrease as renal function decreases. On average, patients with creatinine clearance

of 45 mL/min will have a 56% increase in LY231514 total systemic exposure (AUC) relative to patients with creatinine clearance of 90 mL/min.

B. Pharmacodynamics

From the product label. No new information is submitted.

LY231514 is an antifolate that exerts its antineoplastic activity by disrupting crucial folate-dependent metabolic processes that are essential for cell replication. In vitro studies have shown that LY231514 behaves as a multi-targeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate- dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides. LY231514 is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, LY231514 is rapidly and efficiently converted to polyglutamate forms by the enzyme folyl polyglutamate synthase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

In vitro studies have also suggested that LY231514 may be active against certain tumor cells that are resistant to methotrexate, 5-fluorouracil, and raltitrexed. Additionally, preclinical animal studies have suggested that folic acid and itamin B12 supplementation reduces the risk of severe drug-induced toxicities while preserving the antitumor activity of LY231514.

Absolute neutrophil counts (ANC) following single-agent administration of LY231514 to non-vitamin-supplemented patients were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, is influenced primarily by the magnitude of systemic exposure (AUC). A 5- to 6-fold increase in LY231514 AUC produces a 5- to 6-fold lowering of the ANC nadir. Though less pronounced than AUC, increased cystathionine or homocysteine concentrations correlate with a lowering of the ANC nadir, supporting the use of vitamin supplementation. There is no cumulative effect of LY231514 exposure on ANC nadir over multiple treatment cycles.

Time to ANC nadir also correlates with LY231514 systemic exposure (AUC), and varied from 8 to 9.6 days after LY231514 administration over a range of exposures from 38.3 to 316.8 μg•hr/mL. Return to baseline ANC occurs from 4.2 to 7.5 days following the nadir over the same range of exposures.

IV. Description of Clinical Data and Sources

A. Overall Data

Data derived primarily from a phase 3 study titled "A Phase 3 Trial of Alimta vs Docetaxel in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Who Were Previously Treated with Chemotherapy". This was a multicenter study conducted at 135 study centers. Five-hundred-seventy one patients comprised the intent-to-treat patient population. The primary objective of this study was to compare the overall survival following treatment with ALIMTA (LY231514) versus docetaxel in patients with locally advanced or metastatic (Stage IIIA, IIIB, or IV) non-small cell lung cancer (NSCLC) who were previously treated with chemotherapy. The first patient enrolled on 20 March 2001, the last on 06 February 2002.

B. Listing of Submitted Clinical Trials

One phase 3 trial of LY231514 vs Docetaxel in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who were previously treated with chemotherapy.

Supporting studies

Tax 317- Phase III docetaxel in previously treated NSCLC. Shepherd et al. J Clin Oncol 18:2095-2103, 2000.

Tax 320- Phase III docetaxel in previously treated NSCLC. Fossella et al. J Clin Oncol 18:2354-2362, 2000.

Two additional Randomized studies of docetaxel in 2nd line NSCLC

Camps, IASLC 2003, oral presentation

Gridelli, IASLC 2003, oral presentation

C. Postmarketing Experience

None

D. Literature Review

Hanna N, Shepherd FA, Rosell R, Pereira JR, De Marinis F, Fosella FV, Kayitalire L, Paul S, Einhorn L, Bunn PA. 2003. A phase III study of LY231514 vs. docetaxel in patients with recurrent non-small-cell lung cancer (NSCLC) who were previously treated with chemotherapy. Proc Am Soc Clin Oncol. 22:622, 2003 Abstract # 2503.

Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000;18:2095-103.

Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000;18:2354-62.

See also references at the end of the Appendix.

V. Clinical Review Methods

A. How the Review was Conducted

Databases provided by the sponsor were analyzed to independently confirm the sponsor's efficacy and safety results. Queries were sent to the sponsor to clarify issues that arose during the review. Any discrepancies between reviewer and sponsor were communicated to the sponsor to achieve mutually acceptable conclusions.

B. Overview of Materials Consulted in Review

The safety and efficacy review is based primarily on data provided in EDR \\CDSESUB1\N21677\ N_000\2003-11-03 and summarized in "Clinical Study Report: A Phase 3 Trial of ALIMTA versus Docetaxel in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Who Were Previously Treated with Chemotherapy". Results of four supporting phase 2 NSCLC trials, two first-line and 2 second-line were also provided.

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

Consistency of efficacy results (survival, time to progression, response rates was sought. Data from each of the 135 participating medical centers was reviewed to assure that results were relatively consistent at all sites. Pertinent NSCLC literature was reviewed to determine whether study results were consistent with expected results in a comparable patient population treated with other chemotherapy agents or with other treatment modalities

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Yes

E. Evaluation of Financial Disclosure

The sponsor has submitted certification that Eli Lilly and Company has not entered into any financial arrangement with any of its clinical investigators who participated in H3E-MC-JMEI with the exception of individuals listed below. This certification was signed on 9/25/03 by Binh Nguyen, M.D., Ph.D. Medical Director.

(Redacted Information (Table) per FOI)

* In some cases patients were consented but not enrolled in the trial.

VI. Integrated Review of Efficacy

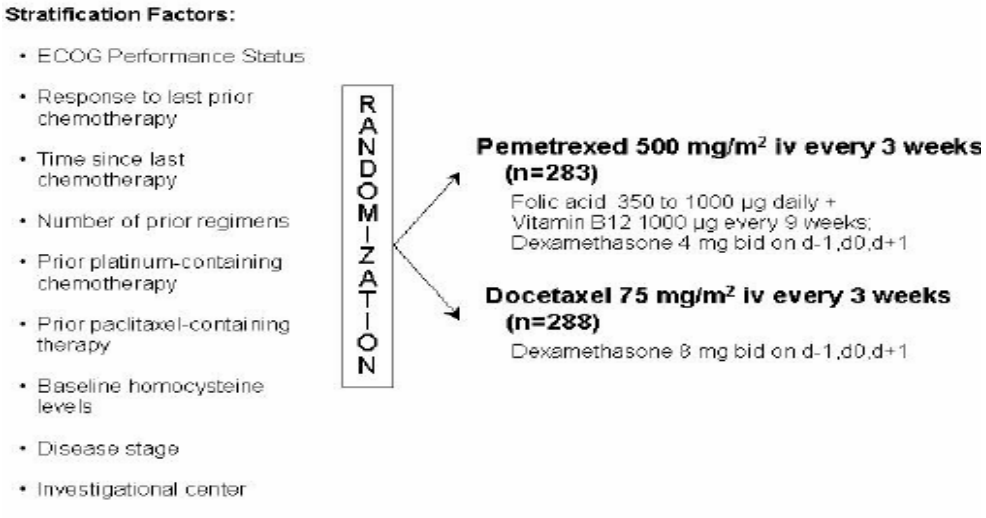
A. Brief Statement of Conclusions

The sponsor claimed that survival of LY231514 treated patients was non-inferior to survival of docetaxel treated patients. FDA statistical analysis indicated that non-inferiority was not demonstrated. Even if non-inferiority was demonstrated, however, it would not be credible because of imbalances in post-study chemotherapy. Thirty fewer docetaxel treated patients received post-study chemotherapy compared to LY231514 treated patients (RT population). While 32% of LY231514 treated patients received post-study docetaxel it was observed that patients receiving any post-study chemotherapy drug(s) survived longer than those who did not. The majority of patients on both arms who did not receive post-study chemotherapy were performance status 0 or 1 at their last study visit and, conceivably, could have received additional treatment.

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

The efficacy review is based primarily on one multicenter trial. See Figure 1 for the schema of study H3E-MC-JMEI

Figure 1 Schema - Study H3E-MC-JMEI



C. Detailed Review of Trials by Indication

Table 2 lists the principal investigators and the corresponding participating institutions.

Table 2: **Principal Investigators and Address**

Trial Country	Inv. Site Ref #	Investigator	Address
Argentina	070	Rosenberg, Moises	Hospital Ferrer, Finochietto 849, Ciudad De Buenos Aires,
Argentina	071	Bagnes, Claudia	Hospital Dr. Tornu, Ex Combatientes De Malvinas 3002, Buenos Aires,
Argentina	072	Jovtis, Silvia	Complejo Medico Churruca Visca, Uspallata 3400, Buenos Aires,
Argentina	073	Coppola, Federico	Hospital Aleman, Av.Pueyrredon 1640, Buenos Aires,
Austria	050	Pirker, Robert	Akh Wien Universitätskliniken, Währinger Gürtel 18-20, Wien,
Austria	051	Baumgartner, G	Kh Der Stadt Wien Lainz, Wolkersbergenstraße 1, Wien,
Austria	052	Aigner, K	Kh Der Elisabethinen Linz, Fadingerstraße 1, Linz,
Austria	053	Eckmayr, Josef	Kh Der Barmherzigen Schwestern Wels, Grießkirchner Straße
Belgium	850	Van Steenkiste, J	Univ Ziekenhuis Gasthuisberg Leuven,
Belgium	851	Bosquée, L	Centre Hospitalier Régional De La Citadelle, Liège, B-4000,
Belgium	852	Rosier, Jean F	Hopital De Jolimont, B-7100, Belgium
Brazil	011	Pereira, José R	Instituto Arnaldo Vieira De Carvalho, Sao Paulo, 01221-020,
Brazil	033	Barrios, Carlos H	Hospital São Lucas, Porto Alegre, RS, 90610-000,
Brazil `	034	Malzyner, Artur	Clínica De Oncologia Médica, São Paulo, SP, 01406-100,
Canada	200	Shepherd, FA	Princess Margaret Hospital, Toronto, Ontario,
Canada	201a	Stewart, David J	Ottawa General Hospital,
Canada	203	Hirsh, Vera	Royal Victoria Hospital, Montreal, Quebec,
Canada	204	Palmer, MC	Cross Cancer Institute, Edmonton, Alberta,
Czech Rep	750	Roubec, Jaromir	Fakultni Nemocnice S Poliklinikou,
France	301	Pujol, Jean-Louis	Chu De Montpellier Hopital
France	302	Gervais, Radj	Centre Francois Baclesse, Caen
France	303	Urban, Thierry	Chu D'angers, Angers
France	305	Perol, Maurice	Hopital De La Croix Rousse, Lyon
France	306	Depierre, Alain	Hopital Saint Jacques,
France	310	Lafitte, Jean-Jaques	Chru De Lille Hopital Calmette, Lille
France	311	Robinet, Gilles	Hospital Du Morvan, Brest
France	314	Spaeth, Dominique	Centre Alexis Vautrin, Vandoeuvre Les Nancy
Germany	400	Manegold, C	Thoraxklinik Der Lva Baden, Heidelberg,
Germany	401	Mezger, Jorg	St. Vincentius-Krankenhäuser, Karlsruhe,
Germany	402	Kortsik, Cornelius	St. Hildegardis Krankenhaus, Mainz,
Germany	403	Saal, Johannes	St Franziskus Hospital Waldstr. 17, Flensburg
Germany	404	Muller, Thomas	Krankenhaus Hofheim Am Taunus, Hofheim
Germany	405	Hossfield, DK	Universitäts Krankenhaus Eppendorf (Uke), Hamburg,
Germany	406	Welte, Tobias	Universitätsklinikum Otto-Von Guericke, Magdeburg,
Germany	407	Huber, Rudolf M	Klinikum Der Universitat Munchen,
Germany	408	Gatzemeier, Med U	Krankenhaus Großhansdorf, Großhansdorf, D- 22927,
Germany	409	Von Pawel, J	Fachklinik München-Gauting, Gauting D-82131,
Germany	410	Kaukel, E	Allgemeines Krankenhaus Harburg, Hamburg, D-21075,
Germany	413	Jermann, Monika	Universitätsspital Zürich, Zürich, Switzerland
Germany	414	Herrmann, R	Kantonsspital Basel, Basel, CH-4031, Switzerland
Hungary	753	Kovacs, Gabor	Orszagos Koranyi Tbc Es Pulmonologiai Intezet, Budapest, 1529,
Hungary	754	Magyar, P	Semmelweis Medical University, Budapest, 1125,
India	001	Sharma, Atul	Institute Rotary Cancer Hospital, New Delhi, 110029,
India	002	Sekhon, Jagdev S	Dayanand Medical College, Punjab, 141001,
India	003	Nayak, Radheshyam	St. John Medical College, Bangalore, Karnataka, 560-034,
India	004	John, Subhashini	Christian Medical College, Tamil Nadu, 632
India	006	Doval, DC	Rajiv Gandhi Cancer Institute, Delhi, 110 085
India	009	Julka, PK	All India Institute of Medical Sciences, New Delhi, 110 029,
Israel	351	Gottfried, Maya	Meir Hospital, Kfar Saba, 44281,
Italy	500	De Marinis, F	Azienda Ospedaliera S., Roma, 00149,
Italy	501	Rinaldi, M	Istituti Fisioterapici Ospedalieri, Roma, 00144,
Italy	502	Crino, L	Ospedale Bellaira, Bologna, 40139,

Italy	506	Adamo, V	Universita Di Messina/Policlinico, Messina, 98100,
Korea	060	Bang, Yung-Jue	Seoul National University Hospital, Seoul, 110-744
Korea,	061	Park, Keun-Chil	Samsung Medical Center, Seoul, 135-710,
Korea	062	Kim, Joo-Hang	Yonsei University Medical Center, Seoul, 120-752,
Pakistan	700	Zaidi, M	Baquai Institute of Oncology, Karachi, 75510,
Pakistan	702	Shaharyar,	Mayo Hospital, Lahore, 54000,
Pakistan	703	Ansari, Tariq	Combine Military Hospital, Rawalpindi,
Pakistan	706	Siddiqui, Tariq	The Aga Khan University, Karachi, 29667
Poland	007	Jassem, J	Akademia Medyczna, Instytut Radioterapii, Gdansk, 80-211,
Poland	008	Roszkowski, K	Instytut Gruzlicy I Chorob Pluc, Warszawa, 01-138,
Portugal	080	Jose De Melo,	Maria Hospital De Pulido Valente, Lisboa, 1769-001,
Portugal	081	Bernardo, Manuela	Hospital De Santo Antonio Dos Capuchos, Lisboa, 1169-050,
Portugal	082	Duro Da Costa, Jose	Instituto Português De Oncologia Dr. Francisco Gentil, Lisboa, 1099-023,
Portugal	083	Teixeira, Encarnação	Hospital De Santa Maria, Lisboa, 1649-035,
Portugal	084	Barata, Fernando	Centro Hospitalar De Coimbra, Coimbra, 3040-853,
Portugal	086	Sanches, Evaristo	Instituto Português De Oncologia Dr. Francisco Gentil, Porto 4200-072,
Portugal	087	Queiroga, Henrique	Hospital De São João, Porto, 4200-319,
Portugal	088	Parente, Bárbara	Centro Hospitalar De Vila Nova De Gaia, Gaia, 4434-502,
Portugal	089	Passos, Mario	Centro Hospitalar Do Funchal, Funchal, 9004-514,
Russia	013	Garin, AM	Blokhin Cancer Research Center, Moscow, 115478,
Russia	014	Lichinitser, MR	Blokhin Cancer Research Center, Moscow, 115478
Russia	015	Gorbunova, VA	Blokhin Cancer Research Center, Moscow, 115478
Singapore	020	Lim, Hong-Liang	National University Hospital, Singapore, 119074,
Singapore	022	Leong, Swan-Swan	National Cancer Center, Singapore, 169610,
South Africa	016	Abratt, RP	Groote Schuur Hospital, Cape Town, 7925,
South Africa	017	Ruff, Paul	Johannesburg General Hospital, Gauteng, 2193,
South Africa	023	Brennan, Sean	East Cape Oncology Centre St. George's Hospital, Eastern Cape, 6001,
Spain	600	Rosell, R	Hospital De Badalona Germans Trias I, Barcelona, 08915,
Spain	601	Esteban, Emilio	Hospital Central De Asturias, Asturias, 33006,
Spain	603	Barceló Galíndez, J	Hospital De Cruces, Vizcaya, 48903,
Spain	604	Felip, E	Ciutat Sanitaria De La Vall De Hebron, Barcelona, 08035,
Spain	605	Garrido, Pilar	Hospital Ramon Y Cajal, Madrid, 28034,
Taiwan	650	Tsai, Chun-Ming	Taipei Veterans General Hospital, Taipei, 112,
Taiwan,	651	Chang, Gee-Chen	Taichung Veterans General Hospital, Taiwan
Taiwan	652	Hsu, Hon-Ki	Kaohsiung Veterans General Hospital, Taiwan
Taiwan	653	Wu, Ming-Fang	Chung Shan Medical and Dental College, Taiwan,
Taiwan	654	Hsia, Te-Chun	China Medical College Hospital, Taiwan,
Taiwan	655	Su, Wu-Chou	National Cheng Kung University Hospital, Taiwan,
Taiwan	656	Yang, Chih-Hsin	National Taiwan University Hospital, Taiwan,
Taiwan	657	Tsao, Thomas C	Chang Gung Memorial Hospital, Taiwan
United States	100	Bhatia, Sumeet	Community Care Center Inc., Indianapolis, IN 46202,
United States	101	Albain, Kathy	Loyola Univ School of Medicine, Maywood, IL 60153,
United States	104	Scott, Miho Toi	Hematology Oncology Associates, Fort Collins, CO 80528,
United States	105	Fossella, F	MD Anderson Cancer Center, Houston, TX 77030,
United States	106	Figueroa, Jose A	Joe Arrington Cancer Center, Lubbock, TX 79410,
United States	108	Beck, Joseph T	Highland Oncology Group, Springdale, AR 72764,
United States	110	Shuster, Todd	Lahey Clinc, Burlington, MA 01805,
United States	111	Desch, Christopher	Hematology Oncology Associates, Richmond, VA 23226,
United States	112	Feldmann, John E	Mobile Infirmary Medical Center, Mobile, AL 36607,
United States	114	Justice, GR	Pacific Coast Hematolgy and Oncology, Fountain Valley, CA 92708,
United States	116	Liebmann, J	New Mexico Hematology/Oncology Consultants, Albuquerque, NM 87109,
United States	117	Makalinao, Alex	California Hematology Oncology Group, Torrance, CA 90505,
United States	120	Nimeh, NF	Cleo Craig Cancer Research Clinic, Lawton, OK 73505,
United States	121	Schwartzberg, Lee	The West Clinic, Memphis, TN, 38117
United States	123	Tezcan, Haluk	North Idaho Cancer Center, Coeur D'Alene, ID 83814,
United States	126	Valdivieso, Manuel	Univ of Texas Southwestern Med Center , Dallas, TX 75235,
United States	127	Dickman, E	Primary Meridia Hillcrest Hospital, Mayfield Heights, OH 44124,
United States	129	Jazieh, Abdul-Rahman	Cincinnati College of Medicine, Cincinnati, OH 45267,
United States	130	Peereboom, David	Cleveland Clinic Foundation, Cleveland, OH 44195,
United States	131	Nattam, S	Fort Wayne Hematology Oncology, Fort Wayne, IN 46815,

United States	132	Priego, VM	Bethesda, MD, 20817,
United States	133	Webb, Timothy	Primary Genesis Cancer Center, Hot Springs, AR 71913,
United States	134	Eisenberg, PD	Marin Oncology Associates, Greenbrae, CA, 94904
United States	135	Dudek, Arkadiusz	University of Minnesota Medical School, Minneapolis, MN 55455,
United States	136	Hart, Ronald	Oncology of Wisconsin, Milwaukee, WI, 53215,
United States	137a	Ellerton, JA	Southern Nevada Cancer Research Foundation, Las Vegas, NV 89106,
United States	138	Mason, Bernard A	Pennsylvania Oncology Hematology Assoc., Philadelphia, PA 19106,
United States	139	Larson, Tim	Metro Minnesota CCOP, St. Louis Park, MN 55416,
United States	140	Kuebler, Phillip J.	Columbus CCOP, Columbus, OH 43206,
United States	142	Arnold, Susanne	University of Kentucky, Lexington, KY 40536,
United States	144	Eckardt, JR	St John's Mercy Medical Center, St. Louis, MO 63141,
United States	146	Kennedy, Peter	Metropolitan Oncology, Los Angeles, CA 90057,
United States	148	Malefatto, Jerry P.	Oncology Associates of Bridgeport, Trumbull, CT 06611,
United States	149	Christiansen, Neal P	South Carolina Oncology Associates, Columbia, SC 29203,
United States	154	Treat, Joseph	Temple University, Philadelphia, PA 19140,
United States	155	Dobbs, Tracy W	Baptist Regional Cancer Center, Knoxville, TN 37920,
United States	156	Perry, Michael C	Ellis Fischel Cancer Center, Columbia, MO 65203,
United States	158	Bearden, James D	Spartanburg Regional Healthcare System, Spartanburg SC, 29303
United States	160	Hanna, Nassar	Indiana Cancer Pavilion, Indianapolis, IN 46202,
United States	161	Graziano, Stephen	Regional Oncology Center, Syracuse, NY 13210,
United States	164	Lyss, Alan	Missouri Baptist Medical Center, St. Louis, MO 63131,
United States	165	Rinaldi, DA	Louisiana Oncology Associates, Lafayette, LA 70506,
United States	180	Ansari, R	Memorial Hospital of South Bend, South Bend, IN 46601,
United States	182	Pennington, Ken	Oncology Institute of Greater Lafayette, Lafayette, IN 47904,
United States	183	Fisher, William B.	Medical Consultants, Muncie, IN 47304,

a Because of regulatory violations, this investigator was disqualified.

Table 3: Summary of Response Rate By Site - ITT Population

	Docetaxel			LY231514		
Site	N	Responders	Response Rate (%)	N	Responders	Response Rate (%)
1	2	0	0	0		
2	3	1	33	1	0	0
3	1	0	0	4	0	0
4	2	0	0	0		
6	1	0	0	2	0	0
7	1	0	0	1	1	100
9	2	0	0	0		
11	13	3	23	11	2	18
13	0			1	0	0
15	0			2	0	0
16	1	1	100	2	1	50
17	1	0	0	2	0	0
20	5	1	20	5	0	0
22	4	1	25	5	2	40
33	2	0	0	0		
34	3	0	0	3	0	0
50	0			2	0	0
51	3	0	0	1	0	0
52	4	0	0	2	0	0
53	2	0	0	2	1	50
60	2	0	0	1	0	0
61	6	0	0	3	1	33
62	3	0	0	2	0	0
70	2	0	0	1	0	0
71	3	0	0	3	0	0
72	0			1	0	0
73	0			1	0	0
80	1	0	0	0		
81	1	0	0	2	0	0
82	1	0	0	1	0	0
83	1	0	0	2	0	0
84	4	0	0	2	1	50
86	1	0	0	0		
87	0			1	0	0
88	0			3	1	33
89	4	0	0	1	0	0
100	1	0	0	0		
101	1	0	0	0		
104	0			2	0	0
105	8	2	25	8	2	25
106	1	0	0	1	0	0
108	2	0	0	3	1	33
110	2	0	0	2	0	0
111	1	0	0	6	1	17
112	0			0		
114	1	1	100	1	0	0
116	1	0	0	0		
117	3	0	0	3	0	0

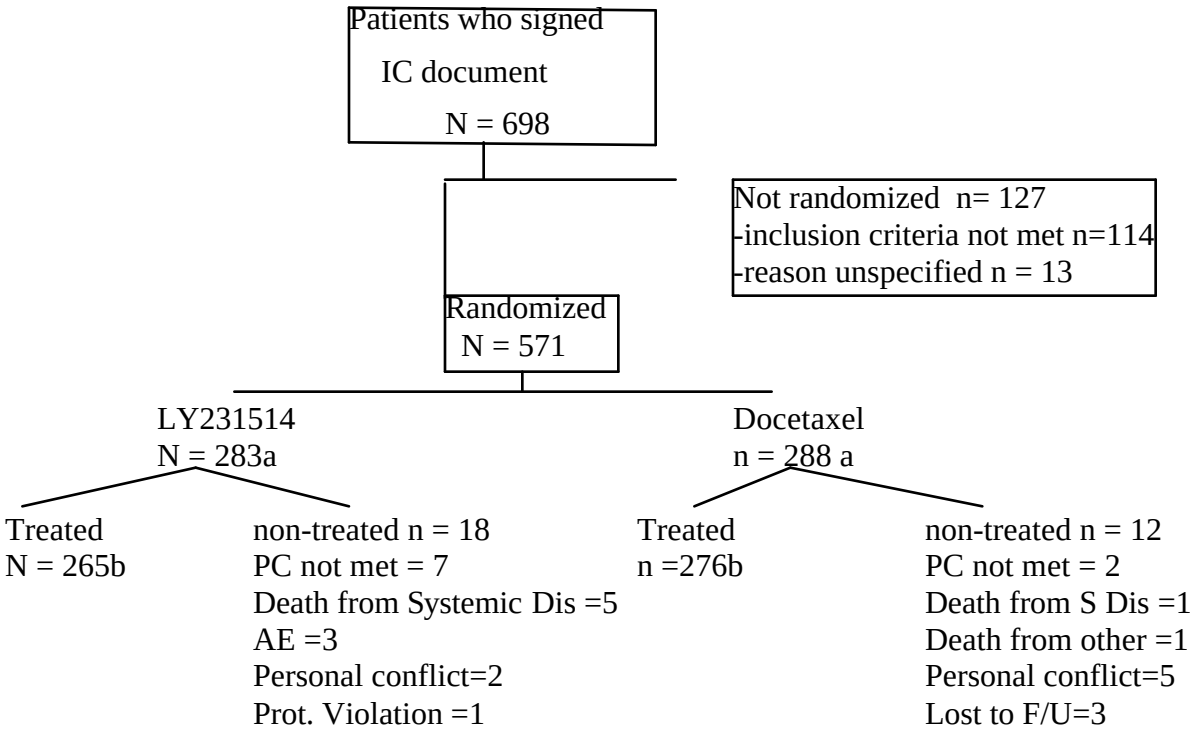
	Docetaxel			LY231514		
Site	N	Responders	Response Rate (%)	N	Responders	Response Rate (%)
120	1	0	0	0		
121	1	0	0	0		
123	1	0	0	0		
126	1	0	0	0		
127	1	0	0	0		
129	1	0	0	1	0	0
130	0			1	0	0
131	3	0	0	1	0	0
132	1	0	0	0		
133	1	0	0	0		
134	0			2	0	0
135	3	1	33	2	1	50
136	0			1	0	0
138	1	0	0	0		
139	0			4	0	0
140	2	0	0	2	0	0
142	1	0	0	0		
144	0			1	0	0
148	1	0	0	0		
149	1	0	0	0		
152	2	0	0	1	0	0
155	1	0	0	1	0	0
156	2	0	0	4	0	0
160	5	0	0	2	0	0
161	3	0	0	2	0	0
164	3	1	33	3	0	0
165	2	0	0	0		
180	0			1	0	0
182	1	0	0	0		
183	0			1	0	0
200	3	1	33	6	1	17
201	1	0	0	2	1	50
203	2	1	50	1	0	0
204	0			2	0	0
301	2	0	0	2	0	0
302	7	0	0	2	0	0
303	0			1	0	0
305	1	0	0	1	0	0
306	1	1	100	0		
310	0			1	1	100
311	1	0	0	1	0	0
314	1	0	0	0		
351	2	0	0	0		
400	6	1	17	2	0	0
401	0			2	0	0
402	3	0	0	5	1	20
403	4	0	0	0		
404	4	0	0	4	0	0
405	3	0	0	3	0	0
406	1	0	0	2	0	0

		Docetaxel			LY231514	
Site	N	Responder	Response Rate	N	Responder	Response Rate (%)
407	1	0	0	0		
408	6	0	0	8	1	13
409	10	1	10	7	1	14
410	2	0	0	3	0	0
413	2	0	0	3	0	0
414	5	0	0	7	0	0
500	10	1	10	10	0	0
501	0			1	0	0
502	0			1	0	0
506	0			0		
600	4	0	0	2	0	0
601	1	0	0	2	0	0
603	1	0	0	1	0	0
604	2	0	0	3	0	0
605	0			1	0	0
650	5	2	40	3	0	0
651	3	1	33	4	0	0
652	1	0	0	1	0	0
653	3	0	0	4	0	0
654	4	0	0	2	0	0
655	0			2	0	0
656	4	1	25	2	1	50
657	4	2	50	9	0	0
700	0			2	0	0
702	5	0	0	4	0	0
703	1	0	0	1	0	0
706	1	0	0	0		
750	1	0	0	3	0	0
753	3	0	0	1	0	0
754	6	0	0	3	1	33
800	3	0	0	1	0	0
801	1	0	0	1	0	0
803	0			1	0	0
850	1	0	0	1	0	0
851	1	0	0	1	0	0
852	2	0	0	1	0	0

Table 3 indicates that responses were relatively evenly distributed among sites and countries so that any one site did not unduly influence study results.

Study JMEI entered 698 patients at 135 investigational sites in 23 countries. Of these, 571 (81.8%) patients were randomly assigned (enrolled) to either the LY231514 arm or the docetaxel arm. Figure 2 describes the disposition of patients who entered the trial.

Figure 2: Disposition of Patients



a = Intent to treat (ITT) population

b = randomized and treated (RT) subgroup

Table 4 presents the key patient characteristics by treatment arm. The two treatment arms were well-balanced with respect to demographic and disease characteristics.

Table 4 Patient characteristics

Variable	ALL (N=571)	LY231514 (N=283)	Docetaxel (N=288)
Sex: No. (%)			
Female	160 (28.0)	89 (31.4)	71 (24.7)
Male	411 (72.0)	194 (68.6)	217 (75.3)
Origin: No. (%)			
African Descent	16 (2.8)	8 (2.8)	8 (2.8)
Western Asian	43 (7.5)	20 (7.1)	23 (8.0)
Caucasian	403 (70.6)	203 (71.7)	200 (69.4)
East/Southeast A	93 (16.3)	44 (15.5)	49 (17.0)
Hispanic	10 (1.8)	4 (1.4)	6 (2.1)
Other	6 (1.1)	4 (1.4)	2 (0.7)
Age:			
Mean	58.24	58.44	58.05
Median	58.00	59.00	57.00
Performance Status:			
ECOG PS 0	100 (18.6)	52 (19.7)	48 (17.5)
ECOG PS 1	374 (69.5)	182 (68.9)	192 (70.1)
ECOG PS 2	64 (11.9)	30 (11.4)	34 (12.4)
Histological Subtype:			
Adenocarcinoma	301 (52.7)	158 (55.8)	143 (49.6)
Squamous	171 (29.9)	78 (27.6)	93 (32.3)
Other	99 (17.3)	47 (16.6)	52 (18.1)
Homocysteine			
Low (< 12 Umol/L)	399 (70.1)	202 (71.4)	197 (68.9)
High (>= 12 Umol/L)	170 (29.9)	81 (28.6)	89 (31.1)
Stage Of Disease			
Stage III	144 (25.2)	71 (25.1)	73 (25.3)
Stage IV	427 (74.8)	212 (74.9)	215 (74.7)
Prior Chemo Regimens			
1 Regimen	538 (94.2)	270 (95.4)	268 (93.1)
2 Regimens	33 (5.8)	13 (4.6)	20 (6.9)
Prior Platinum			
Had No Prior Platinum	50 (8.8)	21 (7.4)	29 (10.1)
Had Prior Platinum	521 (91.2)	262 (92.6)	259 (89.9)
Prior Taxane			
Had No Prior Taxane	418 (73.2)	210 (74.2)	208 (72.2)
Had Prior Taxane	153 (26.8)	73 (25.8)	80 (27.8)
Best Response To Chemo			
Complete Response	16 (2.8)	12 (4.2)	4 (1.4)
Partial Response	190 (33.3)	89 (31.4)	101 (35.1)
Stable Disease	199 (34.9)	106 (37.5)	93 (32.3)
Progressive Disease	140 (24.5)	67 (23.7)	73 (25.3)
Unknown, NE, or Not Done	26 (4.5)	9 (3.2)	17 (5.9)
TIME SINCE LAST CHEMO			
<3 mos since last chemo	277 (49.2)	140 (50.4)	137 (48.1)
>3 mos since last chemo	286 (50.8)	138 (49.6)	148 (51.9)

Table 5 indicates therapy received prior to enrollment into the current study.

Table 5: Prior Therapies

	LY231514 (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)
Metastatic setting		
One line of therapy	143 (50.5)	146 (50.7)
Two lines of therapy	4 (1.4)	2 (0.7)

Primary Efficacy Analysis

Overall Survival

Analyses by FDA statisticians, Yong-Cheng Wang, Ph.D. and Rajeshwari Sridhara, Ph.D.

Overall survival was the primary efficacy endpoint of Study JMEI. Two statistical tests for the primary endpoint were defined in the protocol amendment: (1) Test for superiority of alimta relative to docetaxel (H_{01}: HR ≥ 1), and (2) Test for non-inferiority based on a protocol-defined fixed margin (H_{02}: HR ≥ 1.11). Since these two tests were pre-specified in the protocol, the analyses based on these two tests are presented below.

Table 6 summarizes the results of the superiority test and fixed margin non-inferiority test of the primary endpoint for ITT population. It failed to reach the significance level 0.05 in superiority test (p=0.9300; log-rank) and fixed margin non-inferiority test (p=0.2558).

Table 6: Confirmatory Analyses[a] of Overall Survival – ITT Population

	Sponsor Analysis		FDA Analysis	
	Alimta (N = 283)	Docetaxel (N = 288)	Alimta (N = 283)	Docetaxel (N = 288)
Events	206	203	206	203
Survival time (months)				
Median	8.3	7.9	8.3	7.9
(95% CI)	(7.0, 9.4)	(6.3, 9.2)	(7.0, 9.4)	(6.3, 9.2)
Superiority test				
p-value of log-rank test[b]	Not reported		0.9300	
p-value of Wilcoxon test[b]	Not reported		0.5944	
Non-inferiority fixed margin test				
p-value of NI fixed margin test[b]	0.226		0.2558	
Hazard ratio[c]	0.99		0.992	
95% CI for hazard ratio[c]	(0.82, 1.20)		(0.817, 1.204)	

[a] Superiority and fixed margin non-inferiority analyses as defined in the protocol.

[b] P-value is based on the test results for the two treatment groups.

[c] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable.

Exploratory Analyses (Fraction Retention Non-inferiority) for the Primary Endpoint

The NDA submission also included the third statistical test for the primary endpoint: Test for non-inferiority based on a percentage of the docetaxel benefit retained by alimta (H_{03}: $\delta \leq 50\%$), where δ is called *fraction retention*, which is the percentage of the control effect retained by alimta, and where docetaxel is the active control treatment in the current trial. Since this test was not pre-specified in the protocol, the analyses based on this test are only exploratory.

In general when only one small historical trial is used to estimate the control effect, the lower 95% confidence limit (LCL) is used as the estimated control effect. However, the sponsor used the point estimate in the estimation of the control effect. We report the results of fraction retention non-inferiority tests with two different estimates of control effect in Table 7. It failed to reach the significance level 0.05 in the 50% fraction retention non-inferiority test (p=0.0525 and 0.6395 based on the point estimate and 95% LCL of control effect, respectively).

Table 7: Exploratory Analyses[a] of Overall Survival – ITT Population

	Sponsor Analysis		FDA Analysis	
	Alimta (N = 283)	Docetaxel (N = 288)	Alimta (N = 283)	Docetaxel (N = 288)
Events	206	203	206	203
Fraction retention non-inferiority test based on the point estimate of control effect (HR(P/C) = 1.7857)				
Non-inferiority fraction retention test				
Estimate of control effect	0.59[d]		0.56[e]	
NI p-value for testing 50% retention[b]	0.047		0.0525	
95% conditional CI of estimated percent of efficacy retained by alimta[c]	(52%, 157%)		(48.56%, 158.97%)	
Fraction retention non-inferiority test based on the 95% LCL of control effect (HR(P/C) = 1.1364)				
Non-inferiority fraction retention test				
NI p-value for testing 50% retention[b]	Not reported		0.6395	
95% conditional CI of estimated percent of efficacy retained by alimta[c]	Not reported		Not available	

[a] Fraction retention non-inferiority analyses which were not pre-specified in the protocol.

[b] P-value is based on the test results for the two treatment groups by Rothmann's method for a 50% retention.

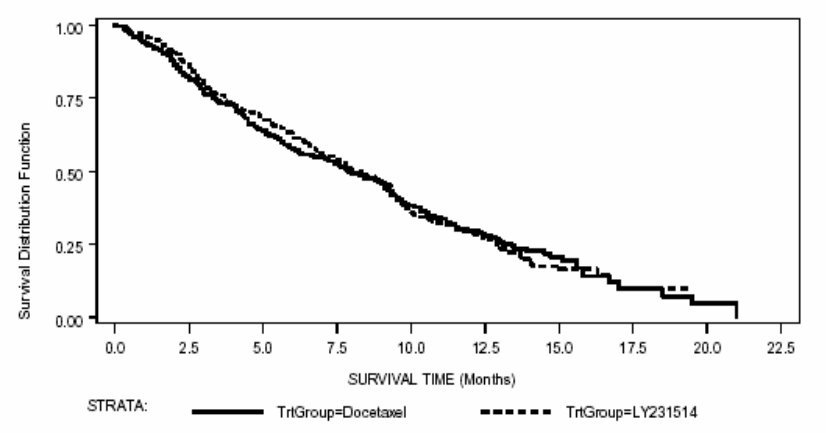
[c] 95% conditional CI is based on the fixed control effect as the estimate by the historical data.

[d] The sponsor's estimate based on middle point of 95% CI of log-HR (BSC vs. docetaxel) from historical trial for ITT population.

[e] Point estimate of HR in the historical trial for ITT population, published in docetaxel (taxotere) label.

Figure 3 demonstrates the displays the K-M survival curves for the ITT population.

Figure 3 Overall survival ITT Population



Post-study chemotherapy in the ITT population is listed in Table 8 and post-study chemotherapy in the RT population is listed in Table 9. As indicated in Tables 32% of LY231514 treated patients received docetaxel at the time of treatment change. Patients initially receiving docetaxel received a variety of other drugs when docetaxel was discontinued.

Table 8: Post-study Anticancer Drug Therapy - ITT Population

Post-study Therapy	LV231514 (N=283) n (%)	Docetaxel (N=288) n (%)
All post-study anticancer therapy[1]	163 (57.6)	148 (51.4)
Surgery, radiation, or other treatment	58 (20.5)	69 (2.4)
Post-study chemotherapy[2]	132 (46.6)	107 (37.2)
Platinum		
Carboplatin	6 (2.1)	7 (2.4)
Cisplatin	4 (1.4)	8 (2.8)
Docetaxcl	90 (31.8)	11 (3.8)
Paclitaxel	4 (1.4)	3 (1.0)
Vinorelbine	6(2.1)	25 (8.7)
Gemcitabine	18 (6.4)	32 (11.1)
Gefitinib (Iressa)	5 (1.8)	21 (7.3)
Etoposide	2 (0.7)	5 (1.7)
Mitomycin	1 (0.4)	5 (1.7)
Other chemotherapy	19 (6.7)	24 (8.3)

Abbreviations: ITT = intention to treat; N = number of patients in the treatment arm;
n = number of patients receiving specific post-study anticancer drug therapy.
1 Patients may have received more than one form of therapy.
2 Patients may have received more than one drug.

Table 9: Post-study Anticancer Drug Therapy - RT Population

Post-study Therapy	LY231514 (N=265) n (%)	Docetaxel (N=276) n (%)
All post-study anticancer therapy[1]	156 (58.9)	148 (53.6)
Surgery, Radiation, or Other treatment	56 (21.1)	69 (25)
Post-study chemotherapy[2]	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 (lressa)	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)

Abbreviations: RF = randomized and treated; N = number of patients in the treatment arm;
n = number of patients receiving specific post-study anticancer drug therapy;
1 Patients may have received more than one form of therapy.
2 Patients may have received more than one drug.

The effect of post-study chemotherapy on survival is shown in Table 10. As shown post-

study chemotherapy was not comparable between the two treatment groups. Thirty more docetaxel treated patients did not receive post-study chemotherapy as compared to LY231514 treated patients. Eighty five of the LY231514 treated patients (32%) received post-study docetaxel. Patients who received post-study chemotherapy had prolonged survival compared to patients who received no post-study chemotherapy.

Table 10: Effect of Post-study chemotherapy on survival - RT Population

	LY231514		Docetaxel	
Patient population	**(n=265)**	**MS**	**(n=276)**	**MS**
No post-study chemotherapy	139	6.2 mo	169	5.0 mo
Post-study docetaxel therapy	85	9.6 mo	11	10.1 mo
Other chemotherapy	41	10.6 mo	96	11.2 mo

It is conceivable that the reason that no post-study chemotherapy was given was that progressing patients had poor performance status and thus were not candidates for additional therapy. This might also explain the shorter survival of the no post-study chemotherapy patients. In this regard Table summarizes performance status of the no chemotherapy patients at their last study visit. It is evident that the majority of patients (docetaxel 75%, LY231514 79% were performance status 0 or 1 and might, conceivably, have received chemotherapy.

Table 11: No post-study chemotherapy. Last performance status

Last performance status	**LY231514 N=139**	**Docetaxel N =169**
0	10	11
1	98	112
2	28	37
3	1	6
4	0	1
unknown	2	2

Secondary Analyses

Time to Progressive Disease

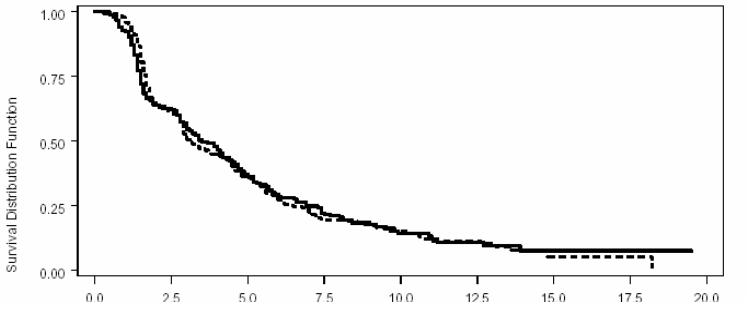
Table 12 presents a summary of TTPD for the ITT population and RT subgroup. Thirty-six of the patients with progressive disease (23 docetaxel treated and 13 LY231514 treated had clinical disease progression. No documentation was provided for these patients so that the occurrence of progression could not be confirmed. While it was elected to accept the progression dates of these individuals, it does make the endpoint somewhat soft.

Table 12: Time to Progressive Disease (Months)

	ITT Patients (N=571)		RT Patients (N=541)	
	LY231514 (n=283)	Docetaxel (n=288)	LY231514 (n=265)	Docetaxel (n=276)
Minimum	.5	.3	.5	.3
25th percentile	1.7	1.5	1.7	1.5
Median	3.4	3.1	3.1	3.5
75th percentile	7.0	7.3	6.4	6.9
Maximum	18.2	19.5	18.2	19.5
Percent 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
Percent censored	24.7	27.8	20.0	24.6
Hazard ratio	.97		1.01	
95% CI for hazard ratio	(.80-1.17)		(.83-1.22)	
Wald p-value	.721		.951	

Figure 4 displays the K-M curves for TTPD for the RT patient group. Similar curves were obtained for the ITT population.

Figure 4: Time to Progressive Disease (Months)- RT Group



Tumor Response Analyses

A total of 264 patients in the LY231514 arm and 274 patients in the docetaxel arm were qualified for protocol-defined tumor response analyses (QR).

Best Tumor Response

Table 13 presents a summary of the investigator-determined best tumor response for the QR population by treatment arm. The number of patients with the best response of complete response (CR), partial response (PR), partial response in nonmeasurable disease (PRNM), or stable disease (SD) was similar between the treatment arms.

Table 13: Best Objective Tumor Response - QR Population

	LY231514 (N=264)	Docetaxel (N=274)	p-value
Response (%)[1]	24 (9.1)	24 (8.8)	>.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)	.931

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

[1] Patients with CR, PR, or PRNM.

The median time to response, measured from the date of randomization to the date of first objective status assessment of CR or PR or PRNM was 1.7 months for the 24 LY231514 responders and 2.9 months for the 24 Docetaxel responders. Corresponding mean times to response were 2.2 months and 2.8 months, respectively.

Duration of Tumor Response

Table 14 presents a summary of the duration of tumor response (in months) for the tumor responders by treatment arm. The duration of tumor response was measured from the date of first objective status assessment of CR, PR, or PRNM until the first date of documented disease progression or death due to any cause.

Table 14: Duration of Response (Months)

	LY231514 (n=24)	Docetaxel (n=24)
Median	4.6	5.3
Percent patients with duration of response lasting at least:		
3 months	70.8	75.0
6 months	45.8	36.1
9 months	27.8	16.9
Percent censored	25.0	16.7
Hazard ratio	.77	
95% CI for hazard ratio	(.40 - 1.47)	
Wald p-value	.427	

Symptoms

Fifty-0ne percent of LY231514 treated patients and 46% of docetaxel treated patients had improved or stable average lung cancer symptoms (anorexia, fatigue, cough, dyspnea, hemoptysis, pain; p=0.33).

D. Efficacy Conclusions

The sponsor claimed that survival of LY231514 treated patients was non-inferior to survival of docetaxel treated patients. FDA statistical analysis indicated that non-inferiority was not demonstrated. Even if non-inferiority was demonstrated, however, it would not be credible because of post-study chemotherapy. Thirty fewer docetaxel treated patients received post-study chemotherapy compared to LY231514 treated patients (randomized and treated population [RT]) Comparable findings were obtained with the ITT population. While 32% of LY231514 treated patients received post-study docetaxel it was observed that patients receiving any post-study chemotherapy drug(s) survived longer than those who did not. The majority of patients on both arms who did not receive post-study chemotherapy were performance status 0 or 1 at their last study visit and, conceivably, could have received additional treatment.

Response rate, time to progression and symptom improvement was comparable for the two study arms.

VII. Integrated Review of Safety

A. Sponsor's Conclusions

LY231514 produces less neutropenia, febrile neutropenia, infection, alopecia and diarrhea. There are fewer hospitalizations, although more days were spent in the hospital. There was less use of granulocyte colony stimulating factors. There are significantly fewer grade 3 or 4 toxicities of any type.

FDA Comment - Docetaxel grade 3/4 toxicities were primarily neutropenia and febrile neutropenia. There was also a statistically sifgnificant increase in myalgias, arthralgias, diarrhea and neurotoxicity. There were more RBC transfusions in LY231514 treated patients. Toxicities significantly more frequent in LY231514 treated patients include weight loss, nausea, vomiting, constipation, skin rash, increased alanine and aspartate aminotransferases and decreased creatinine clearance.

B. Description of Patient Exposure - Per Sponsor

Of the 283 patients randomly assigned to the LY231514 arm, 265 (93.6%) received at least one dose of LY231514, and of the 288 patients randomly assigned to the docetaxel arm, 276 (95.8%) received at least one dose of docetaxel. The most common reason for not receiving therapy was "protocol criteria not met" for patients on the LY231514 arm and "personal conflict" on the docetaxel arm.

Table 15 displays a summary of the number of completed treatment cycles for the RT patients.

Table 15: Summary of treatment cycles

	LY231514 (N=265)	**Docetaxel (N=276)**
Mean	4.4	3.9
Median	4.0	4.0
Range	1-20	1-14
No. (%) of patients who completed at least:		
Cycle 1	265 (100)	276 (100)
Cycle 2	239 (90.2)	238 (86.2)
Cycle 3	153 (57.7)	160 (58)
Cycle 4	136 (51.3)	139 (50.4)
Cycle 5	100 (37.7)	102 (37)
Cycle 6	90 (34.0)	88 (31.9)
Cycle 7	50 (18.9)	30 (10.9)
Cycle 8	38 (14.3)	24 (8.7)
Cycle 9	20 (7.5)	10 (3.6)
Cycle 10	15 (5.7)	7 (2.5)
>Cycle 10	14 (5.3)	5 (1.8)

Table 16 summarizes the distribution of the weekly mean dose of LY231514 administered per patient during the study compared with docetaxel patients. Patients on both treatment arms received >94% of the planned dose. A total of 1164 doses (cycles) of LY231514 were administered to 265 patients on the LY231514 arm and 1085 doses (cycles) of docetaxel were administered to 276 patients on the docetaxel arm.

Table 16: Distribution of Weekly Mean Dose per Patient

	LY231514 (N=265)	**Docetaxel (N=276)**
Planned mean/patient (mg/m^2/week)	166.7	25
Delivered weekly mean / patient[1]	161.0	23.6
Percent of planned DI (delivered/planned)	96.6%	94.4%

Abbreviations: DI = dose intensity.

C. Methods and Specific Findings of Safety Review

Safety assessments consisted of monitoring and recording all adverse events (AEs) and SAEs (with their severity and relationship to study drug), the regular monitoring of hematology, and blood chemistry, regular measurement of vital signs, the performance of physical examinations and documentation of all concomitant medications and therapies.

Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as events that emerged after administration of at least one dose of the study drug, or events present at the time of enrollment that worsened after administration of at least one dose of the study drug. Two hundred sixty five patients on the LY231514 arm and 276 patients on the docetaxel arm were qualified for the analyses because they received at least one dose of study drug. A total of 259 (97.7%) patients on the LY231514 arm and 272 (98.6%) patients on the docetaxel arm reported at least one TEAE.

Table 17 summarizes the clinically significant TEAEs experienced by $\geq$10% of the patients by system organ class, by treatment arm, regardless of drug causality; a patient could have experienced more than one event.

In general, the overall incidence of TEAEs was similar for the two treatment arms (LY231514: 97.7%; docetaxel: 98.6%). The five most commonly reported events in the LY231514 arm were fatigue (50.2%), anorexia (40.0%), nausea (37.0%), dyspnea (31.3%), and anemia (28.7%). The five most commonly reported events in the docetaxel arm were neutropenia (43.8%), fatigue (41.7%), alopecia (39.1%), dyspnea (35.1%), and leukopenia (33.7%). Of these, the incidence of neutropenia ($p<.001$), alopecia ($p<.001$), and leukopenia ($p<.001$) were statistically significantly lower in the LY231514 arm while the incidence of fatigue ($p=.048$) and nausea ($p<.001$) were statistically significantly lower in the docetaxel arm.

More patients on the docetaxel arm experienced TEAEs related to blood and lymphatic system (LY231514: 36.6%; docetaxel: 62.3%; $p<.001$). In addition to neutropenia and leukopenia, the incidence of febrile neutropenia (LY231514: 1.9%; docetaxel: 13.4%; $p<.001$) was statistically significantly higher in the docetaxel arm. Thrombocytopenia (LY231514: 9.1%; docetaxel: 1.8%; $p<.001$) was significantly lower in the docetaxel arm compared with the LY231514 arm.

Other clinically significant TEAEs that were different between the treatment arms included weight loss (LY231514: 28.7%; docetaxel: 15.9%), constipation (LY231515: 21.9%;docetaxel 12.3%), increased ALT (LY231514: 8.7%; docetaxel: 2.2%), increased AST (LY231514: 7.5%; docetaxel: 1.1%) decreased creatinine clearance (LY231514: 4.5%; docetaxel: 0.4%), vomiting (LY231514: 24.5%; docetaxel: 17.4%), and rash (LY231514: 14.0%; docetaxel: 6.9%), all of which were significantly higher in the LY231514 arm. Diarrhea (LY231514: 22.6%; docetaxel 33%), myalgia (LY231514: 8.7%; docetaxel: 15.2%) and neurotoxicity (LY231514: 0.8%; docetaxel: 3.6%) were significantly higher in the docetaxel arm.

Table 17: TAES occurring in >=10% of patients

MEDDRA Preferred Term		LY231514 (N=265)		DOCETAXEL (N=276)		LY vs. DOC
SYSTEM ORGAN CLASS:		n	%	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%	<.001
	Neutropenia	27	10.2%	121	43.8%	<.001
	Anemia NOS	76	28.7%	71	25.7%	
	Leukopenia NOS	33	12.5%	93	33.7%	<.001
	Febrile neutropenia	5	1.9%	37	13.4%	<.001
	Thrombocytopenia	24	9.1%	5	1.8%	<.001
Cardiac disorders	PATIENTS WITH >= 1 EVENT	32	12.1%	35	12.7%	
	Cardiac failure NOS	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%	.023
Gastrointestinal disorders	PATIENTS WITH >= 1 EVENT	179	67.5%	171	62.0%	
	Nausea	98	37.0%	59	21.4%	<.001
	Diarrhea NOS	60	22.6%	91	33.0%	.010
	Vomiting NOS	65	24.5%	48	17.4%	.045
	Constipation	58	21.9%	34	12.3%	.004
	Stomatitis	23	8.7%	34	12.3%	
	Abdominal pain NOS	21	7.9%	23	8.3%	
General disorders and administration site conditions	PATIENTS WITH >= 1 EVENT	212	80.0%	199	72.1%	.035
	Fatigue	133	50.2%	115	41.7%	.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 NOS	19	7.2%	21	7.6%	
	Oedema NOS	14	5.3%	23	8.3%	
	Weight decreased	76	28.7%	44	15.9%	<.001
Hepatobiliary disorders	Hepatic failure	1	0.4%	0	0.0%	
Immune system disorders	Hypersensitivity NOS	3	1.1%	5	1.8%	
Infections and infestations	PATIENTS WITH >= 1 EVENT	77	29.1%	78	28.3%	
	Sepsis NOS	1	0.4%	5	1.8%	
Lab Investigations	PATIENTS WITH >= 1 EVENT	22	8.3%	20	7.2%	
	Alanine aminotransferase increased	23	8.7%	6	2.2%	<.001
	Aspartate aminotransferase increased	20	7.5%	3	1.1%	<.001
	Creatinine renal clearance decreased	12	4.5%	1	0.4%	.001
	Blood creatinine increased	6	2.3%	1	0.4%	.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 NOS	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%	.024
	Arthralgia	19	7.2%	36	13.0%	.032
Nervous system disorders	PATIENTS WITH >= 1 EVENT	86	32.5%	106	38.4%	
	Headache	28	10.6%	30	10.9%	
	Neurotoxicity NOS	2	0.8%	10	3.6%	.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 NOS	2	0.8%	0	0.0%	
Respiratory, thoracic and mediastinal disorders	PATIENTS WITH >= 1 EVENT	177	66.8%	173	62.7%	
	Dyspnoea NOS	83	31.3%	97	35.1%	
	Cough	72	27.2%	65	23.6%	
	Haemoptysis	32	12.1%	28	10.1%	
Skin and subcutaneous tissue	PATIENTS WITH >= 1 EVENT	107	40.4%	134	48.6%	.058

disorders	Alopecia	19	7.2%	108	39.1%	<.001
	Rash NOS	37	14.0%	19	6.9%	.007
	Erythema	3	1.1%	8	2.9%	

Table 18 displays an overview of the number of serious adverse events (SAEs), serious, unexpected, reportable adverse events (SURs), adverse events that resulted in discontinuation from the study, and deaths that occurred during the study. In general, patients in LY231514 arm experienced fewer number of serious adverse events, SURs, nonserious, clinically significant adverse events, and deaths. Drug-related SAEs were statistically significantly fewer in the LY231514 arm.

Table 18: Serious adverse events

	Number of Patients with an Event			
	Regardless of Drug Causality		Possibly Drug Related	
	LY231514 (N=265) n (%)	Docetaxel (N=276) n (%)	LY231514 (N=265) n (%)	Docetaxel (N=276) n (%)
Patients with ≥1 SAE	99 (37.4)	120 (43.5)	27 (10.2)	66 (23.9)
SUR events[1]	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 because of SAEs	13 (4.9)	14 (5.1)	3 (1.1)	9 (3.3)
Deaths (on-study)	18 (6.8)	32 (11.6)	2 (0.8)	5 (1.8)

Abbreviations: SUR = serious, unexpected, and reportable; SAEs = serious adverse events.
[1] As of 11 February 2003.

Deaths

Five of the 283 patients randomly assigned to the LY231514 arm and 1 of the 288 patients randomly assigned to the docetaxel arm died from study disease following randomization but prior to receiving study drug. One additional patient on the docetaxel arm died from other causes prior to study therapy.

Table 19 presents a summary of the number of patients who died while participating in the study and those who died within 30 days of last dose of study drug. A total of 18 deaths on the LY231514 arm and 32 deaths on the docetaxel arm were reported during the treatment phase of the study; of these, 2 (0.8%) deaths on the LY231514 arm (Patients 71-7214, 114-141) and 5 (1.8%) deaths on the docetaxel arm (Patients 51-5572, 302-3021, 62-6622, 20-2200, 650-6204) were considered by the investigators study drug related. Thirteen (4.9%) additional patients in the LY231514 arm and 8 (2.9%) patients in the docetaxel arm died within 30 days of administration of the last dose of the study drug.

Table 19: Deaths

Reasons for Death	LY231514 (N=265) n (%)	Docetaxel (N=276) n (%)	LY231514 (N=265) n (%)	Docetaxel (N=276) n (%)
	On Study		Off Study[a]	
Study drug related	2 (0.8)	5 (1.8)	1 (0.4)	0
Cardiac arrest	1 (0.4)	0	0	0
Hepatic failure	1 (0.4)	0	0	0
Pulmonary embolism	0	1 (0.4)	0	0
Lung disorder	0	1 (0.4)	0	0
Pneumonia	0	1 (0.4)	0	0
Pneumonia and sepsis	0	0	1 (0.4)	0
Sepsis	0	1 (0.4)	0	0
Septic shock	0	1 (0.4)	0	0
Study Disease	9 (3.4)	19 (6.9)	9 (3.8)	7 (2.5)
Other Causes	7 (2.6)	8 (2.9)	3 (1.1)	1 (0.4)
Pulmonary embolism	2 (0.8)	0	0	0
ARDS	1 (0.4)	0	0	0
Cardiopulmonary failure	1 (0.4)	2 (0.7)	0	0
Dyspnea	1 (0.4)	0	0	0
Myocardial infarction	1 (0.4)	0	2 (0.8)	0
Pneumonia	1 (0.4)	0	1 (0.4)	1 (0.4)
Cardiac tamponade	0	1 (0.4)	0	0
Cardiovascular disorder	0	1 (0.4)	0	0
Cerebrovascular accident	0	1 (0.4)	0	0
Chronic obstructive airways disease	0	1 (0.4)	0	0
Unexplained	0	1 (0.4)	0	0
Superior vena caval occlusion	0	1 (0.4)	0	0
Total	**18 (6.8)**	**32 (11.6)**	**13 (4.9)**	**8 (2.9)**

abbeviations: ARDS = acute respiratory distress syndrome.

[a] Within 30 days of study drug discontinuation.

Serious Adverse Events

Table 20 summarizes the SAEs experienced by ≥2% of the RT patients by treatment arm. The difference in the overall occurrence of SAEs between the two treatment arms was not statistically significant. The five most frequently reported SAEs in the LY231514 arm were pneumonia (6.8%), dyspnea (4.9%), pyrexia (4.5%), anemia (3.8%), and abdominal pain (2.3%). There was no incidence of neutropenia as an SAE in the LY231514 arm. The five most commonly reported SAEs in the docetaxel arm were febrile neutropenia (11.2%), dyspnea (9.1%), neutropenia (6.2%), pneumonia (5.1%), and pyrexia (3.6%). The incidence of neutropenia and febrile neutropenia were statistically significantly higher in the docetaxel arm ($p<.001$).

Table 20 SAE's

Event Classification	LY231514 (N=265) n (%)	DOCETAXEL (N=276) n (%)	TOTAL (N=541) n (%)	p-value
PATIENT WITH >= 1 EVENT	99 (37.4)	120 (43.5)	219 (40.5)	
Dyspnea NOS	13 (4.9)	25 (9.1)	38 (7.0)	.065
Febrile neutropenia	4 (1.5)	31 (11.2)	35 (6.5)	<.001
Pneumonia NOS	18 (6.8)	14 (5.1)	32 (5.9)	
Pyrexia	12 (4.5)	10 (3.6)	22 (4.1)	
Anemia NOS	10 (3.8)	7 (2.5)	17 (3.1)	
Neutropenia	0 (0.0)	17 (6.2)	17 (3.1)	<.001
Asthenia	4 (1.5)	8 (2.9)	12 (2.2)	
Pleural effusion	1 (0.4)	6 (2.2)	7 (1.3)	
Abdominal pain NOS	6 (2.3)	0 (0.0)	6 (1.1)	.013

Frequencies analyzed using a Fisher's Exact test

A total of 13 (4.9%) patients on the LY231514 arm discontinued because of an SAE; of these, 3 (1.1%) discontinuations were considered study drug related. In the docetaxel arm, a total of 14 (5.1%) patients discontinued because of an SAE; of these, 9 (3.3%) discontinuations were considered study drug related. The most common cause of discontinuation on the LY231514 arm was fatigue (0.8%) and on the docetaxel arm febrile neutropenia (1.1%) and pyrexia (0.7%).

Table 21 summarizes the number of patients who experienced at least one Grade 3 or 4 hematologic or nonhematologic toxicity in the RT population by treatment arm. The most common Grade 3 or 4 hematologic toxicity among patients was neutropenia, which occurred at a significantly higher rate in the docetaxel arm (40.2%) than in the LY231514 arm (5.3%; p<.001). Incidence of Grade 3 or 4 thrombocytopenia was low in both arms. Grade 3 or 4 anemia was similar between the treatment arms.

The overall incidence of Grade 3 or 4 nonhematologic laboratory toxicities was very low in this study. On the LY231514 arm, the most common Grade 3 or 4 nonhematologic toxicities were increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), occurring in 1.9% and 1.1% of the patients. On the docetaxel arm, the most common nonhematologic toxicity was hyponatremia (1.1%). No Grade 3 or 4 elevations of ALT were reported among the patients on the docetaxel arm compared with the LY231514 arm (p=.028).

Table 21: CTC Grade 3/4 Laboratory Toxicity

Event Classification	LY231514 (N=265) n (%)	Docetaxel (N=276) n (%)	TOTAL (N=541) n (%)	p-
Neutrophils/granulocytes	14 (5.3)	111 (40.2)	125 (23.1)	<.001
Leukocytes	11 (4.2)	75 (27.2)	86 (15.9)	<.001
Hemoglobin	11 (4.2)	12 (4.3)	23 (4.3)	1.00
Lymphopenia	3 (1.1)	9 (3.3)	12 (2.2)	.143
Platelets	5 (1.9)	1 (0.4)	6 (1.1)	.116
SGPT(ALT)	5 (1.9)	0 (0.0)	5 (0.9)	.028
Hyponatremia	0 (0.0)	3 (1.1)	3 (0.6)	
SGOT(AST)	3 (1.1)	0 (0.0)	3 (0.6)	
Amylase	1 (0.4)	0 (0.0)	1 (0.2)	
Bilirubin	1 (0.4)	0 (0.0)	1 (0.2)	
Hyperkalemia	1 (0.4)	0 (0.0)	1 (0.2)	
Hypocalcemia	1 (0.4)	0 (0.0)	1 (0.2)	
Hypokalemia	1 (0.4)	0 (0.0)	1 (0.2)	
Lipase	1 (0.4)	0 (0.0)	1 (0.2)	

Frequencies analyzed using a Fisher's Exact test

Table 22 displays the percent of cycles in which CTC Grade 3 or 4 laboratory toxicities occurred in the RT population. A total of 1164 and 1085 cycles of therapy were administered to patients on the LY231514 arm and docetaxel arm, respectively. Grade 3 or 4 neutropenia was reported in 288 cycles (26.5%) for patients on the docetaxel arm compared with 17 cycles (1.5%) for patients on the LY231514 arm.

Table 22: Percent of cycles with CTC Grade 3/4 Lab Toxicity

Event Classification	LY231514 (N=1164)		DOCETAXEL (N=1085)		p-value
	n	avg. %	n	avg. %	Fisher's
Hemoglobin	15	1.3	13	1.2	1.000
Hypocalcemia	3	0.3	0	0	
Hyponatremia	0	0	4	0.4	.054
Leukocytes	15	1.3	165	15.2	<.001
Lymphopenia	3	0.3	12	1.1	.018
Neutrophils	17	1.5	288	26.5	<.001
Platelets	9	0.8	1	0.1	.022
SGOT(AST)	3	0.3	0	0	
SGPT(ALT)	5	0.4	0	0	.063

Nonlaboratory Toxicities

Table 23 summarizes the number of patients who experienced at least one Grade 3 or 4 nonlaboratory toxicity in the RT population by treatment arm. CTC Grade 3 or 4 fatigue was the most commonly reported nonlaboratory toxicity in the LY231514 arm

(5.3%) whereas Grade 3 or 4 febrile neutropenia was the most common toxicity in the docetaxel arm (12.7%). Infection with Grade 3 or 4 neutropenia was the only other toxicity that was significantly different between the treatment arms. Grade 3 or 4 toxicities of nausea, vomiting, anorexia, and stomatitis were similar in the two arms. Grade 3 or 4 myalgia and arthralgia and neurosensory toxicities occurred in significantly fewer patients in the LY231514 arm compared with the docetaxel arm. Alopecia (all grades) was significantly higher in the docetaxel arm.

Table 23: CTC Grade 3/4 Non-Laboratory Toxicity

Event Classification	LY231514 (N=265) n (%)	Docetaxel (N=276) n (%)	TOTAL (N=541) n (%)	p-value
Febrile neutropenia	5 (1.9)	35 (12.7)	40 (7.4)	<.001
Fatigue	14 (5.3)	15 (5.4)	29 (5.4)	1.00
Anorexia	5 (1.9)	7 (2.5)	12 (2.2)	.772
Nausea	7 (2.6)	5 (1.8)	12 (2.2)	.570
Infection with grade 3 or 4 Neutropenia	0 (0.0)	9 (3.3)	9 (1.7)	.004
Diarrhea without colostomy	1 (0.4)	7 (2.5)	8 (1.5)	.069
Alopecia	1 (0.4)	6 (2.2)	7 (1.3)	.123
Vomiting	4 (1.5)	3 (1.1)	7 (1.3)	.720
Stomatitis/pharyngitis	3 (1.1)	3 (1.1)	6 (1.1)	1.00
Arthralgia	0 (0.0)	5 (1.8)	5 (0.9)	.062
Dyspnea	0 (0.0)	5 (1.8)	5 (0.9)	.062
Myalgia	1 (0.4)	4 (1.4)	5 (0.9)	.373
Muscle weakness	2 (0.8)	2 (0.7)	4 (0.7)	1.00
Neuropathy-motor	1 (0.4)	3 (1.1)	4 (0.7)	.624
Other Dermatology/Skin	2 (0.8)	2 (0.7)	4 (0.7)	1.00
Abdominal pain or cramping	0 (0.0)	3 (1.1)	3 (0.6)	.
Allergic reaction/Hypersensitivity	0 (0.0)	3 (1.1)	3 (0.6)	.
Bone pain	0 (0.0)	3 (1.1)	3 (0.6)	.
Neuropathy-sensory	0 (0.0)	3 (1.1)	3 (0.6)	.
Supraventricular arrhythmias	2 (0.8)	1 (0.4)	3 (0.6)	.
Constitutional Symptoms-Other	2 (0.8)	0 (0.0)	2 (0.4)	.
Headache	1 (0.4)	1 (0.4)	2 (0.4)	.
Infection without Neutropenia	1 (0.4)	1 (0.4)	2 (0.4)	.
Other neurology	0 (0.0)	2 (0.7)	2 (0.4)	.
Pneumonitis/pulmonary infiltrates	0 (0.0)	2 (0.7)	2 (0.4)	.
Pulmonary-Other	0 (0.0)	2 (0.7)	2 (0.4)	.
Renal/Genitourinary-Other	2 (0.8)	0 (0.0)	2 (0.4)	.
Adult Respiratory Distress Syndrome	0 (0.0)	1 (0.4)	1 (0.2)	.
Dehydration	1 (0.4)	0 (0.0)	1 (0.2)	.
Dysphagia, esophagitis, odynophagia	1 (0.4)	0 (0.0)	1 (0.2)	.
Hypotension	0 (0.0)	1 (0.4)	1 (0.2)	.
Injection site reaction	0 (0.0)	1 (0.4)	1 (0.2)	.
Insomnia	0 (0.0)	1 (0.4)	1 (0.2)	.

Liver dysfunction/failure	1 (0.4)	0 (0.0)	1 (0.2)	.
Mood alteration-depression	0 (0.0)	1 (0.4)	1 (0.2)	.
Other endocrine	1 (0.4)	0 (0.0)	1 (0.2)	.
Other hepatic	1 (0.4)	0 (0.0)	1 (0.2)	.
Other Gastrointestinal	0 (0.0)	1 (0.4)	1 (0.2)	.
Pelvic pain	1 (0.4)	0 (0.0)	1 (0.2)	.
Proctitis	0 (0.0)	1 (0.4)	1 (0.2)	.
Pruritus	1 (0.4)	0 (0.0)	1 (0.2)	.
Rectal bleeeding/hematochezia	0 (0.0)	1 (0.4)	1 (0.2)	.
Sinus tachycardia	0 (0.0)	1 (0.4)	1 (0.2)	.
Sweating	0 (0.0)	1 (0.4)	1 (0.2)	.
Urticaria	1 (0.4)	0 (0.0)	1 (0.2)	.

Frequencies analyzed using a Fisher's Exact test

Transfusions

Table 24 summarizes the number of transfusions and the number of units of each type of transfusion received by patients while on study by treatment arm. The number of transfusions in the study was small; 45 (17%) patients on the LY231514 arm and 32 (11.6%) patients on the docetaxel arm received =1 transfusion.
On both treatment arms, the most common transfusion was red blood cells (RBC). Although the incidence of CTC Grade 2, 3, or 4 anemia was similar between the arms, more patients on the LY231514 arm received transfusions of RBC while 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 24 Transfusions

	LY231514		**Docetaxel**	
Type of Transfusion	**N=265**		**N=276**	
Patients with ≥1 Transfusion[1] (n, %)	**45 (17.0%)**		**32 (11.6%)**	
	Units	**Patients n (%)**	**Units**	**Patients 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: RBC = red blood cell; RT = randomized and treated.
[1] Patients received more than one type of transfusion.
[2] Patients received 1 to 3 units of RBC; 1 unit = one bag of packed RBC.
[3] Patients received 6 to 15 units of platelets per transfusion.

Hospitalizations

Table 25 presents a summary of hospitalizations for the RT population. If multiple reasons for a hospitalization were listed, the hospitalization was only counted once; the reason was assigned in the following order: febrile neutropenia, drug-related adverse event, non drug-

related adverse event, study drug administration, protocol tests, and social reasons. Hospitalizations are recorded in 3 ways; by no. of cycles of therapy, by admissions and by number of days of hospitalization.

It is evident from the table that, by any of the above ways of classifying hospitalizations more patients on the docetaxel arm were hospitalized during the course of the study than on the LY231514 arm for febrile neutropenia. In an unblinded study it is often difficult to distinguish drug-related from non drug-related AE's so that the numbers for the two treatment arms are probably comparable. The other numbers in the table are probably irrelevent in determining which drug has a better safety profile.

Table 25 Hospitalizations

	LY231514 (N=265)	Docetaxel (N=276)
No. of cycles of therapy	1164	1085
Hospitalizations, n (%)[a]	129 (48.7)	146 (52.9)
Study drug administration	53 (20.0)	57 (20.7)
Adverse events (all)	84 (31.7)	112 (40.6)
Febrile neutropenia (only Investigator-collected data)	4 (1.5)	37 (13.4)
Other drug-related	17 (6.4)	29 (10.5)
Non drug-related[b]	69 (26.0)	66 (23.9)
Protocol tests	43 (16.2)	31 (11.2)
Social reasons	17 (6.4)	16 (5.8)
Hospitalizations (admissions)	337	364
Study drug administration	123	151
Adverse events (all)	113	147
Febrile neutropenia (only Investigator-collected data)	4	43
Other drug-related	17	29
Non drug-related[b]	92	75
Protocol tests	72	49
Social reasons	29	17
Hospitalizations (days)	1722	1410
Study drug administration	314	314
Adverse events (all)	885	833
Febrile neutropenia (only Investigator-collected data)	29	195
Other drug-related	131	151
Non drug-related[b]	725	487
Protocol tests	143	100
Social reasons	380	163

Abbreviations: n = number of patients hospitalized.

[a] Patients may have been admitted for multiple reasons.

[b] As determined by investigator.

Concomitant Medications
The concomitant medications considered in this summary were 5-HT3 antagonists, G-CSFs, erythropoietin, and parenteral antibiotics. The number of patients receiving 5-HT3 antagonists was similar between arms and the incidence of nausea and vomiting were not different between arms based on Grade 3 or 4 CTC toxicities. More docetaxel treated patients received G-CSF, erythropoietin and antibiotics than did LY231514 treated patients.

Electrocardiograms

Preclinical studies in beagle dogs (anesthetized and ambulant) showed some degree of depression of cardiac function at high doses (2100 mg/m2) but no effect on cardiac function at low doses (640 mg/m2). In addition, no signal indicated any effect on cardiac repolarization at the lower dose in dogs.

In Study JMEI, electrocardiograms (ECGs) were obtained on 202 patients (138 male, 64 female). ECGs were performed at baseline, during the first infusion of LY231514 (peak concentration recording), and prior to the beginning of the second cycle (final postbaseline recording). A total of 163 patients had evaluable ECGs. Mean change in QTcB from baseline to the peak concentration recording was 2.64 msec. Twenty-one days after LY231514 infusion, this value decreased to -0.81 msec. No patient experienced a QTcB prolongation >60 msec.

Five patients (Patients 84-3244, 164-645, 302-3025, 402-4041, and 655-6301), experienced a QTcB prolongation (30 to 60 msec) at peak concentration of LY231514. Two other patients (Patients 404-4084 and 652-6242) experienced a QTcB prolongation (30 to 60 msec) 21 days after LY231514 infusion. LY231514 is not expected to be present at plasma or cell level just prior to the next cycle.

The effect on QTcB was similar between males and females or between the younger and older patients.

D. Adequacy of Safety Testing

Safety evaluation was adequate and was consistent with previously reviewed LY231514 data from the mesothelioma trial and it is also consistent with past experience with other antifols.

E. Summary of Critical Safety Findings and Limitations of Data

LY231514 produced significantly less hematologic toxicity and less febrile neutropenia than did docetaxel. Myalgias, arthralgias and neurotoxicity were also significantly lower in the LY231514 arm. There were fewer hospitalizations and less need for granulocyte colony stimulating factors with LY231514 treatment but LY231514 patients spent more days in the hospital. LY231514 patients required more red blood cell transfusions. The

incidence of fatigue, weight loss, nausea, vomiting and constipation were statistically significantly higher in the LY231514 arm. Other clinically significant AEs that were different between the treatment arms included increased alanine and aspartate aminotransferases (LY231514 higher incidence), skin rash (LY231514 higher incidence) and decreased creatinine clearance (LY231514 higher incidence.

There is also an issue regarding vitamin supplementation in LY231514 treated patients but ot in docetaxel treated patients. Twenty-nine percent of the latter patients had elevated homocysteinne (Hcys) levels. Hyperhomocysteinemia is risk factor for atherosclerotic disease in the coronary, cerebral, and peripheral arterial circulations. It also appears to be a risk factor for venous thromboembolism and for neuronal cell damage. Low dietary intake of vitamins B6, B12 and folic acid is the most prevalent cause of hyperhomocysteinemia. Vitamin B12 and folic acid supplementation have been shown to reliably reduce elevated Hcys levels and to reduce hematological and non-hematological toxicity of LY231514 treatment. Hcys was, in fact, better than baseline albumin (another predictor of toxicity) at predicting LY231514 toxicity. There is no reason to suspect that vitamin supplementation, if administered, would not have also reduced toxicity in hyperhomocysteinemic docetaxel treated patients

VIII. Dosing, Regimen, and Administration Issues

The recommended dose of LY231514 is 500 mg/m2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

Administration issues

Corticosteroid — Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after LY231514 administration.
Vitamin Supplementation — To reduce toxicity, patients treated with LY231514 must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of LY231514; and dosing should continue during the full course of therapy and for 21 days after the last dose of LY231514. Patients must also receive one (1) intramuscular injection of vitamin B12 during the week preceding the first dose of LY231514 and every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as LY231514. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 µg, and the dose of vitamin B12 was 1000 µg. The most commonly used dose of oral folic acid in clinical trials was 400 µg.

There is an issue regarding the above vitamin supplementation in LY231514 treated patients but not in docetaxel treated patients. Twenty-nine percent of the latter patients had elevated homocysteine (Hcys) levels. Hyperhomocysteinemia is risk factor for

atherosclerotic disease in the coronary, cerebral, and peripheral arterial circulations. It also appears to be a risk factor for venous thromboembolism and for neuronal cell damage. Low dietary intake of vitamins B6, B12 and folic acid is the most prevalent cause of hyperhomocysteinemia. Vitamin B12 and folic acid supplementation have been shown to reliably reduce elevated Hcys levels and to reduce hematological and non-hematological toxicity of LY231514 treatment. Hcys was, in fact, better than baseline albumin (another predictor of toxicity) at predicting LY231514 toxicity. There is no reason to suspect that vitamin supplementation, if administered, would not have also reduced toxicity in hyperhomocysteinemic docetaxel treated patients

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

There was no statistically significant gender by treatment interaction for any TEAE.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Age

A statistically significant age by treatment interaction was observed for diarrhea (p=0.0496). Among the older patients $\geq$ 65, docetaxel-treated patients experienced a significantly higher frequency of diarrhea compared with LY231514-treated patients (34% versus 13%, p=0.003). There was no difference in the incidence of diarrhea between the treatment arms among the younger patients.

LY231514 is not recommended for use in children, as safety and efficacy have not been established in children.

2. Race/Ethnicity

Approximately 70% of study patients were Caucasian. East and Southeast Asians comprised approximately 17% of the study population. Patients of African descent comprised 3% of the population. There was no significant difference in efficacy or safety results among these ethnic populations.valuation of Pediatric Program

D. Comments on Data Available or Needed in Other Populations

1. Renal or Hepatic Impairment

In clinical studies, patients with creatinine clearance (Ccr) $\geq$ 45 mL/min required no dose adjustments other than those recommended for all patients.

Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients. Therefore, LY231514 should not be administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula or GFR measured by Tc99m-DPTA serum clearance method:

LY231514 is not extensively metabolized by the liver. Dose adjustments should be made based on hepatic impairment experienced during treatment.

2. Pregnancy

Category D LY231514 may cause fetal harm when administered to a pregnant woman.

LY231514 was fetotoxic and teratogenic in mice at i.v. doses of 0.2 mg/kg (0.6 mg/m2) or 5 mg/kg (15 mg/m2) when given on gestation days 6 through 15. LY231514 caused fetal malformations (incomplete ossification of talus and skull bone) at 0.2 mg/kg (about 1/833 the recommended i.v. human dose on a mg/m2 basis), and cleft palate at 5 mg/kg (about 1/33 the recommended i.v. human dose on a mg/m2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. There are no studies of LY231514 in pregnant women. Patients should be advised to avoid becoming pregnant. If LY231514 is used during pregnancy, or if the patient becomes pregnant while taking LY231514, the patient should be apprised of the potential hazard to the fetus.

X. Conclusions and Recommendations

A. Conclusions

The primary efficacy endpoint was survival. The sponsor claimed that survival of LY231514 treated patients was non-inferior to survival of docetaxel treated patients. FDA statistical analysis indicated that non-inferiority was not demonstrated. Even if non-inferiority was demonstrated, however, it would not be credible because of post-study chemotherapy. Thirty fewer docetaxel treated patients received post-study chemotherapy compared to LY231514 treated patients (randomized and treated population [RT]) Comparaable findings were obtained with the ITT population. Patients receiving post-study chemotherapy survived longer than those who did not. The majority of patients on both arms who did not receive post-study chemotherapy were performance status 0 or 1 at their last study visit and, conceivably, could have received additional treatment.

LY231514 produced significantly less hematologic toxicity and less febrile neutropenia than did docetaxel. There were fewer hospitalizations and less need for granulocyte colony stimulating factors with LY231514 treatment. Myalgias and neurotoxicity were significantly higher in the docetaxel arm. AEs that were statistically significantly less frequent on the docetaxel arm were fatigue, nausea, vomiting, weight loss, constipation, elevated alanine aminotransferase and aspartate, skin rash, need for RBC transfusions and decreased creatinine clearance.

There is an issue regarding vitamin supplementation in LY231514 treated patients but not in docetaxel treated patients. Twenty-nine percent of the latter patients had elevated homocysteine (Hcys) levels at baseline. Vitamin B12 and folic acid supplementation have been shown to reliably reduce elevated Hcys levels and to reduce hematological and non-hematological toxicity of LY231514 treatment. Hcys was, in fact, better than baseline albumin (another predictor of toxicity) at predicting LY231514 toxicity. There is no reason to suspect that vitamin supplementation, if administered, would not have also reduced toxicity in hyperhomocysteinemic docetaxel treated patients

B. Recommendations

Deferred pending ODAC review and discussion.

XI. Appendix - Protocol H3E- MC- JMEI

"A Phase 3 Trial of ALIMTA vs Docetaxel in Patients with Locally Advanced or Metastatic Non- Small Cell Lung Cancer (NSCLC) Who Were Previously Treated with Chemotherapy"

1.1. Introduction - Non- Small Cell Lung Cancer (NSCLC)

Lung cancer, one of the most common malignancies in the world, continues to rise in incidence, with an estimate of 1 million new cases and over 900,000 deaths per year. It is the leading cause of cancer death in men worldwide, and is the third highest cause of cancer death among women, after breast and stomach cancer (Pisani et al. 1999). An estimated 164,000 new cases will be diagnosed in the US in 2000, accounting for approximately 13% of all cancer diagnoses and 28% of all US cancer deaths (Greenlee et al. 2000). The majority of lung cancer deaths will be due to metastatic NSCLC.

Almost 80% of lung cancers can be classified as NSCLC, with 65% to 75% of cases presenting as locally advanced (Stage III) or metastatic disease (Stage IV) (Walling 1994; Shepherd 1993; Ihde 1992). Patients diagnosed with Stage IIIA or IIIB disease generally receive chemotherapy as part of standard multimodality treatment, whereas patients with Stage IV disease typically receive chemotherapy as first- line standard therapy.

Prior to the 1980s, the few agents that had activity against NSCLC resulted in response rates less than 10%. In the 1980s, several agents were introduced, including cisplatin, mitomycin- C, ifosfamide, vindesine, vinblastine, carboplatin, and etoposide. Response rates of these drugs as single agents ranged from 10% to 20%, with combinations resulting in response rates of 20% to 40% (Ardizzoni et al. 1999). The combination of cisplatin and etoposide has shown response rates of approximately 20% to 38%, with median survival times of 5 months to 10.8 months (Joss et al. 1984; Ruckdeschel et al. 1986; Veronesi et al. 1988; Paccagnella et al. 1986; Klastersky et al. 1989; Crino et al. 1990; Rosso et al. 1988).

Vinorelbine is approved for first- line treatment of advanced NSCLC in several countries, including US, France, Italy, Spain, Germany, and UK, both as a single agent and in combination with cisplatin. As a single agent, it has shown response rates of 20% or higher, but confers only a modest survival advantage (Dancey et al. 1997; Hainsworth et al. 1995; Rigas 1997; Crawford et al. 1996). The combination of vinorelbine and cisplatin has, in some studies, resulted in improved response rates and survival advantages compared to either agent alone, with 1- year survival rates of 33% to 35% compared to 12% for cisplatin and 30% for vinorelbine (Wozniak et al. 1996; LeChevalier et al. 1994). One study of vinorelbine plus cisplatin versus vinorelbine alone showed a higher response rate for the combination (43% versus 16%), but no advantage in median survival time (33 weeks for vinorelbine plus cisplatin versus 32 weeks for vinorelbine alone) (Depierre et al. 1994).

Gemcitabine and paclitaxel were both approved in 1998 in US for use in combination with cisplatin for the first- line treatment of advanced NSCLC (Drug Approvals, www. fda. gov/ oashi/ cancer/ cdrug. html). Paclitaxel was approved for use in NSCLC in 1998 in UK and France as well. Gemcitabine was also approved for this use in other countries, including UK, Spain, France, Italy, and Germany during 1995 to 1998. Gemcitabine has shown single- agent activity in this setting, with average response rates of 20% (Kaye 1994). In five Phase 2 trials of the gemcitabine/ cisplatin combination, response rates ranged from 38% to 54% and median survival from 8.4 months to 14.3 months (Steward et al. 1996; Abratt et al. 1997; Crino et al. 1997a; Sandler et al. 1995; Anton et al. 1997). Paclitaxel shows single- agent response rates of around 20% (Chang et al. 1993). In a Phase 3 study of paclitaxel combined with cisplatin, without and with filgrastim, response rates were 27% and 32%, and median survival times were 9.5 and 10.5 months, respectively (Bonomi et al. 1996).

Historically, NSCLC has not responded well to second- line chemotherapy, and until recently no treatment regimen had earned regulatory approval in the second- line setting. Response rates to first- generation single- agent therapy with vindesine, epirubicin, etoposide, or cisplatin were 10% or less (Ihde 1992; Minna et al. 1989; Johnson 1990). Several agents have shown activity in clinical trials, but the activity is not consistent across trials. Response rates in second- line clinical trials of paclitaxel range from 0% to 30%, with a median survival time of up to 18 weeks (Murphy et al. 1994; Ruckdeschel et al. 1994; Socinski and Steagal 1997; Hainsworth et al. 1995). Vinorelbine shows similar inconsistency in the second- line setting, with response rates ranging from 0% to 20% (Santoro et al. 1994; Rinaldi et al. 1994; Pronzato et al. 1994). Irinotecan was evaluated against second- line NSCLC in two small studies; response rates were 0% and 14% (Negoro et al. 1991; Nakai et al. 1991). In one study (Crino et al. 1997b), gemcitabine gave a 25% response rate and median survival time of 28.5 weeks; another study was discontinued early due to lack of response (Belani 1998).

In December 1999, Food and Drug Administration (FDA) approved docetaxel in US for use in patients with locally advanced or metastatic NSCLC after failure of prior platinumcontaining chemotherapy. In January 2000 the European Commission approved

docetaxel in the countries of the European Union for treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy. Results of the pivotal and supporting US clinical trials are discussed in detail in Section 1.3, Docetaxel.

1.2. ALIMTA

1.2.1. Background and Phase 1 Results

Inhibition of the enzyme thymidylate synthase (TS) is the primary mechanism of action of LY231514, a folate antimetabolite (Lilly 2000; Shih et al. 1992; Grindey et al. 1992). Thymidylate synthase, a folate- dependent enzyme, catalyzes the transformation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Inhibition of TS results in decreased thymidine, a necessary component for DNA synthesis (Grem 1990; Schilsky 1992).

LY231514 also inhibits dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT), a folate- dependent enzyme involved in purine synthesis (Shih et al. 1996). These targets are related to the cytotoxicity of LY231514 since both thymidine and hypoxanthine are required to circumvent cellular death caused by LY231514 (Schultz et al. 1996). LY231514 gains entry to the cell via the reduced folate carrier and once localized is an excellent substrate for folylpolyglutamate synthase (FPGS). The pentaglutamate form of LY231514 is the predominant intracellular form and is > 60- fold more potent in its inhibition of TS than the monoglutamate (Chen et al. 1996).

LY231514 exhibits highly cytotoxic in vitro activity against the CCRF- CEM human leukemia cell line and has shown significant antitumor activity against thymidine- and hypoxanthine- deficient murine tumor cell lines as well as two human colon xenografts resistant to methotrexate. Several dose schedules were studied in dogs with the predominant toxicities being gastrointestinal and hematologic. Marked schedule dependency was noted, with a 34- fold increase in dose intensity found using once weekly compared to daily dosing. Folinic acid treatment initiated 24 hours after a potentially fatal dose prevented lethality, suggesting a role for folinic acid in the treatment of severe, drug-induced toxicity (Lilly 2000).

Two studies were conducted in dogs to evaluate potential rescue agents (leucovorin and thymidine) for treatment of severe toxicity due to LY231514 administration. Two intravenous doses of 50 mg LY231514/ kg, 3 days apart, were used to produce toxicity. In the leucovorin rescue study, both clinical signs of toxicity and hematologic alterations were reversed by co- administration of leucovorin, a reduced form of folate. In the thymidine rescue study, subsequent (24 hours after last LY231514 dose) administration of thymidine, the end product of TS, as a continuous infusion for 3 days was successful in rescuing dogs from life- threatening toxicity associated with LY231514.

Given the schedule dependency observed in animal models, Phase 1 studies were conducted exploring three treatment schedules: daily times 5 every 3 weeks (H3E- BP-

001); weekly times 4 every 6 weeks (H3E- MC- JMAB); and once every 3 weeks (H3EMC- JMAA).

Thirty- eight patients were treated at doses ranging from 0.2 mg/ m2 to 5.2 mg/ m2 daily times 5 every 3 weeks in Study BP- 001 (McDonald et al. 1996). The maximum tolerated dose (MTD) was 4 mg/ m2/ day, with dose limiting toxicities (DLTs) of reversible neutropenia and liver enzyme disturbance. Other toxicities included mucositis, diarrhea, rash, fatigue, and elevated transaminases. Minor responses were observed in 2 patients with colorectal and non- small cell lung cancer (NSCLC).

In Study JMAB, 24 patients were treated with a 10- minute infusion of LY231514 once a week for 4 weeks, with cycles repeated every 6 weeks (Rinaldi et al. 1995). Doses ranged from 10 mg/m2/ week to 40 mg/m2/ week. The DLT was myelosuppression, particularly leukopenia and neutropenia. Neutropenia prevented weekly dosing in some patients. Nonhematologic toxicities included mild fatigue, anorexia, and nausea. DLT was observed at 40 mg/m2/week, and the recommended dose for Phase 2 evaluation was 30 mg/m2/ week. The weekly schedule was not pursued in Phase 2 trials.

In Study JMAA, LY231514 was administered to 37 patients as a 10- minute infusion once every 3 weeks at doses ranging from 50 mg/ m2 to 700 mg/ m2 (Rinaldi et al. 1996). The DLTs on this schedule were neutropenia, thrombocytopenia, and fatigue. Of the 20 patients treated at 600 mg/m2, Common Toxicity Criteria (CTC) Grade 4 neutropenia and CTC Grade 4 thrombocytopenia occurred in 4 and 1 patients, respectively, during the first cycle. CTC Grade 2 toxicities at that dose level included rash, mucositis, nausea, vomiting, fatigue, anorexia, and elevations of liver transaminases. Ten patients who developed rashes received dexamethasone 4 mg twice daily for 3 days starting 1 day prior to treatment with LY231514, which improved or prevented the rash during subsequent cycles of therapy. There was evidence of cumulative toxicities of neutropenia, thrombocytopenia, and mucositis, which may have been due to the prolonged intracellular half- life of the polyglutamate of LY231514 and decreasing renal function over time with decreased renal drug clearance. Based on this study, the recommended dose for Phase 2 studies was 600 mg/m2. Partial responses were observed in 2 patients with pancreatic cancer and 2 patients with advanced colorectal cancer. Three of the 4 patients with partial responses had failed previous treatment with thymidylate synthase inhibitors including either 5- FU, FUDR, or raltitrexed.

Two patients experienced severe toxicity during Cycle 1 in Study JMAS, which is an LY231514 plus folic acid Phase 1 study. One of these patients was on stable doses of naproxen (500 mg twice per day) concurrent with LY231514 at 800 mg/ m2. The other patient was on stable doses of a long- acting nonsteroidal anti- inflammatory drug concurrent with LY231514 at 900 mg/m2. At these dose levels, it is more likely that LY231514 may compete with aspirin or other NSAIDs for renal tubular secretion. Until the pharmacokinetic parameters have been calculated for these 2 patients, the possibility that concurrent NSAID therapy decreased LY231514 clearance (predisposing these patients to severe toxicity) cannot be ruled out. Additional considerations include the

potential renal toxicity of chronic NSAID therapy and the nutritional and folate status of these patients.

Pharmacokinetic determinations were made in 20 patients with various cancers (primarily colorectal cancer) at the MTD (600 mg/m2) in Study JMAA. A mean maximum concentration of 137 µg/mL was attained, with a mean half- life of 3.1 hours (range, 2.2 hours to 7.2 hours). Mean respective clearance and steady- state volume of distribution values of 40 mL/min/m2 and 7.0 L/m2 were also measured. This mean clearance value is similar to that of creatinine clearance in the age range of the patients enrolled (approximately 45 to 55 mL/min/m2), and the volume of distribution reflects limited distribution outside the bloodstream.

Samples collected after the first dose in each course of therapy showed the disposition of LY231514 to be linear over the entire dose range (0.2 mg/ m2 to 700 mg/ m2). The clearance of the compound is primarily renal, with 80% or greater of the dose recovered unchanged in the urine during the first 24 hours after dosing. No accumulation appears to occur with multiple courses, and the disposition of LY231514 does not change after multiple doses. LY231514 clearance does appear to decrease with age, although this decrease is most likely related to decreasing renal function associated with aging.

1.2.2. Single Agent Phase 2 Study Results

Two single agent Phase 2 studies in colorectal cancer (H3E- MC- JMAC; H3E- MC JMAO), one in pancreas cancer (H3E- MC- JMAD), two in NSCLC (H3E- MC- JMAN; H3E- MC- JMAL), and one in breast cancer (H3E- MC- JMAG) began in late 1995. These studies primarily included chemonaive patients, or, in the case of the breast cancer study, patients who had received limited prior chemotherapy in the metastatic setting. Another study (H3E- MC- JMBR), begun in 1997, looked at LY231514 in second- line treatment of NSCLC patients, some of whom had received a platinum- containing regimen. Most of these studies used a starting dose of 600 mg/m2 once every 21 days. However, due to unexpected toxicity in initial Phase 2 trials, the starting dose for all subsequent LY231514 trials, including Study JMBR, was reduced to 500 mg/m2. The efficacy results of these trials are summarized in Table JMEI. 1.

Study JMAN, a multi-institutional study in NSCLC has been completed in Canada Rusthoven et al. 1999). All patients were chemonaive. The majority of patients on the Canadian study used the lower starting dose of 500 mg/m2, which was reduced from 600 mg/m2 during the course of the study after 1 of the first 3 patients experienced CTC Grade 3 mucositis and Grade 4 vomiting and myalgia. Seven partial responses have been observed in 30 evaluable patients for an overall response rate of 23.3% (95% CI 9.9% to 42.3%). All responding patients were treated at the 500 mg/m2 dose level.

Study JMAL, LY231514 in previously untreated NSCLC, carried out jointly between Australia and South Africa, enrolled 53 patients, with 42 evaluable for response at the time of the most recently published results. All patients received LY231514 600 mg/m2

every 3 weeks in this study. Seven partial responses have been noted for an overall response rate of 17% (Clarke et al. 1998).

Study JMBR, a second- line NSCLC trial, was conducted in several European countries and in Australia (unpublished data). Patients had to have had failure of prior chemotherapy, as defined by disease progression during, or within 3 months after, the prior chemotherapy. A total of 82 patients enrolled, with 80 evaluable for response. Of the evaluable patients, 42 had received platinum- containing prior regimens, and 38 had received prior regimens that did not contain platinum. All patients received a starting dose of LY231514 500 mg/m2. The overall response rate was 11.2%, with 1 CR and 8 PRs. Four of the responding patients had received prior platinum. Prior therapies of responding patients included cisplatin, carboplatin, gemcitabine, vinorelbine, mitomycin, paclitaxel, docetaxel, or etoposide. Overall median survival time is 5.8 months, with 21.3% of patients censored.

Table JMEI. 1. Phase 2 Experience

Study	JMACa	JMADb	JMANc	JMAOd	JMAGe	JMALf	JMBRg
Site	US	US	Canada	Canada	UK	Aus/ S Africa	Europe/ Aus
Tumor	colorectal	pancreas	NSCLC	colorectal	breast	NSCLC	NSCLC
Pts	1st line	1st line	1st line	1st line	Mixed	1st line	2nd line
No. Pts	41	35	30	29	36	42	80
Cycles							
Median	4	2	3	3	4	4	2
Range	1-12	1- 12	1- 8	1- 8	1- 9	1- 9	1- 7
CR	1	1	0	0	1	0	1
PR	5	1	7	5	10	7	8
Overall RR							
(%)	15.4	5.7	23	17	31	17	11.2
(95% CI, %)	(4.1- 26.7)	(0.7- 19.1)	(9.9- 42.3)	(8- 39.7)	(16- 46)	(7- 31)	NA

a John et al. 1998 b Miller et al. 1998 c Rusthoven et al. 1999 d Cripps et al. 1997 e Smith et al. 1997 f Clarke et al. 1998 g unpublished data Abbreviation: NA = not available

In the first 646 patients who have been treated on the once every 3 weeks schedule in the Phase 2 setting at 600 mg/m2 and who are evaluable for safety analysis, the most frequent, serious toxicity has been hematologic in nature. CTC Grade 3 and 4 hematologic toxicity included neutropenia (23% and 24%, respectively) and thrombocytopenia (7% and 5%, respectively). Although severe neutropenia is common, the frequency of serious infection has been low (CTC Grade 4 infection 2%). Likewise, thrombocytopenia has been apparent, and yet serious episodes of bleeding have been rare (< 1%). While 6% of patients experienced CTC Grade 3 (3% with Grade 4) skin rash, prophylactic

dexamethasone is reported to ameliorate or prevent the rash in subsequent cycles. Other Grade 3 and 4 nonhematologic toxicities included stomatitis, diarrhea, vomiting, and infection. As seen in clinical studies of other antifolates, transient Grade 3 and 4 elevations of liver transaminases are common but not dose limiting. There have been no cases of persistent transaminase elevation. Tables JMEI. 2 and JMEI. 3 summarize the laboratory and nonlaboratory toxicity data from the Phase 2 studies conducted at a starting dose of 600 mg/m2.

Toxicity at 600 mg/m2 has been compared to that at 500 mg/m2. For hematologic parameters there appears to be no difference between the incidence of Grade 3 and 4 toxicity or Grade 4 toxicity alone. For nonhematologic parameters there is also no difference except for rash, fatigue, and stomatitis, which appear to be less severe at 600 mg/ m2. Of note, patients who were administered LY231514 500 mg/m2 in previous trials received concomitant dexamethasone after the onset of toxicity, whereas patients at the 600 mg/m2 dose level were given dexamethasone prophylactically. The reduced toxicity profile at the 600 mg/m2 dose level is thus likely a result of prophylactic corticosteroid administration, and is not considered a dose response effect of LY231514 treatment.

Table JMEI. 2. Laboratory Toxicity (n= 646)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
ANC	11	18	23	24
Leukocytes	17	25	30	12
Platelets	25	6	7	5
Hb	32	41	12	2
ALT	38	20	13	< 1
AST	45	21	8	< 1
Bilirubin	0	14	7	2
Creatinine	12	3	< 1	0
Alk phos	43	11	5	0

Table JMEI. 3. Nonlaboratory Toxicity (n= 558)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Cutaneous	17	30	6	3
Diarrhea	14	8	3	2
Infection	7	7	2	2
Nausea	30	23	8	< 1
Fatigue	16	18	6	0
Pulmonary	2	4	2	1
Stomatitis	20	11	4	< 1
Vomiting	15	20	3	2

1.2.3. Folic Acid and Vitamin B12 Supplementation

It is well established that toxicity induced by antifolate antimetabolites can be reversed and/ or prevented by treatment with folic acid or its reduced forms (Grindey et al. 1991; Nelson et al. 1990; Laohavinij et al. 1996). An initial multivariate analysis was conducted in late 1997 to assess the relationship of metabolites of folic acid and vitamins B12 and B6, drug exposure, and other pre- specified baseline patient characteristics to toxicity following therapy with LY231514 (Niyikiza et al. 1998). Data were examined from 139 Phase 2 patients with tumors of the colon, breast, pancreas, and esophagus who had been treated with LY231514 at 600 mg/m2 intravenously over 10 minutes once every 21 days. These patients had homocysteine (Hcys), cystathionine, and methylmalonic acid levels measured at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity, and to predict which patients are at high risk of experiencing such toxicity. Prognostic factors then considered were age, gender, prior therapy, baseline albumin, liver enzymes, absolute neutrophil count (ANC), platelets, vitamin metabolites, and AUC. The findings from this investigation led to the following conclusions:

• Toxicity resulting from therapy with LY231514 appears to be higher in patients with elevated pre- therapy homocysteine levels.

• Elevated baseline homocysteine levels (>= 10 µM, for the 139 patients included in this initial analysis) highly correlate with severe hematological and nonhematological toxicity following therapy with LY231514.

• Homocysteine was found to be better than baseline albumin (another predictor of toxicity identified in the analysis) at predicting toxicity and was not altered with LY231514 therapy.

The same multivariate analysis was repeated on data from 305 patients who had their baseline homocysteine levels measured and recorded using a single laboratory. To eliminate the confounding factor of the effect of folic acid supplementation on toxicity, patients on Study JMAS who received folic acid supplementation (n= 38) were removed from the analysis, leaving a final sample size of 267 patients. Prognostic factors considered in this second wave of analysis were age, gender, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, pre- therapy weight, AUC, tumor type, and prior treatment.

Baseline homocysteine was identified as a highly statistically significant predictor of febrile neutropenia ($p < 0.0001$), Grade 4 neutropenia ($p = 0.0191$), Grade 4 thrombocytopenia ($p < 0.0001$), and Grade 3 or 4 diarrhea ($p < 0.0001$).

Homocysteine level has also been shown to be a sensitive indicator of folate and vitamin B12 status (Vu et al. 1991; Allen et al. 1993). Indeed, an interim report of a Phase 1 study

of LY231514 and folic acid suggests that folic acid supplementation permits dose escalation by ameliorating LY231514- associated toxicity (Hammond et al. 1998). Folic acid and vitamin B12 supplementation, resulting in a reduction of serum homocysteine, could serve to minimize the risk of severe toxicity during LY231514 therapy.

As of December 1999, all patients in LY231514 trials are being given folic acid and vitamin B12 supplementation as part of their treatment regimen. Early data have become available comparing the toxicity profiles of patients who received folic acid and vitamin B12 compared to the toxicity profiles of patients from earlier trials who did not receive supplementation. There have been no deaths from causes related to LY231514 toxicity in the approximately 250 patients who have received folic acid and vitamin B12 with LY231514. In contrast, of 1169 earlier patients who did not receive folic acid and vitamin B12, 3.9% died from causes at least possibly related to LY231514. Before vitamin supplementation was added to all LY231514 treatment regimens, 37% of patients experienced Grade 4 hematologic or Grade 3 or 4 nonhematologic toxicity. An analysis of 78 patients who have received vitamins along with LY231514 has shown that only 6.4% experienced such toxicity (Lilly 2000).

1.3. Docetaxel

Docetaxel is a member of the taxoid family, prepared by esterification of a naturally occurring precursor extracted from the renewable needle biomass of Taxus baccata (European yew) (Cortes and Pazdur 1995). Like paclitaxel, a natural product of T. brevifolia, docetaxel targets tubulin, promoting and stabilizing the microtubule assembly, thus preventing depolymerization and blocking mitosis (Ringel and Horwitz 1991). In vitro and in vivo assays have shown docetaxel to be twice as active as paclitaxel at stabilizing microtubules (Eisenhauer 1995).

Docetaxel has demonstrated activity in Phase 2 clinical trials against a variety of human solid tumors, with reproducible response rates greater than 20% in non- small cell lung, breast, ovarian, gastric, squamous head and neck, and bladder cancers (Eisenhauer 1995). Preclinical studies have found docetaxel to be schedule- independent; splitting the total dose did not alter the antitumor activity. Docetaxel has demonstrated synergy with other cytotoxic agents in preclinical studies (Bissery et al. 1993; Bissery et al. 1992; Chou et al. 1992; Kelland and Abel 1992).

The primary dose- limiting toxicity (DLT) in Phase 1 testing was non- cumulative neutropenia. Thrombocytopenia and anemia occurred less frequently. The major nonhematological toxicities were oral mucositis and fluid retention, with alopecia, mild cutaneous reactions, nausea, vomiting, diarrhea, mild paresthesia, and asthenia occurring less frequently (Pazdur et al. 1992; Bisset et al. 1993; Burris et al.1993; Extra et al.1993). Premedication with corticosteroids such as dexamethasone has been effective in reducing the incidence and severity of fluid retention and cutaneous toxicities (Schrijvers et al. 1993). Heavily pre- treated patients are not at increased risk of severe neutropenia (Pazdur et al. 1992); however, patients with elevated bilirubin, or patients with both

elevated transaminases (> 1.5x upper limit of normal [ULN]) and elevated alkaline phosphatase (> 2.5x ULN) are at increased risk of Grade 4 neutropenia, febrile neutropenia, infections, Grade 4 thrombocytopenia, Grade 4 stomatitis, Grade 4 cutaneous toxicities, and toxic death (Rhone- Poulenc Rorer 1997).

In December 1999, docetaxel was approved in US for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum- containing chemotherapy. It was approved in the European Union in January 2000 for treatment of locally advanced or metastatic NSCLC after failure of prior chemotherapy, not specifying prior platinum. Six Phase 2 single agent trials of docetaxel in previously treated patients resulted in response rates from 8% to 21%. Median survival times were 5.7 to 11.2 months, compared with approximately 4.5 months for best supportive care in this patient population. One- year survival rates ranged from 18% to 41%. Most of the patients in these studies (240 of 272) received docetaxel 100 mg/m2; however response rates of 14% and 20% were observed at the 60 mg/ m2 and 75 mg/m2 dose levels, respectively (FDA CDER 64th Meeting of the Oncologic Drugs Advisory Committee, 1999).

One pivotal Phase 3 trial compared second- line docetaxel (at 75 mg/ m2 and 100 mg/m2 doses) to best supportive care (Study TAX317). Response rate on the docetaxel arm was 7.1%; duration of response was 26.1 weeks. Time to progression was 10.6 weeks for docetaxel versus 6.7 weeks for best supportive care. Median survival was 7.0 months for patients on the docetaxel arm versus 4.6 months for patients receiving best supportive care. Patients receiving the 75 mg/ m2 docetaxel dose had a median survival time of 7.5 months. One year survival rates were 37% for docetaxel 75 mg/m2, 19% for docetaxel 100 mg/ m2, and 19% for best supportive care. The main toxicity was neutropenia, with Grade 3 or 4 neutropenia occurring in 67% of patients receiving the 75 mg/m2 dose, and in 86% of patients dosed at the 100 mg/m2 level (Shepherd et al. 2000).

The second pivotal Phase 3 trial compared docetaxel 100 mg/ m2 (D100) or docetaxel 75 mg/m2 (D75) to a control of either vinorelbine or ifosfamide in previously treated patients (Study TAX320). Response rates were 10.8% for D100, and 6.7% for D75, versus 0.8% for vinorelbine or ifosfamide. Time to progression was 8.4 weeks for both docetaxel arms, compared to 7.9 weeks for the control arm. Median survival was 5.5 months for D100, and 5.7 months for D75, versus 5.6 months for vinorelbine or ifosfamide. One-year survival rate was 21% for D100, and 32% for D75, versus 19% in the vinorelbine or ifosfamide control arm. Patients receiving docetaxel seemed to experience some clinical benefit (Fosella et al. 2000).

The current recommended docetaxel dose is 60 to 100 mg/ m2 intravenously every 21 days, preceded by premedication with oral corticosteroids, such as dexamethasone, to ameliorate hypersensitivity and fluid retention. The recommended dose for patients with NSCLC is 75 mg/ m2 as a 1-hour intravenous infusion every 21 days (TAXOTERE® Label, www. fda.gov/cder/approval/index. htm).

1.4. Rationale

LY231514 has shown clinical activity against NSCLC in three Phase 2 studies, in both first- and second- line settings. In the two first- line studies, there were 14 partial responses in 72 evaluable patients. There were 9 responses, 1 complete and 8 partial, in 80 evaluable patients in the second- line study, including responses in patients who had prior platinum- containing regimens. The median survival time for patients on LY231514 Study JMBR (5.8 months, with 21.3% of patients censored) is within the range seen in docetaxel studies. Docetaxel has been approved as second- line therapy for NSCLC as a single agent with studies showing response rates ranging from 6% to 21% and survival times of 6 to 11 months in patients with advanced disease. Since docetaxel is the first drug to be approved for second- line NSCLC, it will serve as the comparator to LY231514. LY231514 has shown efficacy comparable to docetaxel in early studies, and it is possible that the toxicity profile of LY231514 may be more favorable than docetaxel's, especially with respect to incidence of Grade 3 or 4 neutropenia.

2. Objectives

2.1. Primary Objective The primary objective of this study is to compare overall survival following treatment with LY231514 versus docetaxel in patients with locally advanced or metastatic (Stage IIIA, IIIB or IV) non- small cell lung cancer who have been previously treated with chemotherapy.

Secondary Objectives The secondary objectives of the study are as follows:
• To characterize and compare the quantitative and qualitative toxicities of LY231514 and docetaxel in this patient population.
• To compare the objective tumor response rate of both therapies.
• To compare time to event efficacy variables of both therapies including:
- duration of response
- time to objective tumor response
- time to treatment failure
- time to documented disease progression
- progression- free survival.

• To compare changes in the average symptom burden index between the LY231514 and docetaxel arms using the Lung Cancer Symptom Scale (LCSS). (See Section 3.9.1.3 for definitions of efficacy measures.)

3. Investigational Plan

3.1. Summary of Study Design This is a randomized, Phase 3, controlled, open- label, multicenter study of LY231514 compared to docetaxel in patients with locally advanced or metastatic (Stage IIIA, IIIB or IV) non- small cell lung cancer who have received prior chemotherapy. A total of at least 520 patients with measurable or evaluable disease will be randomized to receive either LY231514 or docetaxel. Further details on the randomization of patients can be found in Section 3.6.1.

LY231514 Treatment Arm

Patients in the LY231514 arm must receive folic acid supplementation, 350–1000 µg or equivalent (defined in Section 3.6.2.1.1), and at least one injection of 1000 µg vitamin B12. Folic acid should be taken orally daily beginning approximately 1 to 2 weeks prior to the first dose of LY231514 and continue daily until 3 weeks after the last dose of LY231514. A vitamin B12 injection must be given intramuscularly approximately 1 to 2 weeks prior to the first dose of LY231514 and should be repeated approximately every 9 weeks until 3 weeks after the last dose of LY231514. Sufficient folic acid and vitamin B12 treatment prior to LY231514 administration is defined in Section 3.6.3.3.5. Oral dexamethasone, 4 mg twice per day (or equivalent), should be given on the day before, the day of, and the day after LY231514 therapy, unless clinical contraindications exist. LY231514 will be given as a 500 mg/ m2 intravenous infusion on Day 1 of a 21- day cycle.

Docetaxel Treatment Arm

Patients on the docetaxel arm should be premedicated with oral dexamethasone, 16 mg per day (eg, 8 mg bid) for 3 days starting 1 day prior to docetaxel administration (or with equivalent regimen), unless clinical contraindications exist. Docetaxel will be given as a 75 mg/ m2 intravenous infusion on Day 1 of a 21- day cycle. Patients on the docetaxel treatment arm will not be receiving the site- administered folic acid or vitamin B12 as described above.

Both Treatment Arms

After the initial dose, modifications of LY231514 or docetaxel doses are allowed based on patient toxicity (see Sections 3.6.3.3. and 3.6.3.4.). Study therapy may continue until:

- There is evidence of progressive disease.
- The patient experiences unacceptable toxicity.
- The investigator decides that the patient should be discontinued.
- The patient requests discontinuation.
- Discontinuation from study therapy is indicated by the additional guidelines in Section 3.5, Discontinuation from Study Therapy.

After patients discontinue from study therapy, they proceed to the post- study follow up phase of the study. Assessments to take place during this phase are outlined in Section 3.9.3.4 and Protocol Attachment JMEI. 4, Schedule of Events.

3.2. Study Design and Control A two- arm randomized trial designed to compare LY231514 to the active control docetaxel is appropriate. Statistical aspects of the design are discussed in Section 4, while the randomization scheme is outlined in Section 3.6.1.

3.3. Investigator Information The names, titles, and institutions of the investigators are listed in the Contacts for Protocol H3E- MC- JMEI provided with this protocol.

If investigators are added after the study has been approved by Lilly, an ethical review board, or a regulatory agency, these additions will not be considered changes to the protocol, but the Contacts for Protocol H3E- MC- JMEI will be updated to provide this information.

3.3.1. Final Report Signature The Sponsor's responsible medical officer will sign the final clinical study report for this study, confirming that to the best of his/ her knowledge, the report accurately describes the conduct and results of the study.

3.4. Study Population

3.4.1. Entry Procedures An informed consent will be obtained from each patient after the nature of the study is explained.

Criteria for Enrollment

For Lilly studies, the following definitions are used:

Enter The act of obtaining informed consent for participation in a clinical study from patients deemed eligible to participate in the clinical study. Patients entered into a study are those who sign the informed consent document directly or through their legal representative.

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

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

3.4.2.1. Inclusion Criteria Patients may be included in the study only if they meet all of the following criteria:

[1] Histologic or cytologic diagnosis of NSCLC with locally advanced or metastatic disease (Stage IIIA, IIIB or IV at entry) that is not amenable to curative therapy. See Protocol Attachment JMEI. 1, American Joint Committee on Cancer Staging Criteria for NSCLC (Fleming et al. 1997).

[2] Patients must have been previously treated with at least one chemotherapy regimen as outlined below:

- neoadjuvant chemotherapy or

- neoadjuvant followed by adjuvant chemotherapy (only a single regimen is allowed) or
- adjuvant chemotherapy or

- chemotherapy for advanced disease.

Patients are also eligible if they have received one chemotherapy regimen as neoadjuvant, neoadjuvant followed by adjuvant, or adjuvant chemotherapy and a different chemotherapy regimen for advanced disease. Only a single regimen is allowed for prior therapy of advanced disease.

[3] Disease status must be that of measurable and/ or evaluable disease defined as:

Measurable disease. Bidimensionally measurable lesions with clearly defined margins by any of the following:

• Computerized tomography (CT) or magnetic resonance imaging (MRI), with both diameters greater than the distance between cuts of the imaging study.

• Plain x- ray, with at least one diameter 0.5 cm or greater (bone lesions not included).

• Palpation, with both diameters 2 cm or greater.

Evaluable disease.

• Unidimensionally measurable lesions.

• Lesions without clearly defined margins.

• Lesions on CT or MRI scan with either diameter smaller than the distance between cuts.

• Palpable lesions with either diameter less than 2 cm.

• Lesions with both diameters less than 0.5 cm.

• Bone disease documented by a method other than bone scan (bone disease documented by bone scan is considered nonevaluable).

Disease progressing in areas of prior radiation therapy may be included.

[4] Prior chemotherapy must be completed at least 2 weeks prior to study enrollment and the patient must have recovered from the acute toxic effects of the regimen.

[5] Prior radiation therapy allowed to < 25% of the bone marrow (Cristy and Eckerman 1987). Prior radiation to the whole pelvis is not allowed.

Prior radiotherapy must be completed at least 2 weeks before study enrollment. Patients must have recovered from the acute toxic effects of the treatment prior to study enrollment.

[6] Performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) Scale. See Protocol Attachment JMEI. 2.

[7] Estimated life expectancy of at least 8 weeks.

[8] Patient compliance and geographic proximity that allow adequate follow- up.

[9] Adequate organ function including the following:

Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC) $\geq$1.5 × 109/ L, platelets $\geq$100 × 109/ L, and hemoglobin $\geq$9 g/ dL.

Hepatic: bilirubin less than or equal to the upper limit of normal (ULN), aspartate transaminase (AST) and alanine transaminase (ALT) $\leq$1.5 x ULN, alkaline phosphatase $\leq$5 x ULN.

Renal: calculated creatinine clearance (CrCl) $\geq$45 mL/min using the lean body mass formula only (Modified Cockroft and Gault, see Protocol Attachment JMEI. 3; Shargel and Yu 1985). Creatinine clearance enrollment and dosing decisions may be made based on either local lab values (calculated using the modified Cockcroft and Gault formula (see Protocol Attachment JMEI. 3) or Covance values (Covance reports the calculated value directly). A patient may be enrolled using the local lab value only if the Covance lab value is not available. If a patient is enrolled using the local lab, the same local lab must be used throughout the study for dosing decisions. If a patient is enrolled using the Covance value, Covance creatinine clearance values must be used throughout the study for dosing decisions.

[10] Signed informed consent from patient.

[11] Males or females at least 18 years of age.

[12] Male and female patients with reproductive potential must use an approved contraceptive method if appropriate (eg, intrauterine device [IUD], birth control pills, or barrier device) during and for 3 months after the study. Females with childbearing potential must have a negative serum pregnancy test within 7 days prior to study enrollment.

3.4.2.2. Exclusion Criteria

Patients will be excluded from the study for any of the following reasons:

[13] Treatment within the last 30 days with any investigational drug.

[14] Active infection that in the opinion of the investigator would compromise the patient's ability to tolerate therapy.

[15] Pregnancy.

[16] Breast feeding.

[17] Serious concomitant systemic disorders that would compromise the safety of the patient or compromise the patient's ability to complete the study, at the discretion of the investigator.

[18] Second primary malignancy that is clinically detectable at the time of consideration for study enrollment.

[19] Inability to interrupt aspirin or other nonsteroidal anti- inflammatory agents for a 5-day period (8- day period for long- acting agents such as piroxicam).

[20] Brain metastasis. Patients who are symptomatic for brain metastasis must have a pretreatment CT or MRI of the brain. A patient with documented brain metastasis at the time of study entry will be excluded from entering in the study. Patients with prior brain metastasis may be considered if they have completed their treatment for brain metastasis, no longer require corticosteroids, and are asymptomatic.

[21] Presence of clinically detectable (by physical exam) third- space fluid collections, for example, ascites or pleural effusions that cannot be controlled by drainage or other procedures prior to study entry.

[22] Significant weight loss (ie, = 10%) over the previous 6 weeks before study entry.

[23] Prior treatment with either LY231514 or docetaxel.

[24] History of severe hypersensitivity to polysorbate 80.

[25] Inability or unwillingness to take folic acid or vitamin B12 supplementation.

[26] CTC Grade 3 or 4 peripheral neuropathy at study entry.

3.4.2.3. Violation of Criteria for Enrollment The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the study and Lilly or designee must be contacted.

3.4.3. Disease Diagnostic Criteria Patients must have a histologic or cytologic diagnosis of locally advanced or metastatic (Stage IIIA, IIIB or IV) NSCLC at study entry, as staged by the American Joint Committee on Cancer (Protocol Attachment JMEI. 1.).

3.5. Discontinuations from Study Therapy Patients will be discontinued from study therapy under the following circumstances.

• There is evidence of progressive disease.

• The patient experiences unacceptable toxicity.

• The investigator decides that the patient should be withdrawn. If this decision is because of a serious adverse event or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures taken. Lilly or designee is to be notified immediately. See Section 3.9.2, Safety.

• The patient requests discontinuation.

• The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from study therapy occurs immediately upon introduction of the new agent.

• The patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).

• The patient is noncompliant with study procedures.

• The investigator or Lilly, for any reason, stops the study or stops the patient's participation in the study.

Patients who discontinue study drug will have post- study follow- up procedures performed as described in Section 3.9.3.4 and in the Schedule of Events, Protocol Attachment JMEI. 4.

3.6. Dosage and Administration

3.6.1. Patient Assignment Patients will be randomized to receive either LY231514 or docetaxel in this parallel, openlabel trial. Randomization will be balanced between treatment arms according to the following factors:

• ECOG Performance Status (Low [2] or High [0 or 1])

• Prior platinum- containing chemotherapy (Yes or No)

• Prior paclitaxel- containing chemotherapy (Yes or No)

• Baseline homocysteine level (< 12 µ M or = 12 µ M)

• Number of prior chemotherapy regimens (1 or 2)

• Time since last chemotherapy (< 3 months or = 3 months)

• Best response to last prior chemotherapy (CR/ PR/ SD or PD or unknown)

• Disease stage (III[A/ B] or IV)

• Investigational center (by center)

Regarding the inclusion of baseline homocysteine level as one of the factors, a baseline homocysteine level of 12 µ M most clearly distinguished patients with an increased risk of severe hematologic and/ or nonhematologic toxicities following treatment with LY231514 (Lilly 2000). Although folic acid and vitamin B12 supplementation may decrease homocysteine levels from baseline measurements, this study will provide for balancing the numbers of patients with baseline homocysteine levels < 12 µ M or = 12 µ M equally across both treatment groups.

The algorithm of Pocock and Simon, using a probability factor of 0.75, will be applied to balance the treatment arms for these factors (Pocock and Simon 1975). Further details of the Pocock and Simon method are outlined in Protocol Attachment JMEI. 6.

3.6.2. Materials and Supplies

3.6.2.1. LY231514 LY231514 is supplied as a white or off- white lyophilized powder. The drug product is composed of LY231514 disodium and mannitol in a 1: 1 ratio. Sodium hydroxide and/ or hydrochloric acid solution may have been added during processing to adjust pH. Each vial contains LY231514 disodium equivalent to 102 mg or 510 mg of the base compound, LY231514. The vials contain a 2% excess to facilitate the withdrawal of the label amount, 100- or 500- mg/ vial.

Reconstitute the 100 mg vial with 2 mL to 10 mL sodium chloride solution or water for injection, to give a clear solution at a concentration of 10 mg/ mL to 50 mg/ mL. Reconstitute the 500 mg vial with 10 mL to 50 mL sodium chloride solution or water for injection, to give a clear solution at a concentration of 10 mg/ mL to 50 mg/ mL. The appropriate quantity of the contents of the vial(s) should be added to an intravenous bag or bottle containing approximately 100 mL sodium chloride before intravenous

administration. The reconstituted formulation has been shown to be chemically stable for 72 hours under refrigeration (2 ° C to 8 ° C). However, microbial challenge testing has shown LY231514 to be ineffective at inhibiting microbiological growth and the formulation does not contain a preservative. Therefore, although the reconstituted drug product remains chemically stable for up to 72 hours, LY231514 should be administered to the patient within 24 hours of this initial reconstitution. If LY231514 is reconstituted with water for injection and is stored for up to 24 hours before administration to the patient, it must be refrigerated during this time. If LY231514 is both reconstituted and diluted for injection in sodium chloride, any storage prior to administration to the patient may take place at room temperature or under refrigeration. The vials of LY231514 are single- use vials; any unused portion of a vial may not be stored for future use and must be discarded.

3.6.2.1.1. Folic Acid for Patients Randomized to LY231514 Arm The local Lilly affiliate will supply folic acid as one of the following options, with preference in order from option 1 to option 3:

1. 350 – 600 µg folic acid.

2. A multivitamin containing folic acid in the range of 350 µg to 600 µg is acceptable if option 1 is not available.

3. A dose of folic acid between 600 µg and 1000 µg is acceptable only if neither option 1 nor option 2 is available.

For purposes of this study, patients randomized to the LY231514 arm must take oral folic acid. Folic acid should be taken daily beginning approximately 1 to 2 weeks before the first dose of LY231514, continuing daily until 3 weeks after the last dose of LY231514. Sufficient folic acid treatment prior to LY231514 administration is defined in Section 3.6.3.3.5.

3.6.2.1.2. Vitamin B12 for Patients Randomized to the LY231514 Arm Vitamin B12 will be prescribed by the investigator and administered as a 1000 µ g intramuscular injection. A vitamin B12 injection must be administered to patients randomized to the LY231514 arm approximately 1 to 2 weeks before the first dose of LY231514 and should be repeated approximately every 9 weeks until 3 weeks after the last dose of LY231514. Sufficient vitamin B12 treatment prior to LY231514 administration is defined in Section 3.6.3.3.5.

3.6.2.1.3. Dexamethasone Oral dexamethasone or equivalent will be obtained by the investigator in whatever formulation is available locally. Patients on the LY231514 arm should be premedicated according to the outline in Section 3.6.3.1.

3.6.2.2. Docetaxel Docetaxel for Injection Concentrate is available commercially in 80 mg or 20 mg singledose vials as a sterile, pyrogen- free, non- aqueous, viscous solution with

an accompanying sterile, non- pyrogenic diluent (13% ethanol in Water for Injection vial).

Docetaxel 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 mL polysorbate 80 (fill 94.4 mg docetaxel in 2.36 mL polysorbate 80) and diluent for docetaxel 80 mg. 13% (w/ w) ethanol in Water for Injection (fill 7.33 mL).

Docetaxel 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 mL polysorbate 80 (fill 23.6 mg docetaxel in 0.59 mL polysorbate 80) and diluent for docetaxel 20 mg. 13% (w/ w) ethanol in Water for Injection (fill 1.83 mL).

Store unopened vials of docetaxel as directed on label. Retain original package to protect from bright light. Once prepared according to the label directions, solutions of docetaxel should be used as soon as possible. The premix solution (first dilution; docetaxel 10mg/ ml) is stable for 8 hours either at room temperature, 15 ° to 25 ° C (59 ° to 77 ° F), or refrigerated, 2 ° to 8 ° C (36 ° to 46 ° F).

3.6.2.2.1. Dexamethasone Oral dexamethasone or equivalent will be obtained by the investigator in whatever formulation is available locally. Patients on the docetaxel arm should be premedicated according to the outline in Section 3.6.3.2.

3.6.3. Dosage Administration Procedures

A cycle is defined as an interval of 21 days (a delay of cycle due to holidays, weekends and bad weather or other unforeseen circumstances will be permitted and not counted as a protocol violation). A cycle is comprised of one treatment of LY231514 or docetaxel on Day 1. The actual dose to be administered will be determined by calculating the body surface area at the beginning of each cycle. A ± 5% variance in the calculated total dose will be allowed for ease of dose administration.

3.6.3.1. Patients Randomized to the LY231514 Arm

Drug	**Dosage**	**Time**
LY231514	500 mg/M2 iv infusion	Approximately 10 min (8-15 min) on Day 1 of a 21 -day cycle
Folic acid		Oral dose daily beginning approximately 1 to 2 wks prior to the first dose of LY231514 and continuing daily until 3 wks after the last dose of LY231514
Vitamin B12	1000 µg im injection	Approximately 1 to 2 wks prior to the first dose of LY231514 and approximately every 9 weeks until 3 wks after the last dose of LY231514

Dexamethasone (or equivalent)	4 mg, orally twice per day. To be taken on the day before, the day of, and the day after each dose of LY231514, unless clinical contraindications exist. Higher or additional doses are permitted for reasons other than routine rash prophylaxis (eg, antiemetic prophylaxis). In special circumstances, investigators may administer this premedication iv in lieu of oral administration

3.6.3.2. Patients Randomized to the Docetaxel Arm

Drug	**Dose**	**Time**
Docetaxel	75 mg/ M2 iv infusion	Approximately 1 hour on Day 1 of a 21-day cycle
Dexamethasone	8 mg po bid) or equivalent	For 3 days starting 1 day prior to each dose of docetaxel regimen unless clinical contraindications exist, to reduce the severity of fluid retention and hypersensitivity reactions

3.6.3.3. Dose Adjustments or Delays for Subsequent Cycles – LY231514 Patients Only
Any patient on the LY231514 arm who requires a dose reduction will continue to receive a reduced dose for the remainder of the study. Any patient with 2 prior dose reductions who experiences a toxicity that would cause a third dose reduction must be discontinued from study therapy. Treatment may be delayed for up to 42 days from Day 1 of the current cycle to allow a patient sufficient time to recover from study drug- related toxicity. A patient who cannot be administered study drug for 42 days from the time of last treatment must be discontinued from study therapy unless continuation is approved by Lilly.

3.6.3.3.1. Hematologic Toxicity – LY231514 Patients Dose adjustments at the start of a subsequent course of therapy will be based on platelet and neutrophil nadir (lowest value) counts from the preceding cycle of therapy. ANC must be $\geq$1.5 × 109/L and platelets $\geq$100 × 109/L prior to the start of any cycle. Treatment should be delayed to allow time for recovery. Upon recovery, if treatment is resumed, it must be according to the guidelines in Table JMEI. 4.

Table JMEI. 4. Dose Adjustments for LY231514 Based on Nadir Hematologic Values for Preceding Cycle

Platelets (× 109/ L) Nadir		ANC (× 109/ L) Nadir	Percent of Previous Dose
≥50	and	≥0.5	100%
≥50	and	< 0.5	75%
< 50	and	Any	50%

3.6.3.3.2. Clinically Significant Effusions – LY231514 Patients For patients who develop clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) during therapy, consideration should be given to draining the effusion prior to dosing. However, if, in the investigator's opinion, the effusion represents progression of disease, patient should be discontinued from study therapy.

3.6.3.3.3. Diarrhea, Mucositis, and Other Nonhematologic Toxicities – LY231514 Patients

In the event of diarrhea requiring hospitalization (or of at least Grade 3), treatment should be delayed until diarrhea has resolved before proceeding. Treatment should be resumed at 75% of the previous dose level. For other non-hematologic effects greater than or equal to Grade 3 (with the exception of Grade 3 transaminase elevations, nausea, or vomiting), treatment should be delayed until resolution to less than or equal to the patient's original baseline grade before proceeding. Treatment should resume at 75% of the previous dose level if deemed appropriate by the treating physician.

Table JMEI. 5 documents the relevant dose adjustments in case of mucositis.

Table JMEI. 5. Dose Modifications for LY231514 for Mucositis

CTC Toxicity Grade	Percent of Previous Dose
Grade 0- 2	100%
Grade 3- 4	50%
Recurrence of Grade 3 or 4 after treatment at 2 dose reductions	Discontinue patient from study therapy

3.6.3.3.4. Creatinine Clearance – LY231514 Patients If a patient who is being followed by local CrCl develops a CrCl < 45 mL/ min, it is strongly recommended, if possible, that a Covance CrCl be obtained. If the Covance value is = 45 mL/min (as reported by Covance) the next cycle can continue without delay and the patient must be followed with Covance CrCl for the remainder of the study. If it is not possible to obtain Covance CrCl then the next cycle will not begin until the local CrCl is = 45 mL/min. Re-testing is recommended at weekly intervals but will be conducted at the investigator's discretion. If a patient's CrCl

has not returned to >= 45 mL/ min within 42 days of the last dose of LY231514, the patient must be discontinued from study therapy unless continuation is approved by Lilly.

If a patient who is being followed by Covance results develops a CrCl < 45 mL/ min, then the next cycle will not begin until the Covance CrCl is >= 45 mL/ min. Re-testing is recommended at weekly intervals but will be conducted at the investigator's discretion. If a patient's CrCl has not returned to >= 45 mL/ min within 42 days of the last dose of LY231514, the patient must be discontinued from study therapy unless continuation is approved by Lilly.

Safety analysis will be based on the Covance serum creatinine and calculated clearance

3.6.3.3.5. Treatment Delays Due to Insufficient Folic Acid or Vitamin B12 Supplementation – LY231514 Patients Delay the first dose of LY231514 until the patient has taken folic acid for at least 5 of the 7 days immediately preceding the first dose of LY231514, and until the vitamin B12 injection has been administered.

Delay subsequent doses of LY231514 until the patient has taken folic acid for at least 14 of the 21 days before Day 1 of the cycle.

3.6.3.4. Dose Adjustments or Delays for Subsequent Cycles – Docetaxel Patients Only Any patient on the docetaxel arm who requires a dose reduction will continue to receive a reduced dose for the remainder of the study. Any patient with 2 prior dose reductions who experiences a toxicity that would cause a third dose reduction must be discontinued from study therapy. Treatment may be delayed for up to 42 days from Day 1 of the current cycle to allow a patient sufficient time to recover from study drug- related toxicity. A patient who cannot be administered study drug for 42 days from the time of last treatment must be discontinued from study therapy unless continuation is approved by Lilly.

3.6.3.4.1. Hematologic Toxicity – Docetaxel Patients Dose adjustments at the start of a subsequent course of therapy will be based on platelet and neutrophil nadir (lowest value) counts from the preceding cycle of therapy. ANC must be = 1.5 × 109/ L and platelets = 100 × 109/ L prior to the start of any cycle. Treatment should be delayed to allow time for recovery. Upon recovery, if treatment is resumed, it must be according to the guidelines in Table JMEI. 6.

Table JMEI. 6. Dose Adjustments for Docetaxel Based on Nadir Hematologic Values for Preceding Cycle

Platelets (× 109/ L) Nadir		**ANC (× 109/ L) Nadir**	**Percent of Previous Dose**
≥25	and	≥0.5	100%
≥ 25	and	< 0.5 for < 7 days AND no fever	100%
≥25	and	< 0.5 for > 7 days OR fever	75%
< 25	and	≥0.5	75%

< 25	and	< 0.5 for < 7 days AND no fever	75%
< 25	and	< 0.5 for > 7 days OR fever	50%

3.6.3.4.2. Nonhematologic Toxicity – Docetaxel Patients
For most Grade 3 or 4 nonhematologic toxicities, including severe or cumulative cutaneous reactions, but excluding Grade 3 nausea or vomiting, treatment should be delayed until resolution of toxicity to the patient's original baseline grade. Treatment should resume at 75% of the previous dose level if deemed appropriate by the treating physician. (Do not forget to report any inpatient hospitalization as a serious adverse event.) If after two dose reductions, the patient still experiences Grade 3 or 4 nonhematologic toxicity (excluding Grade 3 nausea and vomiting), discontinue the patient from study therapy. Discontinue the patient if Grade 4 vomiting occurs despite antiemetics and 2 dose reductions.

Exceptions to this dose adjustment scheme for nonhematologic toxicities are discussed in Sections 3.6.3.4.3 (Clinically Significant Effusions), 3.6.3.4.4 (Fluid Retention), 3.6.3.4.5 (Peripheral Neuropathy), and 3.6.3.4.6 (Hypersensitivity Reactions).

3.6.3.4.3. Clinically Significant Effusions – Docetaxel Patients For patients who develop clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) during therapy, consideration should be given to draining the effusion prior to dosing. However, if, in the investigator's opinion, the effusion represents progression of disease, patient should be discontinued from study therapy.

3.6.3.4.4. Fluid Retention – Docetaxel Patients Patients may be treated for symptomatic edema (Grade 2 or higher) with diuretics at the investigator's discretion. Spironolactone at a starting dose of 25 mg three times daily plus furosemide 20 – 40 mg as needed is recommended. For docetaxel patients experiencing pleural or peritoneal effusions, please see the guidelines given in Section 3.6.3.4.3.

As outlined in Section 3.6.3.4.2, if fluid retention is Grade 3 or 4, treatment should be delayed until resolution of toxicity to the patient's original baseline grade. Treatment should resume at 75% of the previous dose level if deemed appropriate by the treating physician.

3.6.3.4.5. Grade 3 or 4 Peripheral Neuropathy – Docetaxel Patients Patients who experience Grade 3 or 4 peripheral neuropathy must stop receiving docetaxel. Patients will then enter post- study follow up as described in Section 3.9.3.4 and the Schedule of Events, Protocol Attachment JMEI. 4.

3.6.3.4.6. Hypersensitivity Reactions – Docetaxel Patients If, despite the dexamethasone treatment regimen, patients experience hypersensitivity reactions, treatment should be as indicated in Table JMEI. 7.

Table JMEI. 7. Management of Hypersensitivity Reactions for Patients Receiving Docetaxel

Mild Symptoms: Localized cutaneous reaction such as mild pruritus, flushing, rash	Consider decreasing the rate of infusion until recovery of symptoms; stay at bedside. Then, complete docetaxel infusion at the initial planned rate.
Moderate Symptoms: Any symptom not listed as mild or severe such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure > 80 mm Hg.	Stop docetaxel infusion, give IV dexamethasone 10 mg and/ or IV diphenhydramine 50 mg; resume docetaxel infusion after recovery of symptoms.
Severe symptoms such as bronchospasm, generalized urticaria, systolic blood pressure = 80 mm Hg, angioedema.	Stop docetaxel infusion, give IV diphenhydramine 50 mg and/ or epinephrine as needed. Whenever possible, resume docetaxel infusion within 3 hours after recovery, or reinfuse the patient within 72 hours, pretreating ½ hour prior to infusion with dexamethasone 10mg IV and/ or diphenhydramine 50 mg IV. If severe reaction recurs despite additional premedication, discontinue the patient from study drug therapy.
Anaphylaxis (Grade 4 reaction)	NO FURTHER STUDY DRUG THERAPY

3.6.4. Compliance

LY231514 or docetaxel will be intravenously administered only at the investigational sites. Vitamin B12 supplementation for patients receiving LY231514 will be administered as an intramuscular injection at the investigational sites. As a result, patient compliance monitoring is ensured. Patients who return for subsequent on- drug study visits will receive study drug unless they are encountering toxicity problems or their disease has progressed.

3.6.4.1. Folic Acid Supplementation Compliance: Patients in LY231514 Arm Only In the period before the first dose of LY231514, compliance with folic acid supplementation requirements will be monitored through the use of a medical interview documented in the patient chart.

While on study therapy, compliance with folic acid supplementation requirements will be monitored through medical interviews.

Sufficient folic acid and vitamin B12 treatment prior to LY231514 administration is defined in Section 3.6.3.3.5.

3.7. Concomitant Therapy

Patients are allowed to receive full supportive care therapies concomitantly during the study. No other chemotherapy, immunotherapy, hormonal cancer therapy, surgery for cancer, or experimental medications (with the exception of thymidine) will be permitted while the patients are receiving study therapy. Palliative radiation therapy is permitted for irradiating small areas of painful metastasis that cannot be managed adequately using systemic or local analgesics. Any disease progression requiring other forms of specific antitumor therapy will be cause for early discontinuation of study therapy. The following concomitant therapies warrant special attention:

3.7.1. Colony Stimulating Factors

Routine use of colony stimulating factor (CSF) is not permitted during this study. Patients should not receive prophylactic granulocyte colony stimulating factor (G- CSFs) in any cycle. G- CSFs should be considered only for patients who have ANC < 0.5 × 109/ L, neutropenic fever, or documented infections while neutropenic. Duration of uncomplicated neutropenia before initiation of G- CSF treatment is left to the investigator's discretion. G- CSF must be discontinued at least 24 hours prior to the start of the next cycle of chemotherapy. If a patient develops hematologic toxicities, chemotherapy dose reduction and acute treatment of neutropenia are recommended, rather than chemotherapy dose maintenance and pre- emptive treatment with G- CSFs. Use of erythropoietin is allowed. Use of stimulators of thrombopoiesis is not allowed.

3.7.2. Nonsteroidal Anti- inflammatory Drugs (NSAIDs), LY231514 Arm Only Patients taking NSAIDs or salicylates will not take the NSAID or salicylate 2 days before, the day of, and 2 days after receiving LY231514. If a patient is taking an NSAID or salicylate with a long half- life (eg, naproxen, piroxicam, diflunisal, or nabumetone), it should not be taken 5 days before, the day of, and 2 days after receiving LY231514.

3.7.3. Leucovorin and Thymidine, LY231514 Arm Only

Leucovorin is allowed for CTC Grade 4 leukopenia, CTC Grade 4 neutropenia lasting greater than 3 days, or immediately for CTC Grade 4 thrombocytopenia, or bleeding associated with Grade 3 thrombocytopenia. If leucovorin is to be used it should be started for CTC Grade 4 myelosuppression lasting 3 days or more beginning on the third day of CTC Grade 4 myelosuppression. If leucovorin is to be used it should be started immediately if a patient develops CTC Grade 3 or 4 mucositis. The following doses and schedules are recommended for intravenous use; appropriate doses of the oral formulation may also be used at the investigator's discretion:

• Leucovorin 100 mg/ m2 intravenously once; then

• Leucovorin 50 mg/ m2 intravenously every 6 hours for 8 days.

Note: Several sources cite the use of thymidine as a rescue agent for severe toxicity from other TS inhibitors (Abelson et al. 1983, Grem et al. 1991, Takimoto et al. 1996, Widemann et al. 1997). One patient treated with LY231514 received thymidine as a rescue agent, and was successfully treated for LY231514- related toxicity after failure of leucovorin rescue (Takimoto et al. 1996). If the investigator believes thymidine rescue is indicated in a given patient, the investigator may contact the Cancer Therapy Evaluation Program at National Cancer Institute, US for information on obtaining thymidine.

3.7.4. Therapy for Diarrhea In the event of CTC Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) associated with fever or severe neutropenia (Grade 3 or 4), broad- spectrum antibiotics must be prescribed. Patients with severe diarrhea (requiring intravenous rehydration) associated with severe nausea or vomiting should be managed according to local standard procedures for intravenous hydration and correction of electrolyte imbalances. (Do not forget to report any in- patient hospitalization as a serious adverse event.)

3.7.5. Therapy for Febrile Neutropenia Patients experiencing febrile neutropenia, especially with diarrhea, should be managed according to local standard procedures, with the urgent initiation of intravenous antibiotic therapy.

3.7.6. Antiemetic Therapy With the use of dexamethasone, LY231514 is considered to have only mild to moderate emetic potential. Antiemetic therapy for patients on the LY231514 arm should be administered according to standard local practice for patients receiving mildly to moderately emetic chemotherapy regimens.

Antiemetic therapy for patients on the docetaxel arm should be administered according to standard local practice for patients receiving docetaxel.

3.8. Blinding This is a randomized, open- label study with the identity of the treatment known to the investigator, patient, and Lilly.

3.9. Efficacy and Safety Evaluations See the Schedule of Events (Protocol Attachment JMEI. 4) and Sections 3.9.1.1 and 3.9.3 for timing of evaluations.

3.9.1. Efficacy

3.9.1.1. Efficacy Measures Patients may be entered on study with measurable or evaluable disease (as defined in Section 3.9.1.2) or a combination of both. Disease assessment will be undertaken at baseline and then prior to every other cycle. See further details for timing of assessments in Sections 3.9.1.1.1 and 3.9.1.1.2.

3.9.1.1.1. Baseline Assessments Radiological Assessment: Within 4 weeks prior to enrollment, baseline radiological imaging studies for tumor assessment will be performed on each patient. These studies should entail a CT or MRI scan (where available), and a plain x- ray. Ultrasound will not be permitted as a method of tumor assessment. The same radiological imaging method used at baseline must be used consistently for subsequent tumor assessments. If baseline radiological studies show that disease is assessable by both plain x- ray and CT or MRI scan, subsequent tumor assessments should be monitored by CT or MRI scan.

Clinical Assessment: Within 2 weeks prior to enrollment, physical examination will be performed for measurement of palpable tumor lesions.

3.9.1.1.2. Timing of Subsequent Tumor Assessments
Radiological Assessment: CT or MRI scan or plain x- ray will be routinely repeated prior to drug administration at every other cycle. This should occur approximately every 6 weeks, but the interval from baseline to the first post- baseline imaging will likely be longer, and other intervals may be longer in the event of cycle delays. If the patient's disease has responded to therapy (by CT or MRI scan or plain x- ray), the investigator must confirm the response. Confirmation should occur 3 to 4 weeks (minimum 21 days) from the first evidence of response, using the same radiolological method as at baseline.

Thereafter, a responding patient will have CT or MRI scans or plain x-ray (same method as baseline) prior to drug administration at every other cycle.

Clinical Assessment: Tumor palpation will be repeated prior to drug administration at every other cycle. This should occur approximately every 6 weeks, but the interval from baseline to the first post-baseline imaging will likely be longer, and other intervals may be longer in the event of cycle delays. If the patient's disease has responded to therapy (by palpation), the investigator must confirm the response. Confirmation should be performed 3 to 4 weeks (minimum 21 days) from the first evidence of response.

3.9.1.1.3. Timing of LCSS Measurements

The LCSS patient and observer scales will be administered to assess symptom burden index and health-related quality of life (Protocol Attachment JMEI.5). The patient scale will be administered once at baseline before randomization, and weekly after the first dose of therapy. The observer scale will be administered once at baseline before randomization, and before each cycle thereafter except Cycle 1. Both scales will be administered during post- study follow- up unless the patient is receiving post- study chemotherapy, surgery, or other treatments.

Details of frequency and timing of these tests are outlined in Section 3.9.3 and Protocol Attachment JMEI. 4., Schedule of Events.

3.9.1.2. Efficacy Criteria for Tumor Response

The response status of all patients may be reviewed by a centralized panel of independent investigators and may be reviewed by Lilly. If there is an independent review, and if there is a discrepancy between the assessment of the independent panel and that of the investigator, the independent panel's assessment will take precedence.

The measurability of a tumor is defined as follows. All definitions except those regarding bone disease are from Green and Weiss (1992).

Disease Status

• Measurable disease: Bidimensionally measurable lesions with clearly defined margins by:

1) CT or MRI, with both diameters greater than the distance between cuts of the imaging study, or

2) plain x- ray, with at least one diameter 0.5 cm or greater (bone lesions not included), or

3) palpation, with both diameters 2 cm or greater.

• Evaluable disease: Unidimensionally measurable lesions, lesions with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease documented by a method other than bone scan.

• Nonevaluable disease: Pleural effusions, ascites, disease documented by indirect evidence only (eg, by lab values), or lesions documented by bone scan only.

All documented lesions are to be followed. If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be documented and considered evaluable for the purpose of objective status determination. Included in the evaluations are the following standard criteria:

Objective status (to be recorded at each evaluation)

• Complete response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No disease- related symptoms. No evidence of nonevaluable disease, including normalization of markers and other abnormal lab values. All measurable, evaluable, and nonevaluable lesions and sites must be assessed using the same technique as baseline. Refers to clinical CR. When restaging surgery is required, a separate pathologic response variable is incorporated in the response data.

• Partial response (PR): Applies only to patients with at least one measurable lesion. Greater than or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease.

No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.

• Partial response in nonmeasurable disease (PRNM): A greater than 50% decrease in the estimated area of evaluable but nonmeasurable tumor mass, not to include pleural effusions, as agreed upon by two independent reviewers. Note: Responses in patients with these specific types of evaluable disease and no measurable disease will be reported separately. Patients with both measurable and evaluable disease will be assessed for response according to the standard criteria of CR and PR.

• Stable/ No response: Does not qualify for CR, PR, PRNM, or progression. All measurable and evaluable sites must be assessed using the same techniques as baseline.

• Progression: 50% increase or an increase of 10 cm2 (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR reappearance of any lesion which had disappeared, OR appearance of any new lesion/ site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). For ‘ scan- only’ bone disease, increased uptake does not constitute clear worsening. Worsening of existing nonevaluable disease does not constitute progression.

Exceptions: 1) In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond 4 weeks or there must be additional evidence of progression. 2) Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

• Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

Notes

1) Nonevaluable disease does not affect objective status except in determination of CR (all disease must be absent -- a patient who otherwise has a CR, but who has nonevaluable disease present or not assessed, will be classified as having a PR) and in determination of progression (if NEW sites of nonevaluable disease develop). Patients with only nonevaluable disease cannot be assessed for response.

2) For evaluable disease other than types specified in PRNM, the only objective statuses that apply are CR, stable/ no response, progression, and unknown.

3) Objective statuses must stay the same or improve over time until progression (unknown excepted).

4) PR and PRNM cannot apply to the same patient.

Best Response

Best response is determined from the sequence of objective statuses.

• Disease assessment every 3 to 6 weeks: Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of PRNM or better before progression, but not qualifying for CR are required for PRNM. Two determinations of stable/ no response or better before progression, but not qualifying as CR or PR or PRNM, are required for a best response of stable/ no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) will have a best response of increasing disease. Best response is unknown if the patient does not qualify for a best response of increasing disease and if all objective statuses after the first determination and before progression are unknown. For CR or PR, response must be confirmed; a second assessment should be performed 3 to 4 weeks (minimum 21 days) after the first documentation of response, using the same method of measurement used at baseline.

3.9.1.3. Definition of Efficacy Measures A tumor responder is defined as any patient exhibiting a best study response of CR or PR (based on CT, MRI, or plain x- ray, and/ or palpation).

Among tumor responders, the time to objective tumor response is measured from the date of randomization to the date of first objective status assessment of CR or PR.

Among tumor responders, the duration of tumor response is measured from the date of first objective status assessment of CR or PR until the first date of documented disease progression or death due to any cause. Duration of tumor response will be censored at the date of the last follow- up visit for tumor responders who are still alive and who have not progressed.

Progression- free survival time is defined as the time from the date of randomization to the first date of documented disease progression or death due to any cause. Progressionfree survival time will be censored at the date of the last follow- up visit for patients who are still alive and who have not progressed.

Time to treatment failure is defined as the time from the date of randomization to the date of the first of the following events: early discontinuation of study therapy, progression of disease, or death due to any cause. Time to treatment failure will be censored at the date of the last follow- up visit for patients who did not discontinue early, who are still alive, and who have not progressed.

Time to documented disease progression is defined as the time from the date of randomization to the first date of documented disease progression. Time to documented disease progression will be censored at the date of death for patients who have not had documented disease progression. For patients who are still alive at the time of analysis and who have not had documented disease progression, time to documented disease progression will be censored at the date of the last follow- up visit.

Overall survival time is defined as the time from the date of randomization to date of death due to any cause. Overall survival time will be censored at the date of the last follow- up visit for patients who are still alive.

For each LCSS assessment for each patient, the average symptom burden index will be defined as the mean over all 6 of the symptom- specific questions. For a given assessment, if any of the 6 symptom- specific questions have not been completed, the average symptom burden index will not be calculated. For patients with average symptom burden index assessments from baseline and at least 4 post- baseline assessments, the following definitions will apply:

• A patient will be considered as having improved average symptom burden index if the mean of the average symptom burden index assessments from any four consecutive improved post- baseline assessments is at least 0.5 standard deviation below the baseline average symptom burden index.

• A patient will be considered as having worse average symptom burden index if the mean of the average symptom burden index assessments from any four consecutive worse post-baseline assessments is at least 0.5 standard deviation above the baseline average symptom burden index.

The standard deviation will be estimated from the baseline average symptom burden index assessments. Included in this calculation will be baseline assessments from all randomized patients who have completed all 6 symptom- specific questions at baseline.

3.9.2. Safety

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for appropriate medical care of patients during the study.

The investigator remains responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event resolves or is explained. Frequency of follow- up is left to the discretion of the investigator.

3.9.2.1. Safety Measures Safety measures that will be used in the study include physical examinations, and clinical laboratory tests (hematology, blood chemistries, and CrCl). Patients will be rated for toxicity prior to each cycle using the NCI CTC scale (see the CTC Investigator Guide, Version 2.0, supplied with the clinical report form; Cancer Therapy Evaluation Program 1998).

Resource utilization will be recorded for all patients. This will include notation of protocol- allowed palliative radiation therapy, epidural analgesics, parenteral nutrition, bronchoscopic interventions, and reasons for and durations of hospitalizations.

In addition, electrocardiograms (ECGs) will be performed on approximately 140 patients (approximately 70 males and 70 females) randomized to receive LY231514 at selected study sites to determine whether study drug administration has an effect on the ECG, particularly the ECG QT interval corrected for heart rate (QTc). These ECGs to be performed on 70 male and 70 female patients are in response to regulatory requirements for the purpose of registration. Preclinical studies as well as clinical experience so far have not shown any cardiac effect of LY231514. The ECGs will be reviewed by a centralized, independent panel of cardiologists. See Protocol Attachment JMEI. 7 for schedule of ECG testing of these selected patients.

3.9.2.2. Clinical Adverse Events Lilly has standards for reporting adverse events that are to be followed, regardless of applicable regulatory requirements that may be less stringent. For purposes of collecting and evaluating all information about Lilly drugs used in clinical trials, a clinical trial adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship. Cases of pregnancy should be reported for tracking purposes. Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

Adverse events will be collected after the patient has been enrolled. If a patient experiences an adverse event after the informed consent document is signed (entry) but prior to assignment to treatment (enrollment), the event will NOT be reported unless the investigator feels that the event may have been caused by a protocol procedure.

Prior to enrollment, study site personnel will note the occurrence and nature of each patient’s medical condition(s). During the study, site personnel will again note any change in the condition(s) and/ or the occurrence and nature of any adverse events.

Patients should be closely followed for adverse events while receiving study drug and for 30 days after last dose of study drug in order to detect delayed toxicity. After this period, investigators should only report serious adverse events that are felt to be causally related to study drug therapy or to a protocol procedure.

3.9.2.2.1. Adverse Event Reporting Requirements All adverse events must be reported to Lilly or designee by clinical report form.

In addition, study site personnel must report to Lilly or designee immediately, by telephone, any serious adverse event. See Protocol Attachment JMEI. 8 for information required when reporting serious adverse events.

If a patient's dosage is reduced or treatment is discontinued as a result of an adverse event, study site personnel must clearly document the circumstances and data leading to any such dosage reduction or discontinuation of treatment, using a clinical report form.

3.9.2.2.2. Serious Adverse Events Study site personnel must report immediately by telephone to Lilly or designee any adverse event from this study that results in one of the following outcomes, or is significant for any other reason:

• death

• initial or prolonged inpatient hospitalization

• a life- threatening experience (that is, immediate risk of dying)

• severe or permanent disability

• cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer)

• congenital anomaly

Serious adverse events occurring more than 30 days after a patient is discontinued from study therapy will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure.

3.9.3. Clinical Laboratory Tests and Procedures

3.9.3.1. Prestudy Prior to study enrollment each patient will have the following assessments (see Protocol Attachment JMEI. 4).

No more than 4 weeks before study enrollment:

• Radiologic imaging studies (CT or MRI scan [where available], and plain x- ray) for baseline tumor assessments (See Section 3.9.1.1.1 for details).
• Response to prior chemotherapy.

No more than 2 weeks before study enrollment:

• Medical history and physical examination, including measurements of height, weight, blood pressure, and pulse rate
• Evaluation of performance status (ECOG Scale, Protocol Attachment JMEI. 2)
• Concomitant medication notation

• Tumor measurement of palpable lesions

Approximately 1 to 2 weeks prior to study enrollment:
• Homocysteine (Covance).
• Vitamin metabolite panel: homocysteine, cystathionine, methylmalonic acid, methylcitrate (total, I and II).

Within 7 days of study enrollment:
• Hematology: hemoglobin, leukocytes (WBC), platelets, neutrophils (sum of segmented and bands), lymphocytes, and monocytes
• Blood chemistries: bilirubin, AP, ALT, AST, blood urea nitrogen (BUN), creatinine, calcium, and electrolytes (sodium, potassium)
• Calculated creatinine clearance (see Protocol Attachment JMEI. 3)
• A serum pregnancy test for females with childbearing potential.
• LCSS patient scale baseline evaluation (Protocol Attachment JMEI. 5).
• LCSS observer scale baseline evaluation (Protocol Attachment JMEI. 5).

3.9.3.2. During the Study

3.9.3.2.1. Efficacy Assessments: Weekly:

• The LCSS patient scale should be administered on Day 8 ± 1, Day 15 ± 1, and one day prior to, or the day of, the next cycle of either docetaxel or LY231514 treatment, before the infusion begins. In the case of cycle delays lasting more than 5 days, additional LCSS patient scale assessments should continue to be done weekly.

Prior to each cycle of treatment:

• Weight measurements, and body surface area calculation

• Performance status evaluation

• Limited medical history and physical examination

• The LCSS observer scale is to be completed before the next cycle of chemotherapy is administered.

Prior to every other cycle of treatment:

• CT or MRI scan for patients whose disease is being monitored by CT or MRI scan.

• Plain x- ray for patients whose disease is being monitored by plain x- ray.

• Tumor measurement of palpable lesions (must be done prior to drug administration).

See Section 3.9.1.1.2 for further details and for response confirmation schedule.

3.9.3.2.2. Safety assessments: The following tests and procedures will be performed at specific intervals during the study to monitor study drug safety:

• Limited physical examination to include blood pressure and pulse rate at every cycle.

• Concomitant medication notation, including non- study vitamin supplementation, and number of units required for transfusions at every cycle

• Resource utilization: Notation of protocol- allowed palliative radiation therapy (Section 3.7), epidural analgesics, parenteral nutrition, bronchoscopic interventions, and reasons for and durations of hospitalizations, at every cycle.

• Hematology (± 3 days on Day 8 and Day 15) and within 4 days prior to each cycle

• Blood chemistries (± 3 days on Day 8) and within 4 days prior to each cycle

• For patients on the LY231514 arm only: Calculated creatinine clearance within 4 days prior to each cycle

• Toxicity rating using the NCI CTC scale prior to each cycle (see the CTC Investigator Guide, Version 2.0, supplied with the clinical report form) (Cancer Therapy Evaluation Program 1998)

3.9.3.3. Laboratory Testing and Results Local laboratory will assay:

• Hematology

Covance will assay:

• Blood chemistries

• Homocysteine

• Calculated CrCl

• Serum pregnancy test

If used for enrollment or dosing decisions, the local laboratory will also assay:

• Blood chemistries

• Calculated CrCl

Metabolite Laboratories Incorporated will assay:

• Vitamin metabolite panel

Note: Patients may be enrolled on the basis of local chemistries and calculated CrCl only if the Covance lab values are not available (if local calculated CrCl is used, the same local lab must be used throughout the study for dosing decisions). However, even if a patient is enrolled based on local chemistries, specimens must be collected prior to the initiation of treatment and throughout the study and sent to Covance for blood chemistries. These Covance results will be used for subsequent safety analyses.

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

3.9.3.4. Post- Study Follow- Up Safety

After each patient discontinues study therapy, the investigator should make every effort to continue to evaluate the patient for delayed toxicity by clinical and laboratory evaluations as clinically indicated. Every attempt should be made to obtain hematology and chemistry approximately 30 days after the last dose of LY231514 or docetaxel. The patient must be followed approximately every 30 days until toxicity resolves.

Efficacy

To obtain meaningful data on tumor responses and time to event variables, assessments of disease status will be made at regular intervals throughout study therapy and for up to six months following discontinuation of study therapy. Other than for response confirmation (Section 3.9.1.1.2), the interval between assessments will be approximately 6 weeks. The timing of the first assessment in post- therapy follow- up will therefore be approximately 6 weeks after the previous assessment, and not 6 weeks after the decision to discontinue study therapy. Assessments will consist of a plain x- ray or CT or MRI scan and/ or palpation (same method used during study therapy to quantitatively assess tumor) and will continue to be performed approximately every 6 weeks until the patient has documented progression of disease OR receives post- study chemotherapy, surgery, or other treatment, OR for 6 months from the last dose of study therapy, whichever occurs first. After 6 months, clinical assessment will be performed every 12 weeks, and plain x-ray or CT or MRI scans will be performed as clinically indicated until progression of disease or any additional chemotherapy, radiotherapy, or surgical intervention. During this post- therapy follow- up, information will be collected regarding date of disease progression or death, and any additional chemotherapy, radiotherapy, or surgical intervention. Each patient’s assessments will continue until death or until study closure.

The study will be closed when, in the opinion of the principal investigators and the Lilly physician, sufficient data have been obtained for completion of the final study manuscript.

LCSS Assessments

The LCSS patient and observer scales should be completed at the time the patient discontinues from study therapy. If the patient has not received any post- study chemotherapy, surgery or other treatments for the patient's cancer, the LCSS patient and observer scales should also be completed at approximately 30 days, and again at approximately 3 months after the last dose of study drug. If the patient discontinues from study therapy more than 30 days after the last dose of study drug, the 30- day post- dose LCSS observer scale need not be completed; however, the observer scale should still be completed approximately 3 months after the last dose of study drug.

3.9.4. Safety Monitoring

The Lilly clinical research physician will monitor safety data throughout the course of the study.

3.9.5. Appropriateness and Consistency of Measurements

All efficacy and safety assessments used in these studies are appropriate for an oncology study.

The Lung Cancer Symptom Scale (LCSS) is a validated, lung cancer- specific QoL instrument (Hollen et al. 1994). The LCSS consists of a patient scale and an optional observer scale. The patient scale includes 6 symptoms and 3 summation questions, while the observer scale includes the same 6 symptoms. The patient scale has been translated into English, Chinese, Czech, Dutch, Finnish, Flemish, French, German, Gujarati, Hindi, Italian, Polish, Portuguese, Slovak, Spanish, and Turkish, and has been tested for discriminant validity, reliability, and cross- cultural validity (validation of additional translations is ongoing). Only patients for whom there is a validated translation in a language in which they are fluent will be required to complete the LCSS.

Collection of LCSS data will not interfere with the routine collection of adverse event data reported by the patient, nor will the two sources of data be required to agree. These data will be analyzed with the same rigor as the study objectives relating to safety and efficacy.

3.10. Study Extensions No extensions are planned for this study.

3.11. Quality Control and Quality Assurance To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

• Provide instructional material to the study sites, as appropriate

• Sponsor a start- up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the clinical report forms, and study procedures

• Make periodic visits to the study site

• Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/ or fax

• Review and evaluate clinical report form data and use standard computer edits to detect errors in data collection

• Conduct quality review of database

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly Medical Quality Assurance (MQA) and/ or regulatory agencies at any time. Investigators will be given notice before an MQA audit occurs.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. Investigator files will identify whether any clinical report form entries are source data. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and/ or applicable ethical review boards with direct access to original source documents.

The investigator has the responsibility of explaining the correct use of the investigational agent(s) to the site personnel, ensuring that instructions are followed properly, and maintaining accurate records of study drug dispensing and collection.

4. Sample Size and Data Analysis Methods

4.1. Sample Size

At least 520 patients will be randomized between the two treatment arms: LY231514 or docetaxel. This sample size was chosen based on consideration of the primary comparison of overall survival between treatment arms.

We will assume for purposes of the statistical design that in overall survival, the hazard ratio (HR) of LY231514 to docetaxel is approximately constant over the period of observation. Superiority of LY231514 in overall survival will be defined by HR< 1.00. Noninferiority of LY231514 in overall survival will be defined by HR< 1.11. Considering that the median survival of docetaxel (75 mg/ m2 and 100 mg/ m2 dose groups combined) has been estimated to be 7.0 months versus 4.6 months for best supportive care (Shepherd

2000), our definition of noninferiority preserves 50% of docetaxel's effect on median survival over best supportive care.

HR will be estimated from the study data using the Cox proportional hazards model with therapy arm as the only cofactor (Cox, 1972). From the Cox model, a two- tailed 95% confidence interval for HR will be used to simultaneously evaluate the null hypotheses of HR= 1.00 (LY231514 not superior) and HR= 1.11 (LY231514 inferior). This method is statistically equivalent to the use of the two- tailed log- rank statistic for testing both null hypotheses at the 0.05 testwise significance levels. Under the assumption that 385 total deaths will be observed, Table JMEI. 8 lists the statistical power that the trial will demonstrate significant superiority or noninferiority for different examples of the true value of HR.

Table JMEI. 8. Statistical Power for Various Hazard Ratios

Examples for the true value of HR	Probability of Significant Superiority of LY231514	Probability of Significant Noninferiority of LY231514
1.11		.05
1.00	.05	.17
0.83	.54	.81
0.75	.80	.97

These probabilities are based on the " two- tailed" log- rank statistic, following the work of Freedman (Freedman 1982) and Peterson (Peterson 2000). Assuming no more than 26% censoring, the sample size of 520 patients allows for the observance of 385 deaths. Table JMEI. 8 indicates that for a two- tailed 5% significance level and a true value of HR of 0.75, there is an 80% chance of demonstrating statistically significant superiority of LY231514. For a two- tailed 5% significance level and a true value of HR of 0.83, there is an 81% chance of demonstrating statistically significant noninferiority of LY231514.

Note that both the noninferiority and superiority tests can be performed simultaneously at 5% testwise significance levels while maintaining a 5% study- wise significance level (Dunnett and Gent, 1996). See Attachment JMEI. 9 for a more detailed discussion of the statistical methodology.

4.2. General Considerations The final analysis for this trial will be undertaken after 385 randomized patients are known dead. All statistical comparisons between LY231514 and docetaxel will be judged relative to a significance level of a= 0.05. Confidence intervals for all parameters to be estimated will be constructed using a 95% level. See Attachment JMEI. 9 for a more detailed discussion of the statistical methodology.

The interpretation of study results will be the responsibility of the Lilly clinical research physician and the statistician. The Lilly clinical research physician and the statistician will

also be responsible for the appropriate conduct of an internal review process for both the final study report and any study- related material to be authorized for publication.

4.3. Data to be Analyzed

4.3.1. Qualifications for Efficacy Analysis

4.3.1.1. Intent- To- Treat Population Qualifications All patients randomized to the study will be evaluated for the time- to- event efficacy measures of survival, time to treatment failure, time to tumor progression, time to documented disease progression, and progression- free survival.

4.3.1.2. Tumor Response Population Qualifications All enrolled patients meeting the following criteria will be evaluated for efficacy measures of tumor response rate, time to objective tumor response, and duration of response:
• Histologic or cytologic diagnosis of NSCLC that is not amenable to curative therapy.
• No concurrent systemic chemotherapy.
• Presence of measurable or evaluable disease.
• Treatment with at least one dose of LY231514 or docetaxel.

4.3.1.3. Symptom Burden Index Analysis Qualifications All enrolled patients who have had the baseline LCSS measurement, and at least one post- baseline measurement will be evaluated for symptom burden index. Note that for the specific analyses of rates of improved and worse average symptom burden index measurements, further qualifications have been specified in Section 3.9.1.3.

4.3.2. Qualifications for Safety Analysis All patients who receive at least one dose of LY231514 or docetaxel will be evaluated for safety.

4.4. Patient Disposition A detailed description of patient disposition will be provided for each treatment arm. It will include:
• A definition of patient qualification
• A summary of data on patient discontinuation
• A summary of data on overall qualification status of all patients
• An account of all identified protocol violations.

All patients entered in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

4.5. Patient Characteristics Patient characteristics will include, for each treatment arm, a summary of the following:
• Patient demographics
• Baseline disease characteristics
• Pre- existing conditions

• Historical illness
• Prior therapies
• Concomitant drugs.

Other patient characteristics will be summarized as deemed appropriate.

4.6. Efficacy Analysis

• Time- to- event analyses will be performed on the observed distributions of overall survival time, time to objective tumor response, duration of response, time to documented disease progression, and progression- free survival. The Cox proportional hazards model (with therapy arm as the only cofactor) will be used to estimate for each of these endpoints the true hazard ratio HR of LY231514 to docetaxel (Cox 1972). Note that this is equivalent to the use of the log- rank test for comparisons between regimens for each of these endpoints. Additional supporting analyses will include Kaplan- Meier estimation by regimen (Kaplan and Meier 1958). If substantial imbalances in any important prognostic factors are observed between therapy arms (See Section 4.8), the analyses described above will be adjusted to account for these imbalances (eg the Cox model will be expanded to include those important prognostic factors as additional cofactors).

• Overall survival rates and progression- free survival rates at 3, 6, 9, and 12 months will be compared between regimens. These rates will be estimated using the Kaplan- Meier method and compared between regimens based on normal approximations for the differences between rates.

• Tumor response rates will be compared between regimens using an unadjusted normal approximation for the difference of two binomial proportions. Tumor response rates for each therapy arm will be defined as the number of patients with documented PR or CR divided by the number of patients qualified for tumor response analysis.

• Rates of patients having improved or worse average symptom burden index (as defined in Section 3.9.1.3) will be compared between regimens. These rates will be compared between regimens based on normal approximations for the differences between rates. Additionally, descriptive longitudinal modeling of the LCSS data will be explored. Note that in the event of obvious imbalances in the baseline average symptom burden index between therapy arms, these analyses may be adjusted to account for these imbalances.

See Attachment JMEI. 9 for a more detailed discussion of the statistical methodology.

4.7. Safety Analyses

All patients who are treated with LY231514 or docetaxel will be evaluated for safety. Safety analyses will include a comparison of the following between treatment arms:

• Summaries of the number of blood transfusions required.

• Summaries of the adverse event rates and laboratory changes.

• Listings and frequency tables categorizing laboratory and nonlaboratory adverse events by maximum CTC toxicity grade and relationship to study drug.

• Incidence of hospitalizations of patients.

• Summary of resource utilization.

4.8. Examination of Prognostic Factors

Analyses will be conducted to identify and assess the relevance of possible prognostic factors, including those identified in Section 3.6, and prior progression on a platinum containing regimen.

4.9. Interim Analyses

No interim analyses are planned for this study. Any unplanned interim analyses will be conducted under the auspices of a data monitoring board, which will be created in accordance with Lilly standard operating procedures.

5. Informed Consent, Ethical Review, and Regulatory Considerations

5.1. Informed Consent The informed consent document will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study.

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

As used in this protocol, the term " informed consent" includes all consent and/ or assent given by patients or their legal representatives.

5.2. Ethical Review The investigator will provide Lilly with documentation of ethical review board approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The ethical review board(s) will review the protocol as required.

The investigator will supply the following to the study site’s ethical review board(s):

• The current Clinical Investigator’s Brochure or package labeling and updates during the course of the study

• Informed consent document

• Relevant curricula vitae.

The investigator must provide the following documentation to Lilly or designee:

• The ethical review board's annual reapproval of the protocol, if required by local regulations.

• The ethical review board's approvals of any revisions to the informed consent document or amendments to the protocol.

5.3. Regulatory Considerations This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to a Lilly representative (see Protocol Attachment JMEI. 10).

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Protocol Attachment JMEI. 1 American Joint Committee on Cancer Staging Criteria for Lung Cancer

Stage Grouping

Occult	TX N0 M0
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T1 N1 M0
Stage IIB	T2 N1 M0
	T3 N0 M0
Stage IIIA	T1 N2 M0
	T2 N2 M0
	T3 N1 M0
	T3 N2 M0
Stage IIIB	Any T N3 M0
	T4 Any N M0
Stage IV	Any T Any N M1

Primary Tumor (T):

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
T2 Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension Involving main bronchus, 2 cm or more distal to the carina Invading the visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3 Tumor of any size that directly invades any of the following: Chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, or parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with malignant pleural effusionb aNote: The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to main bronchus, is also classified as T1. bNote: Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non- bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged as T1, T2, or T3.

Regional Lymph Nodes (N):

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis to ipsilateral peribronchial and/ or ipsilateral hilar lymph node(s), and intrapulmonary nodes including involvement by direct extension of the primary tumor
N2 Metastasis to ipsilateral mediastinal and/ or subcarinal lymph node(s)
N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M):

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis Note: M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral).

Protocol Attachment JMEI. 2 Performance Status Scale

Activity Status Description

0 Asymptomatic, fully active, and able to carry on all pre-disease performance without restrictions.

1 Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature, eg, light housework, office work.

2 Symptomatic, ambulatory and capable of all self- care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day.

3 Symptomatic, capable of only limited self- care, confined to bed or chair more than 50% of waking hours, but not bedridden.

4 Completely disabled. Cannot carry on any self-care. Totally bedridden.

5 Dead

Protocol Attachment JMEI. 3 Calculated Creatinine Clearance Modified Cockcroft and Gault

Note: This formula is to be used for calculating CrCl from local lab results only. Covance applies the formula and reports the value in its calculated form.

Weight in kg (W)

Height in cm (H)

Age in years (A)

Serum creatinine in mg/ dL (C)

Serum Creatinine Conversion: µ mol/ L x 0.0113 = mg/ dL

Instruction: Use the gender specific formula to figure Lean Body Weight, then use the Calculated Creatinine Clearance Formula below.

Lean Body Weight (LBW) Males

0.32810 x (W) = _____
0.33929 x (H) = + _____
- 29.5336
LBW = _____

Lean Body Weight (LBW) Females

0.29569 x (W) = _____
0.41813 x (H) = + _____
- 43.2933
LBW = _____

Calculated Creatinine Clearance

[140 - (A)] x (LBW)/71 x (C) = mL/ min

Protocol Attachment JMEI. 4 Schedule of Events

	BL	During Therapy									PS
Cycle/Visit	0	1			2			3			
Relative Day in a Cycle		1	8	15	1	8	15	1	8	15	
Procedure											
All patients:											
Informed consent (before procedures/tests)	X										
Physical examination[a]	X	X			X			X			
Medical history[a]	X				X			X			
Response to prior chemotherapy	X										
Blood pressure and pulse[a]	X	X			X			X			
Body Surface Area	X				X			X			
Concomitant med.notation[a,b]	X				X			X			
Performance Status[a]	X				X			X			
LCSS (patient scale)[k]	X		X	X	X	X	X	X	X	X	X
LCSS (observer scale)[l]	X				X			X			X
Tumor assessment (palpable)[c]	X							X			X
Radiologic tumor Assessment tests[d]	X							X			X
Serum pregnancy test (if indicated)	X										
Chemistry[e]	X		X		X	X	X	X	X	X	X
Hematology[e]	X		X	X	X	X	X	X	X	X	X
Homocysteine[f]	X										
Vitamin metabolite panel[f]	X										
CTC grading[a]		X			X			X			
Resource utilization		X			X			X			
LY231514 arm only:											
Folic acid supplementation[g]	X	X	X	X	X	X	X	X	X	X	X
Vitamin B12 injection[h]	X									X	
Calculated creatinine clearance[i]	X				X			X			
Electrocardiogram (ECG)[j]	X	X			X						
LY231514 therapy		X			X			X			
Docetaxel arm only:											
Calculated creatinine clearance[i]	X										
Docetaxel therapy		X			X			X			

BL = Baseline

PS = Post Study. See footnotes on each procedure and Section 3.9.3.4 for timing details.
a – Prior to infusion
b – Include non- study vitamin supplementation and number of units required for transfusions at every cycle
c – **Baseline**: No more than 2 weeks before enrollment. **On- study therapy**: Prior to infusion. **Post-study follow- up**: Approximately every 6 weeks for 6 months or until disease progression or until patient receives post- study chemotherapy, surgery, or other treatment, whichever occurs first. Thereafter, repeated as clinically indicated in follow- up visits. **Response confirmation**: Responses must be confirmed. Confirmation should be performed 3 – 4 weeks (minimum 21 days) after initial response documentation.
d – **Baseline**: CT or MRI scan (where available) and plain x- ray no more than 4 weeks prior to study enrollment. **On study therapy**: CT or MRI scans or plain x- ray (same method as baseline) are done prior to every other cycle. **Post- study follow- up**: Post- study radiological measurements – CT or MRI scan or plain x- ray (same method used for on study therapy assessment) – will be repeated approximately every 6 weeks for 6 months or until disease progression or until patient receives post-study chemotherapy, surgery, or other treatment, whichever occurs first. Thereafter, they will be repeated as clinically indicated in follow- up visits. **Response confirmation**: Responses must be confirmed using the same method (CT, MRI, or plain x- ray) as at baseline. Confirmation should be performed 3 – 4 weeks (minimum 21 days) after initial response documentation.
e – Within 7 days of study enrollment, then ± 3 days on Day 8 for Chemistry and Hematology and Day 15 for Hematology as indicated, and for both Chemistry and Hematology, within 4 days prior to each cycle, and if possible at the first post-study visit. Hematology panel includes hemoglobin, leukocytes (WBC), platelets, neutrophils (sum of segmented and bands), lymphocytes, and monocytes. Blood chemistry panel includes AP, ALT, AST, blood urea nitrogen, creatinine, calcium, and electrolytes (sodium, potassium).
f – Approximately 1- 2 weeks prior to study enrollment.
g – Daily beginning approximately 1- 2 weeks prior to first dose of LY231514 (upon randomization to LY231514 arm) and continuing daily until 3 weeks after the last dose of LY231514. Compliance will be monitored via medical interview as documented in the patient chart.
h – Given as an intramuscular injection approximately 1 to 2 weeks prior to first dose of LY231514 (upon randomization to LY231514 arm) and repeated approximately every 9 weeks until 3 weeks after the last dose of LY231514.
i – **All patients**: Within 7 days prior to study enrollment. **LY231514 patients only**: Within 4 days prior to each subsequent cycle.
j – For approximately 70 male and 70 female pts at selected sites randomized to LY231514, ECGs will be done as outlined in Protocol Attachment JMEI. 7.
k – One baseline measurement, up to 7 days prior to randomization. Thereafter, administer weekly on Day 8 ± 1, Day 15 ± 1, one day prior to, or day of, the next cycle of either docetaxel or LY231514 treatment, before the infusion begins. In the case of cycle delays greater than 5 days, complete additional measurements weekly. Repeat at discontinuation from study drug, at approximately 30 days after the last dose of study drug, and again at approximately 3 months after the last dose of study drug.
l – One baseline measurement, up to 7 days prior to randomization. Thereafter, administered prior to infusion (except Cycle 1). Repeat at discontinuation from study drug, at approximately 30 days after the last dose of study drug, and again at approximately 3 months after the last dose of study drug.

Protocol Attachment JMEI. 5 Lung Cancer Symptom Scale (LCSS):

Patient Scale Directions: Please place a mark along each line where it would best describe the symptoms of your lung cancer DURING THE PAST DAY (during the past 24 hours).

1. How is your appetite?

As good as it could be ——— As bad as it could be

2. How much fatigue do you have?

None ——— As much as it could be

3. How much coughing do you have?

None ——— As much as it could be

4. How much shortness of breath do you have?

None ——— As much as it could be

5. How much blood do you see in your sputum?

None ——— As much as it could be

6. How much pain do you have?

None ——— As much as it could be

1. How bad are your symptoms from lung cancer?

I have none ——— As bad as they could be

8. How much has your illness affected your ability to carry out normal activities?

Not at all ——— So much that I can do nothing for myself

9. How would you rate the quality of your life today?

Very high ——— Very low

Note: Proper administration requires that each question be presented on a separate card.

Attachment JMEI. 5 Lung Cancer Symptom Scale (LCSS): Observer Scale

Directions: Direct the interview to assess lung cancer symptoms using the timeframe of DURING THE PAST DAY.

1. Loss of appetite: (Score: _____)

100 None.
75 Mild; occasional loss of appetite but does not interfere with food intake.
50 Moderate; occasional loss of appetite which occasionally interferes with food intake.
25 Marked; frequent loss of appetite which generally interferes with food intake.
0 Severe; appetite so poor that medical intervention for feeding (intravenously or feeding tube) is needed.

2. Fatigue: (Score: _____)

100 None.
75 Mild; occasionally troubled by modest fatigue.
50 Moderate; usually troubled by modest fatigue.
25 Marked; occasionally troubled by major fatigue.
0 Severe; usually troubled by major fatigue.

3. Cough: (Score: _____)

100 None.
75 Mild; present and increased over a year ago, but not bothersome; no medications needed.
50 Moderate; bothersome; leads to SOB on occasion.
25 Marked; bothersome; disturbs sleep and other normal functioning.
0 Severe; nearly constant; disrupts any normal activities.

4. Dyspnea: (Score: _____)

100 None.
75 Mild; noticed only with major activity (eg, climbing more than one flight of stairs); SOB does not limit usual activities.
50 Moderate; present when walking at normal pace; interferres with ability to carry out some usual activities.
25 Marked; present with minimal activity; supplemental O2 used only occasionally.
0 Severe; supplemental O2 required most or all of the time.

Attachment JMEI. 5 (concluded) Lung Cancer Symptom Scale (LCSS): Observer Scale

Directions: Direct the interview to assess lung cancer symptoms using the timeframe of DURING THE PAST DAY.

5. Hemoptysis: (Score: _____)

100 None.
75 Mild; blood in sputum, less frequently than daily.
50 Moderate; blood in sputum at least daily but generally just " flecks" as part of the sputum.
25 Marked; sputum is often purely bloody (not just flecks) on a daily basis.
0 Severe; same as marked but blood loss by hemoptysis measurably lowering hemoglobin.

6. Pain: (Score: _____)

100 None.
75 Mild; present but either no medications required or only non- narcotic, non- codeine type oral agents; pain control satisfactory or reasonable.
50 Moderate; codeine or codeine- containing oral medications needed; pain control satisfactory or reasonable.
25 Marked; narcotic oral agents required; pain control satisfactory, or reasonable.
0 Severe; narcotic oral medications required but pain control not satisfactory, or parenteral narcotics are required.