Protocol
Phase II Study of Pemetrexed and Gemcitabine in Patients with Advanced Head and Neck Cancer (SCCHN)

PEMETREXED (LY231514)

Eli Lilly and Company

Principal Investigator: Corey Langer, M.D.
333 Cottman Ave.
Philadelphia, PA 19111

Co-investigator: Roger Cohen, M.D.
333 Cottman Ave.
Philadelphia, PA 19111

Statistician: Samuel Litwin, PhD
333 Cottman Ave
Philadelphia, PA 19111

Study Coordinator: Holly Tuttle, R.N, M.S.N.
Fox Chase Cancer Center Extramural Research Program (FER)
50 Huntingdon Pike 2nd Floor
Rockledge, PA 19046
Phone: 215-728-2451
Fax: 215-728-4784

Version **6/22/06**

Amendment 1 **1/09/2007**

Phase II Study of Pemetrexed and Gemcitabine in Patients with Advanced Head and Neck Cancer (SCCHN)

Table of Contents

1. Introduction

1.1. Pemetrexed

1.1.1. Background and Phase 1 Results

Inhibition of the enzyme thymidylate synthase (TS) is the primary mechanism of action of pemetrexed, a folate antimetabolite[1,2]. Thymidylate synthase, a folate-dependent enzyme, catalyzes the transformation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Inhibition of TS results in a decrease in thymidine, a pyrimidine necessary for DNA synthesis[3,4].

Pemetrexed also inhibits dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT), a folate-dependent enzyme that is involved in purine synthesis(2). These targets are related to the cytotoxicity of pemetrexed, since both thymidine and hypoxanthine are required to circumvent cellular death caused by pemetrexed(5). Pemetrexed gains entry to the cell via the reduced folate carrier and once localized is an excellent substrate for folylpolyglutamate synthetase (FPGS). The pentaglutamate form of pemetrexed is the predominant intracellular form and is >60-fold more potent in its inhibition of TS than the monoglutamate(6).

Phase 1 studies were conducted exploring three treatment schedules: daily times 5 every 21 days; weekly times 4 every 42 days; and once every 21 days. The 10-minute infusion once every 21 days was found to be the schedule that allowed the delivery of the highest dose intensity(7). The dose limiting toxicities (DLTs) on this schedule were neutropenia, thrombocytopenia, and fatigue. Patients who developed rashes received dexamethasone 4 mg twice daily for 3 days starting 1 day prior to treatment with pemetrexed, which improved or prevented the rash during subsequent cycles of therapy. The current dose being investigated in Phase 2 studies is 500 mg/m^2 every 21 days.

1.1.2. Single Agent Phase 2 Studies

Pemetrexed is administered as a single agent once every 21 days at 500 to 600 mg/m^2. It has demonstrated activity in multiple tumor types. These include mesothelioma, non-small cell lung cancer (NSCLC), breast, colorectal, pancreas, bladder, head and neck, and cervical cancer (Lilly 2000). Patients treated in these early studies did not receive folic acid or vitamin B_{12} supplementation.

1.1.3. Folic Acid and Vitamin B12 Supplementation

Although pemetrexed has clinically marked activity in a number of tumor types, a high incidence of hematologic toxicity has been associated with this antifolate. Studies with other antifolate agents inhibiting DHFR and TS have suggested that poor nutritional status contributes to the likelihood a patient will experience severe toxicity when exposed to these drugs(8-11). More specifically, these studies have investigated the relationship between folic acid and toxicity of these agents and have concluded that the addition of folic acid significantly reduces toxicity while preserving the antitumor activity of the drug.

In initial Phase 1 and 2 trials, pemetrexed was administered at 500 and 600 mg/m^2 every 21 days without folic acid or vitamin B_{12} supplementation. Myelosuppression was the principal drug-related toxicity, with a frequency of Grade 3/4 neutropenia of 40% to 50% and Grade 3/4 thrombocytopenia of 15% (n = 880). Since data in mid-1999 suggested an increasing death rate might be associated with the combination of severe gastrointestinal toxicity and severe neutropenia, a multivariate analysis based on 880 patients without folic acid and vitamin B_{12} supplementation was performed to determine which predictors might correlate with drug-related death. This analysis led to the conclusion that Grade 4 neutropenia accompanied by Grade 3/4 infection, Grade 3/4 diarrhea, and tumor type were all significantly associated with drug-related death.

A second multivariate analysis was performed on 305 patients who had baseline vitamin markers measured and recorded. Multiple factors potentially affecting the risk of severe toxicity were included in the analysis. Patients who received folic acid supplementation at any point during therapy or who received any dosing regimen other than LY231514 500 to 600 mg/m^2 were removed from the analysis, leaving a final sample size of 246 patients. Results of this analysis showed that an elevated homocysteine level at baseline was highly correlated with severe toxicity (that is, neutropenia, neutropenia accompanied by infection, diarrhea)(12). More details of this multivariate analysis are available in Protocol Appendix 1.

However, one consultant expert was concerned that some patients with homocysteine levels in the normal range could be relatively folic acid and/or B_{12} deficient and thus also at increased risk for severe toxicity. Therefore, the decision was made to supplement ***all*** patients receiving pemetrexed with dietary folic acid (350 to 1000 µg) and vitamin B_{12} (1000 µg IM injection). Vitamin B_{12} was included in the supplementation because approximately 15% of patients were not expected to achieve lower homocysteine levels with the supplementation of daily folic acid only.

A recent safety assessment of the impact of folic acid and vitamin B_{12} supplementation on the severe toxicities related to pemetrexed therapy has been completed. The overall objectives of this report were to assess the impact of folic acid and vitamin B_{12} supplementation on homocysteine levels over time and to compare the incidence of severe toxicities and drug-related deaths associated with pemetrexed therapy between patients with and without folic acid and vitamin B_{12} supplementation. The analysis confirmed the hypothesis that the administration of vitamin B_{12} and daily folic acid reduces homocysteine and results in a significant reduction of death and toxicity associated with pemetrexed.

1.1.4. Pemetrexed and Head and Neck Cancer

No chemotherapy agent has proven to be superior to methotrexate monotherapy for metastatic head and neck cancer in terms of survival. Unfortunately, the response rate is low (response rate of 10% in SWOG study by Forastiere et al[13]). Investigating pemetrexed in head and neck cancer makes sense since it does work similarly to methotrexate by interfering with folate metabolism, yet appears to be

more active than methotrexate in other solid tumors. A phase II study by Pivot et al[14] appears very promising with an objective response rate of 26.5% and a median response duration of 5.6 months (the median survival for methotrexate in the SWOG study was 5.6 months). It would be logical to investigate pemetrexed in a combined-drug regimen. The logical chemotherapy to combine with pemetrexed would be cisplatin as was done in a pivotal phase III study for mesotholioma[15]; however, there are several problems with this approach. The first is that many patients have already received cisplatin in the locally advanced disease setting. This may mean that subjects are more resistant to cisplatin than other agents. Furthermore, the accumulative toxicity of cisplatin (neuropathy, audiotoxicity, and renal toxicity) may make it difficult to continue using the drug. Also, patients with head and neck cancer are suspected to having significant comorbidity[16], probably due to the risk factors that are associated with the disease (tobacco and alcohol use). Considering the significant toxicities associated with cisplatin, this may make it difficult for subjects with head and neck cancer to tolerate this agent. Furthermore, cooperative groups have been inexplicably pushing the addition of taxanes in the locally advanced setting which can increase problems with neurotoxicity. It would make sense to evaluate chemotherapy agents that are not strongly associated with neurotoxicity. While carboplatin could also be considered, this agent has already been shown to be inferior to cisplatin in this disease setting by the same SWOG study mentioned above[13]. Preclinical data has suggested that gemcitabine may have a synergistic effect with pemetrexed. While it has not been well-studied as a single agent in this setting, many physicians who treat this disease believe that it does have activity. Furthermore, the combination of gemcitabine and pemetrexed does not have any serious cross-toxicities with cisplatin or the taxanes.

1.2. Gemcitabine

Gemcitabine (difluorodeoxycytidine), an analog of cytosine arabinoside (ara-C), is a pyrimidine antimetabolite[17]. The mechanism of action of gemcitabine has been well characterized. Gemcitabine is deaminated by deoxycytidine deaminase to difluorodeoxyuridine or activated by deoxycytidine kinase to difluorodeoxycytidine monophosphate (dFdCMP). Difluorodeoxyuridine is inactive, while dFdCMP is further metabolized to difluorodeoxycytidine diphosphate (dFdCDP) and difluorodeoxycitidine triphosphate (dFdCTP), which, when incorporated into DNA, results in chain termination. In comparison to ara-C incorporation into DNA, dFdCTP is less readily excised from DNA by DNA exonuclease. Thus, dFdCTP accumulates intracellularly to a greater degree than ara-C. This may account, in part, for its different spectrum of preclinical and clinical activity. In addition, gemcitabine inhibits ribonucleotide reductase, an enzyme that produces deoxynucleotides that are required for DNA synthesis. Gemcitabine is active in a variety of murine solid tumors and leukemias, as well as several human tumor xenografts[18].

Initial Phase 1 studies using a short infusion schedule, with drug given weekly for 3 weeks followed by 1 week of rest, established 790 mg/m^2/week as the maximum tolerated dose (MTD). Dose-limiting toxicity (DLT) was

myelosuppression with thrombocytopenia being more significant than granulocytopenia[19]. More recent Phase 1 and 2 trials have established 1250 mg/m^2/week as a well-tolerated dose[20,21]. Principal toxicities reported were hematological, with World Health Organization (WHO) Grade 4 neutropenia and thrombocytopenia occurring rarely; reversible elevation in hepatic transaminases; proteinuria; mild skin rash with and without pruritus; and nausea and vomiting. A review of 201 patients treated with 1250 mg/m^2/week who had not received prior chemotherapy revealed the following toxicity profile: neutropenia WHO Grade 3 and 4 in 23% and 6%, respectively; reversible elevation in hepatic transaminases WHO Grade 3 and 4 in 6% and 2%, respectively; WHO Grade 3 proteinuria occurred in less than 1%; WHO Grade 3 nausea and vomiting in 10%; and mild skin rash in 26% with pruritus occurring in 10%[22]. Other Phase 1 studies have been conducted using other different dosing schedules (i.e., twice weekly and daily times five). These studies reported significantly more nonhematologic toxicities such as flu-like symptoms and rash with DLT being thrombocytopenia[23,24]. The daily times five Phase 1 trial was stopped because of sporadic fever and occasional WHO Grade 3 and 4 hypotension[25].

The pharmacokinetics of gemcitabine has been evaluated[19,26-28]. The maximum plasma gemcitabine concentration was directly proportional to the dose. Plasma concentrations at 800 to 1000 mg/m^2 infused over 30 minutes exceed 50 μM. Elimination, due principally to deamination to diflorodeoxyuridine (dFdU), is rapid with a median terminal half-life of 14 hours and is the only metabolite detected in plasma or urine. In a bi-weekly schedule gemcitabine pharmacokinetics were determined at 13 different doses (40 to 4560 mg/m^2), administered every 2 weeks as a 30-minute infusion to 45 patients with refractory solid cancer. Gemcitabine and its uridine metabolite, dFdU, measured using high-performance liquid chromatography (HPLC), reached plasma peak levels of 50 to 100 μM at 1500 mg/m^2; gemcitabine was eliminated rapidly with a $t_{1/2}$ β of 4 to 20 minutes, while dFdU was still present at a plateau of ± 20 μM from 4 to 24 hours at doses greater than or equal to 960 mg/m^2. Up to 1500 mg/m^2, linear pharmacokinetics were observed for gemcitabine and dFdU. Gemcitabine clearance varied between 1705 to 7368 mL/m^2/min; its volume of distribution was 49 to 200 L/m^2.

In clinical studies, gemcitabine alone or in combination with other chemo-agents has shown activity across tumor types in lung, head and neck, breast, ovary, pancreas, and bladder cancer, and sarcoma.

1.3. Phase I and II pemetrexed plus Gemcitabine results

A Phase 1 study investigating the combination of pemetrexed and gemcitabine was completed at the Mayo Clinic Cancer Center[29]. In this study, patients with solid tumors were enrolled into one of two cohorts. Patients in the original cohort received gemcitabine on Days 1 and 8 of each 21-day cycle, and pemetrexed on Day 1 given 90 minutes after gemcitabine administration. On this dosing schedule, neutropenia led to Day-8 gemcitabine dose reductions in more than 50%

of cycles. After the maximum tolerated dose was defined using the original dosing schedule, a second cohort was employed, in which patients received gemcitabine on Day 1 and gemcitabine followed 90 minutes later by pemetrexed on Day 8. Of note, there was no vitamin supplementation in this study. Preliminary results indicate that the treatment schedule incorporated into the second cohort is better tolerated and should be carried forward into Phase 2 studies. The regimen selected for testing in Phase 2 trials is gemcitabine 1250 mg/m^2 administered on Days 1 and 8 of each 21-day cycle, and pemetrexed 500 mg/m^2, administered on Day 8 of each 21-day cycle.

A phase 2 study (Study JMDL), which is investigating the effects of the combination of pemetrexed plus gemcitabine for the treatment of pancreas cancer, has completed enrollment, with follow-up ongoing. Of the 40 patients enrolled, 39 received study drug and were included in a preliminary analysis. All but 6 of the treated patients received folic acid and vitamin B12 supplementation. Preliminary efficacy results revealed a response rate of 15% (6/39 patients) and an estimated progression-free survival of 3.6 months (95% CI, 2.8 to 4.9 months). With 30% censoring (10 patients alive and 4 patients on treatment), the median survival is 6.5 months. A preliminary safety analysis on data from 35 patients available to date showed CTC Grade 4 neutropenia (15 patients), Grade 3/4 fatigue (3 patients), and Grade 3/4 febrile neutropenia (4 patients) (preliminary data on file as of March 2001). One death has been reported that may have been treatment-related (case number: US_010157273) (Lilly 2001).

A phase II study with pemetrexed and gemcitabine in advanced non-small cell lung cancer showed a low overall response rate (17%), but noted an excellent median time to progression (5.1 months), median survival (11.3 months), and 1-year survival (46%)[30].

While many current studies are examining the combination of gemcitabine on days 1and 8 with pemetrexed on day 8 of a 21-day cycle, there has always been concern about white blood cell count nadir delaying chemotherapy. Generally, pemetrexed has a nadir period of 7-10 days after administration. Phase I and II studies of gemcitabine with other agents (e.g., paclitaxel[31], vinorelbine[32]) have been found to be active and safe. This has led to a recent phase I clinical study investigating the combination of pemetrexed and gemcitabine biweekly (Study JMGC). Gemcitabine was infused over 30 minutes, followed immediately by pemetrexed given intravenously over 10 minutes once on Day 1 and every 14 days. Phase I results on 24 patients identified a maximum tolerated dose of Gemcitabine 1500mg/m2 and pemetrexed 600mg/m2 with two patients out of 6 experiencing neutropenic fever. Therefore, the Phase 2 recommended dose is Gemcitabine 1500mg/m2 and pemetrexed 500mg/m2. Preliminary response suggests activity across multiple dose levels and a need to examine this regimen in a number of tumor types[33].

1.4. Treatment of metastatic Head and Neck Cancer in general

Single-agent methotrexate is the historic standard drug of choice for these patients. Cisplatin has equivalent activity. Higher-dose schedules of methotrexate and

cisplatin have both been investigated in randomized trials. There is no evidence that they improve survival, yet are associated with greater potential toxicity[34].

A number of randomized trials have compared treatment with a single agent to treatment with combination chemotherapy. These trials have been previously reviewed[34] and fail to demonstrate a significant survival advantage with the use of combination chemotherapy in these patients. Three recently published randomized trials are summarized in the following table and are representative of the literature in this area[13,35,36].

RECENT RANDOMIZED TRIALS: RECURRENT/METASTATIC DISEASE

Author	Drugs	Pts	CR + PR	Med Surv (Mos) **
Jacobs et al. [35]	Cisplatin	83	17%	5.0
	5-FU	83	13%	6.1
	Cisplatin	79	32%*	5.5
	5-FU			
Forastiere et al.[13]	Methotrexate	88	10%	5.6
	Carboplatin	86	21%#	5.0
	5-FU			
	Cisplatin	87	32%+	6.6
	5-FU			
Clavel et al.[36]	Cisplatin	113	15%	5.3
	Cisplatin	116	31%##	6.2
	5-FU			
	Cisplatin	127	34%++	8.2
	Methotrexate			
	Bleomycin			
	Vincristine			

* P = .035 vs. cisplatin, P = .005 vs. 5-FU; # P = .05 vs. MTX; + P = .001 vs. MTX

P = .003 vs. cisplatin; ++ P <.001 vs. cisplatin

** Median survivals are estimated from survival curves in the trial by Clavel et al[36]

2. Objectives

2.1. Primary Objective

2.1.1. To assess the response rate of pemetrexed and gemcitabine given every 2 weeks in patients with unresectable or metastatic squamous cell carcinomas of the head and neck.

2.2. Secondary Objective

2.2.1. Evaluate time to progression.

2.2.2. Evaluate overall survival.

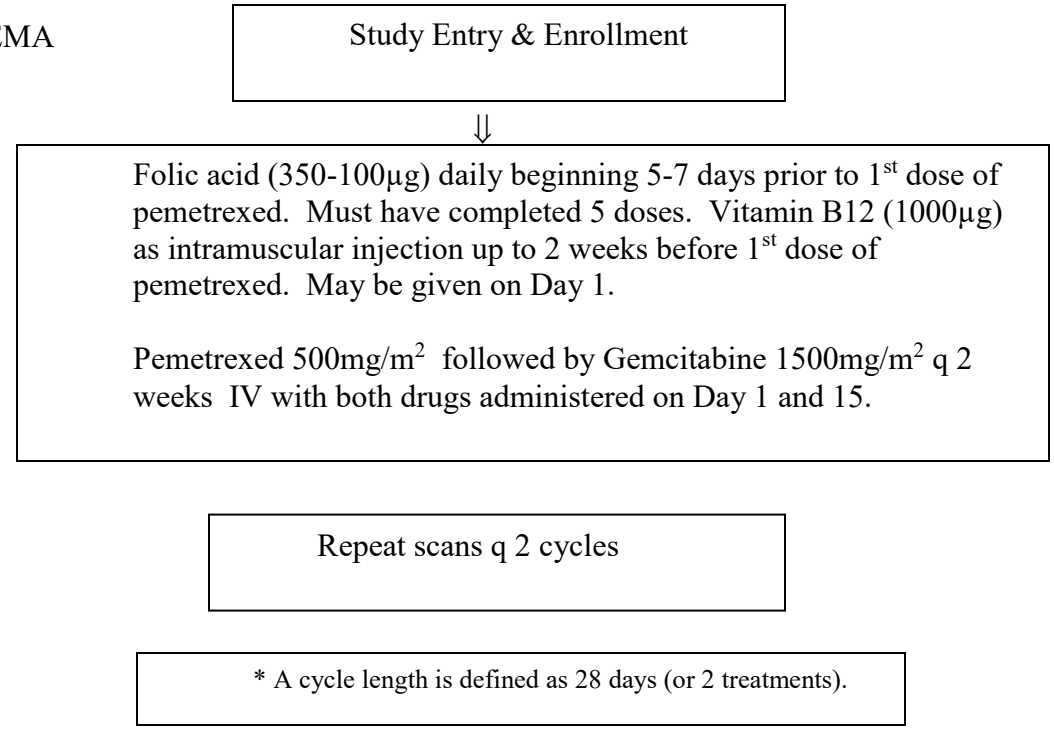
2.2.3. Assess safety and toxicity of this combination in SCCHN.

3. Summary of Study Design

A standard 2-step phase II design will be used. All patients with unresectable or metastatic squamous cell cancer of the head and neck (SCCHN) who are found eligible and enter the study will be treated with pemetrexed 500 mg/m^2 followed by gemcitabine 1500 mg/m^2 every 2 weeks. A cycle length will be 4 weeks. After every 2 cycles, repeat radiographic studies will be done to restage.

Patients will receive protocol therapy until: tumor progression is documented; unacceptable toxicity is experienced; or patient withdraws consent; patient is unable to fulfill the responsibilities of study participation as determined by the treating physician or the principal investigator.

SCHEMA



4. Study Population

4.1Inclusion Criteria

4.1.1 Histologic or cytologic diagnosis of a SCCHN that is either unresectable (as determined by a physician) or metastatic. Must have disease that is not curable by standard treatments.

4.1.2 Karnofsky Performance status of greater than or equal to 60%[37].

4.1.3 Up to one prior systemic chemotherapy, immunotherapy, or biological therapy regimen allowed in the advanced disease or metastatic setting. This does not include prior chemotherapy, immunotherapy, or biological treatment used with radiotherapy (i.e., concurrent with radiation therapy or as an induction regimen prior to definitive radiation therapy).

4.1.4 At least 4 weeks from previous radiation therapy or chemotherapy. Patient must recover from the acute toxic effects of the treatment prior to study enrollment.

4.1.5 Disease status must be that of measurable disease as defined by RECIST criteria[38].

- *Measurable disease*. The presence of at least one measurable lesion.
- *Measurable lesions*: Lesions that can be accurately measured in at least one dimension with the longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm using spiral CT scans.

CT (including spiral CT) scans and MRI are the preferred methods of measurement; however, chest x-rays are acceptable if the lesions are clearly defined and surrounded by aerated lung. Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is required.

4.1.6 Adequate organ function including the following:

4.1.6.1Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L.

4.1.6.2Hepatic: bilirubin ≤1.5 times the upper limit of normal (× ULN), alkaline phosphatase (AP), aspartate transaminase (AST) and alanine transaminase (ALT) ≤3.0 × ULN (AP, AST, and ALT ≤5 × ULN is acceptable if liver has tumor involvement).

4.1.6.3Renal: calculated creatinine clearance (CrCl) ≥45mL/min based on the standard Cockroft and Gault formula. Enrollment and dosing decisions based

on creatinine clearance may be made using local lab values (calculated using the standard Cockroft and Gault formula).

4.1.6.4 Female patients of child-bearing potential must test negative for pregnancy within 14 days of treatment, based on a serum pregnancy test. Men and women must agree to use a reliable method of birth control during the study and for 3 months following the last dose of study drug.

4.1.6.5 Patients must sign an informed consent document and HIPAA consent.

4.1.6.6 Patients must be at least 18 years of age.

4.1.6.7Must be able to take and absorb enteral medications

4.2 Exclusion Criteria

4.2.1 Prior treatment with gemcitabine or pemetrexed within the previous year, unless the chemotherapy agent was used concurrently with radiation therapy (see 4.1.3).

4.2.2 Pregnancy or breast-feeding.

4.2.3 Serious concomitant systemic disorders (eg, active infection) that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to complete the study.

4.2.4 Symptomatic, uncontrolled or untreated brain metastases. If brain metastases have been treated, patients must have been off of steroids used to control neurological symptoms for at least 2 weeks.

4.2.5 Inability or unwillingness to take folic acid, vitamin B_{12} supplementation, or dexamethasone.

4.2.6 Have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.

4.2.7 Inability to interrupt an NSAID or salicylate with a long half-life (eg, piroxicam or nabumetone) for a 5-day period

4.2.8 Presence of clinically relevant (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.

4.2.9 Active, concurrent, invasive malignancy requiring ongoing treatment.

4.2.10 Corticosteroids impermissible unless used for adrenal failure, septic shock or as temporizing measure for symptomatic pain, breathing, or rash.

4.3 Discontinuations

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be withdrawn from the study and Lilly or its designee must be contacted. An exception may be granted in very rare circumstances where there is a compelling safety reason to allow the patient to continue. In these rare cases, the treating investigator or designee must submit supporting documentation on a FER Investigator Initiated Study Protocol Exception form

to the project manager. The request will be presented to the PI and final approval to allow the subject to remain on study will be at Lilly's discretion.

In addition, patients will be discontinued from the study drug and/or from the study in the following circumstances.

- The investigator decides that the patient should be withdrawn from the study. If this decision is made because of a serious adverse event or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be notified immediately of all SAEs. See Safety Section 6.6.
- The patient or attending physician requests that the patient be withdrawn from the study.
- The patient, for any reason, requires treatment with another therapeutic agent, including radiation therapy, that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The investigator, for any reason, stops the study or stops the patient's participation in the study.
- Evidence of progressive disease exists.
- The drug exhibits unacceptable toxicity.
- The patient requires a 3rd dose reduction as per protocol guidelines.
- Treatment delay for any reason > 29 days.
- 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 patient is lost to follow-up.
- The patient experiences symptomatic deterioration in the absence of objective disease progression.

4.4 Pretreatment Studies (see Appendix 4)

- Within 28 days before enrollment
  - ✓ Radiologic test for tumor measurement as defined in section 4.1.5.
  - ✓ Chest X-ray (PA and Lateral)
- Within 14 before the start of treatment
  - ✓ Physical Examination, Medical History, blood pressure and pulse measurements
  - ✓ Body Surface Area (Height and Weight)
  - ✓ Performance Status Assessment. (See Appendix 3).
  - ✓ Laboratory Studies (Hematology, Chemistry See Appendix 5).
  - ✓ Pregnancy test (for women of child bearing potential)

4.5 Registration Procedure

- Subjects will be registered through FER by calling the project manager, Monday through Friday between 9:00 am and 5:00 pm, at 215-728-2451 to alert that the site has a subject for registration. The site will fax the Registration Form and the Inclusion and Exclusion Checklists signed by the site PI to FER at 215-728-4784. FER will notify the site by phone and return the completed Registration Form, including study identification number, by fax once eligibility has been confirmed. Subjects must be registered and have received a study identification number prior to the initiation of study therapy.

5. Treatment and Dose Modifications

5.1 Treatments Administered

Each cycle is defined as a twenty-eight (28) day treatment period consisting of two treatments 2 weeks apart (D1, D15 = 1st cycle; D29, D43 = 2nd cycle) A cycle is comprised of one treatment of pemetrexed followed by gemcitabine with each agent administered Day 1 and Day 15 every 28 days (cycle = 28 days). The actual dose of pemetrexed or gemcitabine 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. A delay of cycle as a result of holidays, weekends, bad weather, or other unforeseen circumstances will be permitted and not counted as a protocol violation, and will not require waiver. The reason for the schedule change must be documented in the subject's chart. The reason must be captured in the remarks section of the Case Report Form (CRF).

The investigator or a designee is responsible for explaining the correct use of the investigational agent(s) to the patient and site personnel, verifying that instructions are followed properly, maintaining accurate drug accountability records including receipt, dispensing and waste of all unused medication according to the site's policy and procedure.

5.2 Materials and Supplies

5.2.1 Pemetrexed (supplied by Eli Lilly)

The freeze-dried drug product is composed of LY231514 disodium and mannitol in a 1:1 ratio. Sodium hydroxide and/or hydrochloric acid solution may be added during processing to adjust the pH. The vial size is 500 mg. 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 from the 500-mg vial. The drug product is stable when stored at room temperature.

Reconstituting the 500 mg vial contents with 10 mL to 50 mL of sodium chloride injection gives a clear solution with a concentration of 10 mg/mL to 50 mg/mL. The reconstituted formulation is in the pH range of 6.8 to 7.5 and has been shown to be chemically stable for 72 hours at refrigerated or room

temperature. Vial contents should be inspected for particulate matter before and after the drug product is withdrawn from a vial into a syringe.

The concentrated solution cannot be administered without further dilution. For purposes of clinical administration an appropriate quantity of the contents of the reconstituted vial must be further diluted into an infusion solution of 75 to 125 mL of 0.9% sodium chloride for injection. After dilution the shelf-life of the product is 24 hours at room temperature. LY231514 is not sensitive to light. Vials of LY231514 contain no anti-microbial preservative, and they are single-use vials. Any unused portion of a vial may not be stored for future use or used for other patients, and unused portions of product in a vial must be discarded.

LY231514 is incompatible in solution with acidic medications or media and must not be mixed or administered simultaneously through the same infusion line. The infusion line should be flushed prior to administration of any concomitant medication. LY231514 is compatible with standard PVC administration sets and IV solution bags.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See Table 1 for dose and timing.

5.2.2 Gemcitabine (supplied by Eli Lilly)

Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 g of gemcitabine as the hydrochloride salt, mannitol, and sodium acetate. The lyophilized product should be stored at controlled room temperatures (20°C to 25°C). To reconstitute, add 5 mL 0.9% Sodium Chloride to the 200mg vial or 25 mL of normal saline to the 1 gm vial. Each dilution yields a gemcitabine concentration of 38 mg/mL. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride to concentrations as low as 0.1 mg/ml. Once the drug has been reconstituted it should be stored at room temperature and used within 24 hours. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

Any unused portion of a vial may not be stored for future use or used for other patients, and unused portions of product in a vial must be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See Table 1 for dose and timing.

5.2.3 Folic Acid (commercial)

Folic Acid (350-1000 μg) orally, must be given daily beginning approximately 5-7 days (at least 5 doses) prior to first dose of pemetrexed and continuing daily until 3 weeks after the last dose of study therapy.

5.2.4 Vitamin B_{12} (commercial)

Vitamin B_{12} (1000 µg) will be administered as an intramuscular injection up to 2 weeks prior to first dose of pemetrexed and repeated every 2 to 3 cycles (i.e., approximately every 8 weeks) starting with the third cycle until 3 weeks after the last dose of study therapy. The second and subsequent injections may be given ± 1 week in order to time it for the same day as chemotherapy treatment. The first dose may be given on D1 of treatment as long as it is given prior to the pemetrexed infusion.

5.2.5 Dexamethasone (commercial)

Dexamethasone (4 mg orally or equivalent) will be prescribed by the investigator in whatever formulation is available locally. Patients should be premedicated according to the outline(s) in Table 1.

Table 1

Drug	Dose	Time
pemetrexed	500 mg/m^2 IVinfusion	10 minutes (8 to 15). To be given before gemcitabine. D1 & D15
Sodium chloride for injection	100 mL IV infusion	IV infusion at least 15 minutes after pemetrexed infusion. D1 & D15
Gemcitabine IV Administration	1500 mg/m2 IV infusion	Day 1 & D15 after sodium chloride infusion, over 30 minutes
Folic acid Oral dose	350-1000 mcg Dose per MD discretion	Daily beginning 5-7 days prior to the first dose of pemetrexed (must have received 5 doses), and continuing daily until 3 weeks after the last dose of pemetrexed. Delay for insufficient folic acid treatment prior to pemetrexed administration is defined in Section 5.3.2.
Vitamin B12	1000 µg intramuscular injection	Up to 2 weeks prior to the first dose of pemetrexed (may be given on D1 prior to pemetrexed) and repeated every 2 to 3 cycles (i.e., approximately every 8 weeks) starting with the third cycle until 3 weeks after the last dose of study therapy. The second and subsequent injections may be given ± 1 week in order to time it for the same day as chemotherapy treatment. Delay for insufficient Vit B12 prior to pemetrexed administration is defined in section 5.3.2
Dexamethasone	4 mg, orally twice per day (or equivalent)	Should be taken on the day before, the day of, and the day after each dose of pemetrexed/gemcitabine, unless clinical contraindications exist. Higher or additional doses are permitted for reasons other than routine rash prophylaxis (eg, antiemetic prophylaxis).

5.3 Dose Adjustments or Delays for Subsequent Cycles

Dose reductions (with the exception of mucositis, diarrhea, renal, and hematologic toxicities which are detailed in separate sections below) are 25% of the initial targeted dose. Subsequent dose reduction is an additional 25% of initial target dose (i.e. 50%). Any patient 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 withdrawn from study therapy. Treatment may be delayed for up to 29 days from the time it is due to resume, to allow a patient sufficient time to recover from study drug-related toxicity or intercurrent co-morbidity. Patients who are unable to resume treatment in this 29 day period will be withdrawn from study. Omitted doses mid-cycle (day 15) will not be made up; for instance, if day 15 dosing is withheld because of toxicity, it will not be made up on day 22 of that treatment cycle.

5.3.1 Toxicity

Hematologic Toxicity

ANC must be $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L prior to the 1st cycle. Dose adjustments at the start of a subsequent cycle of therapy will be based on platelet and neutrophil counts from the day of scheduled treatment. Treatment should be delayed to allow sufficient time for recovery. Upon recovery, if treatment is resumed, it should be according to the guidelines in Table 2

Table 2 Dose Adjustments for Pemetrexed and Gemcitabine

ANC ($\times 10^9$/L)		Platelets ($\times 10^9$/L)	Percent of Previous Dose
≥1000	and	≥100	100%
≥500 and < 1000	And/or	≥50 and <100	50%
< 500	or	<50	Day 15 dosing is omitted. Day 1 dosing will be delayed for 1 week. If repeat counts are adequate, treat with the dose according to this table. If counts are still inadequate, delay one or more weeks. Remove from the study, if treatment delay > 29 days.

Diarrhea

In the event of diarrhea requiring hospitalization (or of at least Grade 3), treatment should be delayed until diarrhea has resolved to Grade ≤ 1 before proceeding. Treatment should be resumed at 75% of the previous dose level.

Mucositis

Table 3 documents the relevant dose adjustments in case of mucositis.

Table 3 Dose Modifications for Pemetrexed and Gemcitabine for Mucositis

CTC Toxicity Grade	Percent of Previous Dose
Grade 0-1	100%
Grade 2 Grade 3-4 Recurrence of Grade 3 or 4 after treatment at two dose reductions	50% withhold Withdraw patient from study

Renal Toxicity

The standard Cockcroft-Gault formula must be used to calculate CrCl for enrollment or dosing. No dosage adjustment is needed in patients with creatinine clearance $\geq$ 45 mL/min. Insufficient numbers of patients have been studied with creatinine clearance <45 mL/min to give a dose recommendation. Therefore, Pemetrexed should not be administered to patients whose creatinine clearance is <45 mL/min. However, gemcitabine, at appropriate dose, can be continued. Pemetrexed can be resumed once creatinine clearance is > 45mL/min

For males:

$$\text{CrCl (mL/min)} = \frac{\text{(140-age) x (weight in kg)}}{\text{72 x serum creatinine in mg/dL}}$$

For females:

$$\text{CrCl (mL/min)} = 0.85 \times \frac{\text{(140-age) x (weight in kg)}}{\text{72 x serum creatinine in mg/dL}}$$

Other Non-hematologic Toxicities

For other attributable, nonhematologic toxicities $\geq$ 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 baseline value before proceeding. Treatment should resume at 75% of the previous dose level for both medications if deemed appropriate by the treating physician.

5.3.2 Treatment Delays As a Result of Insufficient Folic Acid or Vitamin B12 Supplementation

Delay the first dose of study drug until the patient has taken folic acid for at least 5 of the 7 days before Day 1 of Cycle 1, and until the vitamin B12 injection has been administered.

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

5.3.3 Leucovorin

Because folic acid and vitamin B12 supplementation has significantly reduced the number of episodes of Grade 4 hematologic and Grade 3/4 nonhematologic toxicities associated with Pemetrexed therapy, a need for leucovorin as rescue agents is not anticipated. However, this section provides information should rescue be necessary.

In clinical trials, leucovorin was permitted for CTC grade 4 leukopenia lasting > 3 days, CTC Grade 4 neutropenia lasting > 3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associate with Grade 3 thrombocytopenia, or Grade 3 or 4 muscositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100mg/m2, intravenously once, followed by leucovorin, 50 mg/m2, intravenously or orally every 6 hours for up to 8 doses. Resumption of therapy must be delayed until leucovorin is completed or discontinued.

5.3.4 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) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting must be hospitalized for intravenous hydration and correction of electrolyte imbalances and administration of leucovorin

5.3.5 Clinically significant effusions

For patients who develop or have baseline clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) before Pemetrexed 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, the patient should be discontinued from study therapy. Ideally, cytologic confirmation is required to designate progressive disease status.

5.3.6 Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

5.4 Concomitant Therapy

Patients are allowed to receive full supportive care therapies concomitantly during the study. Steroids may be administered for adrenal failure, septic shock, or as temporizing measure for symptomatic pain, breathing, or rash. Megace (Megesterol acetate) or similar agents as appetite stimulants are allowed. No other chemotherapy, immunotherapy, hormonal cancer therapy, radiation therapy, surgery for cancer, or experimental medications (with the exception of thymidine) will be permitted while the patients are participating in this study. 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.

5.4.1 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-CSF) in any cycle. G-CSF may be used only for patients who have ANC $<0.5 \times 10^9$/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. Use of erythropoietin is allowed. Use of stimulators of thrombopoiesis is not allowed.

5.4.2 Nonsteroidal Anti-Inflammatory Drugs

Patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) or salicylates will not take the NSAID or salicylate 2 days before, the day of, and 2 days after receiving pemetrexed. If a patient is taking an NSAID or salicylate with a long half-life (eg, piroxicam or nabumetone), it should not be taken 5 days before, the day of, and 2 days after receiving pemetrexed.

6. Efficacy and Safety Evaluations

6.1 Efficacy Measures

Within 28 days of enrollment, baseline tumor measurement(s) will be performed on each patient. CT (including spiral CT) scans and MRI are the preferred methods of measurement, but chest x-ray is acceptable if the lesion(s) is clearly defined and surrounded by aerated lung. Ultrasound will not be permitted as a method of tumor measurement. The same method used at baseline **must be used consistently** for tumor assessment and will be repeated every 8 weeks (-1 week)(prior to every other cycle).

6.2 Disease Status

- Measurable disease is defined as the presence of at least one measurable lesion. If only one lesion is present, the neoplastic nature of the disease site should be confirmed by cytology and/or histology. Lesions should be accurately measured in at least one dimension (with the longest diameter recorded) ≥ 20 mm using conventional techniques or ≥ 10 mm using spiral CT scans. All measurements should be in metric notation and made using either a ruler or calipers. For the case of skin lesions, documentation by color photography, including a metric ruler to estimate the size of the lesion is required.

  If conventional CT or MRI is used, the cuts should be contiguous and ≤10 mm per slice in thickness. Cuts for spiral CT scans should be 5 mm when a contiguous reconstruction algorithm is used. Chest x-rays, although not preferred, are acceptable if the lesions are clearly delineated and the surrounding lung is aerated.

- Non-measurable disease is defined as all other lesions including small lesions (longest diameter < 20 mm using conventional techniques or < 10 mm with spiral CT scans). These include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and abdominal masses that are not confirmed/followed by imaging techniques.

  All measurable lesions (referred to as target lesions) up to a maximum of 5 lesions per organ and 10 lesions per patient are to be followed. Selected lesions should be representative of all organs involved and should be selected based on size (longest diameter) and the suitability for accurate repeated measurements. The sum of the longest diameters of all target lesions will be calculated and recorded at the baseline measurement. This sum will be used as a reference by which to characterize the objective tumor response.

  If a measurable lesion is hidden or obliterated by a surrounding process (eg, pleural effusion, enlarging lymph nodes), an asterisk should be placed in the appropriate space for the dimension, and an explanation should be given for the failure to measure the lesion.

  All other lesions (measurable and nonmeasurable) will be documented at baseline. While measurements of these nontarget lesions are not required, the presence or absence of each site should be recorded at each follow up.

  Included in the evaluations are the following standard criteria:

6.3 Objective status (to be recorded at each evaluation)

- Complete response (CR): Disappearance of all target and nontarget lesions and normalization of tumor marker level. No new lesions. No disease-related symptoms. All target lesions must be assessed using the same technique as baseline. Refers to clinical CR.

- Partial response (PR): Greater than or equal to a 30% decrease from baseline in the sum of the longest diameters of the target lesions and either incomplete response/stable disease or lack of disease progression of the nontarget lesions. Incomplete response/stable disease is defined as the persistence of one or more nontarget lesions and/or the maintenance of tumor marker levels above normal limits. No new lesions. All measurable lesions and sites must be assessed using the same techniques as baseline.
- Stable disease (SD): Target lesions do not qualify for CR, PR, or progression and nontarget lesions do not progress. No new lesions. All lesions must be assessed using the same techniques as baseline.
- Progressive disease (PD): Greater than or equal to a 20% increase in the sum of the longest diameters of the target lesions as referenced to the smallest sum of the longest diameters recorded since treatment started and/or the appearance of one or more new lesions and/or progression of nontarget lesions.
- Confirmation: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met.

  Exceptions: 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. Lesions that appear to increase in size as a result of the presence of necrotic tissue will not be considered to have progressed.
- Unknown: Symptomatic deterioration in the absence of documented progression with one or more measurable sites not assessed.

Notes

1) Patients with a global deterioration of their health requiring discontinuation from the study who have not progressed at the time of discontinuation should be labeled as having symptomatic deterioration. Every attempt should be made to follow the patient until disease progression is noted.
2) It may be difficult to determine residual disease from normal tissue. If an evaluation of CR depends on this determination, then residual lesion should be investigated by fine needle aspirate or biopsy before confirming the CR.
3) For nontargeted lesions, the objective response cannot be PR.
4) All lesions used for measurement must be prospectively selected.

6.4 Best Response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the

patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Table 4 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 4. Overall response

Overall response	Target lesions	Nontarget lesions	New lesions
CR	CR	CR	No
PR	CR	Incomplete response/SD	No
PR	PR	Non-PD	No
SD	SD	Non-PD	No
PD	PD	Any	Yes or No
PD	Any	PD	Yes or No
PD	Any	Any	Yes

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

6.5 Definition of Efficacy Measures

6.5.1 A **responder** will be defined as any patient who exhibits a CR or PR.

6.5.2 Time to objective tumor response is defined as the time from study enrollment to the first observation of an objective tumor response.

6.5.3 The **duration of a CR or PR** is defined as the time from first objective status assessment of CR or PR to the first time of progression or death as a result of any cause.

Progression-free survival time is defined as the time from study enrollment to the first date of disease progression or death as a result of any cause. Progression-free 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 study enrollment to the first observation of disease progression, death as a result of any cause, or early discontinuation of treatment. 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 disease progression is defined as the time from study enrollment to the first date of disease progression. Time to disease progression will be censored at the date of death for patients who have not had documented disease progression.

6.5.4 Overall survival time is defined as the time from study enrollment to time of death as a result of any cause. Survival time will be censored at the date of the last follow-up visit for patients who are still alive.

6.6 Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting FER 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 for following, 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 is resolved or explained. Frequency of follow-up is left to the discretion of the investigator.

6.6.1 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 we will use the following procedure.

Adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines January 2001).* Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

Serious Adverse Event (SAE) is one that is fatal or life threatening, permanently disabling, requires inpatient hospitalization or prolongation of existing hospitalization, or is a congenital anomaly, or results in any important medical event when based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator.

Severity Ratings The investigator will evaluate the severity of each adverse event utilizing the NCI Common Toxicity Criteria Version 3.0 Severity is expressed in numerical grade using the following definitions:

- **Grade 1:** Mild-noticeable to the patient, does not interfere with the patient's daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study drug.

- **Grade 2:** Moderate-interferes with the patient's daily activities, possibly requires additional therapy, but does not require discontinuation of study drug.
- **Grade 3:** Severe-severely limits the patient's daily activities and may require discontinuation of the study drug.
- **Grade 4:** Life-threatening or disabling
- **Grade 5:** Fatal

Relationship to Study Drug/Attribution

- **Definite –**clearly related
- **Probably Related**-the event occurs within a reasonable time period following drug administration or follows a known response for the drug and cannot be reasonably explained by known patient characteristics (including use of concomitant medications).
- **Possible** –may be related
- **Unlikely** –doubtfully related
- **Definitely Not Related**-the event is not known to be caused by the study drug.

Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

Unexpected Adverse Event is one not identified in nature, severity, or frequency in the Investigator's Brochure or the product package insert for the study drug.

PROCEDURE:

Prior to enrollment, study site personnel will note the occurrence and nature of each patient's medical condition(s) in the appropriate section of the medical record to be captured in the case report form. During the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

If a patient experiences an adverse event after the informed consent document is signed (entry) but the patient is never assigned to treatment (enrollment), the event will ONLY be reported if the investigator believes that the event may have been caused by a protocol procedure.

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 in the medical record to be captured in the case report forms.

Investigator Reporting Responsibilities:

1. Upon identification of an AE, the investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. All AEs and SAEs will be recorded in the case report forms on the "AE/Toxicity Form" with details about the grade and attribution of each episode. The action taken with respect to the study drug, and the patient's outcome should be recorded in the remarks section of the "Treatment Flow Sheet". All events will be recorded on case report forms each cycle until they resolve.

3. All SAEs will be recorded on "FDA Form 3500 MedWatch" and faxed to the FER project manager at 215-728-4784. The site should call the FER project manager to alert them of an incoming SAE fax. After submitting the initial report it may be necessary to submit additional reports by the investigator should the event require further investigation.

4. Each investigator is responsible to report all AEs/SAEs to IRB following guidelines set by that IRB. FER reserves the right to request an event be reported to the IRB at their discretion. Copies of all documentation of events reviewed by the IRB must be sent to FER Clinical Research Office.

5. Reporting SAEs:

   Study site personnel must report to FER immediately, any **serious** adverse event.

   Adverse events must be reported to regulatory authorities according to the definitions and timelines specified in the local laws and regulations:

   - Unexpected Event: Grade 2-3 with possible, probably or definite attribution requires written report to FER within 3 working days.
   - Unexpected Grade 4-5 regardless of attribution requires report by phone/fax within 24 hours and a written report within 3 working days. This includes deaths within 30 days of last study drug.
   - Expected Event: Grade 4-5 regardless of attribution requires report by phone/fax within 24 hours and a written report within 3 working days

6. If the results of an investigator or FER investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

7. Any serious or unexpected adverse event that is possibly, probably or definitely related to the study will be reported by FER in writing to Lilly within 5 working days of notification of the event. Death from any cause will be reported immediately by FER to Lilly. The report will be distributed to all investigational sites within 15 working days of notification of the event for review by each respective IRB

8. Lilly is responsible for notifying the FDA of all applicable events.

The FER fax number for SAEs is 215-728-4784

FER will forward all reports to the required places.

6.7 Post-Therapy Follow-up

6.7.1 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 pemetrexed and gemcitabine. The patient must be followed approximately every 30 days until toxicity resolves.

6.7.2 Efficacy

To obtain meaningful data on tumor responses and time to event variables, assessments of disease status will be made at regular intervals after patients discontinue from the study. A CT or MRI scan (same method as at baseline) must be done no less than 4 weeks after the first documentation of a response, to confirm the response. Other than for response confirmation, a CT or MRI scan will be performed approximately every 8 weeks for 6 months post-study or until disease progression, whichever occurs first. After 6 months, clinical assessment will be done every 12 weeks, and CT or MRI scans will be done as clinically indicated until progression of disease. During this time information will be collected regarding date of disease progression or death, and any post-study chemotherapy, radiotherapy, or surgical intervention. Each patient's assessments will continue until death.

If patient decides to follow-up at a different institution, attempts to obtain data will still be made unless patient withdraws consent.

7. Statistical Considerations

7.1 Targeted Response Rate

For a total of 32 subjects, 16 will be accrued during stage 1 and 16 during stage 2. Given that the 'true' response probability is 10%, there is a 51.47% probability of ending the trial during stage 1. However, if the 'true' response probability is 25%, then there is an 6.35% probability that the trial will be stopped in stage 1. The type I error of the design is 0.0882, and the power is 0.825. If 1 or fewer responses are observed during the first stage, then the trial is stopped early. If 5 or fewer responses are observed by the end of the trial, then no further investigation of the drug is warranted. Operating characteristics of this design are summarized in the table below:

n2	a2	n1	a1
32	5	16	1

p1 = 0.1000 p2 = 0.2500

p(S.le.a1|n1): 0.5147 p(S.le.a1|n1): 0.0635
p(S.gt.a2|n2): 0.0882 p(S.gt.a2|n2): 0.8253
p(early stop): 0.5147 p(early stop): 0.0635
ASN: 23.8 ASN: 31.0

overall type I error: 0.0882
overall power: 0.8253

We will assume there will be a 10% rate of inevaluable patients, so 3 additional subjects will be accrued in stage 2. Therefore we expect to accrue a minimum of 16 patients and a maximum of 35 patients using this design.

7.2 Qualifications for Efficacy Analysis

All enrolled patients meeting the following criteria will be evaluated for efficacy:

- Histologic or cytologic diagnosis of SCCHN that is not amenable to curative therapy.
- No concurrent systemic chemotherapy except for study treatment.
- Presence of one-dimensional measurable disease as defined in Section 6.2, and the investigator has consistently followed protocol guidelines for tumor measurement.
- Treatment with at least one dose of pemetrexed and gemcitabine.

7.3 Qualifications for Safety Analysis

All patients who receive at least one dose of pemetrexed and gemcitabine will be evaluated for safety.

7.4 Primary Outcome

7.4.1 The primary objective of the study is the tumor response rate. Please refer to Section 6.2 for definitions of response categories. The study tumor response rate will be reported, including a 95% confidence interval. The estimate of tumor response rate will be given by:

$$\text{Response Rate} = \frac{\text{Sum of \# of PRs and \# of CRs observed}}{\text{\# of patients qualified for efficacy analy}}$$

7.5 Secondary Outcomes

The secondary objectives will be to measure time to progression and overall survival. All patients who meet the efficacy criteria for qualifications will be evaluated. The

analysis will include Kaplan-Meier curves. Time to progression will be from the date of the first treatment to the time that any of the following conditions are met:

- There is progression of disease as defined in Section 6.3.
- Death of any cause.
- The initiation of new treatment (e.g., radiation therapy, chemotherapy, immunotherapy).

7.6 Safety Analyses

All patients who are treated with pemetrexed and gemcitabine will be evaluated for safety. Safety analyses will include the following:

- 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.

All adverse events will be summarized 1) without regard to causal relationship and 2) by causal relationship to study drugs, based on the Investigator's opinion. Worst toxicity grades per patient will be tabulated for selected adverse events and laboratory measurements. Any serious adverse event or adverse event resulting in premature and permanent discontinuation of any study drug will be described in detail. Adverse events and other symptoms will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

A Data Safety Monitoring Plan has been implemented to monitor safety parameters during the study. Ongoing, on site monitoring will confirm proper conduct of this study for each subject and identify any protocol violations and unreported adverse events in a timely manner. Any events determined to be significant will be reported immediately to the principal investigator. FER administrative staff will review data regularly with the principal investigator or his designee. Data will be collected from individual case report forms when the subject has completed the study and all queries are resolved. This review will include complete accrual listing demographic information, response, toxicity tables, summaries of incidence severity and resolution of adverse events, including laboratory results abnormalities, summary of any pertinent findings from monitoring/auditing visits and a description of all known or suspected protocol violations.

Each participating practice must designate a single on-site principal investigator with primary responsibility for the conduct of the study in his practice. This site-specific principal investigator is responsible for identification of all adverse events at their site and must verify that appropriate procedures are being followed. SAE's experienced by a subject participating in a clinical trial must be reported according to section 6.6.1 adverse event reporting in clinical trials. FER is responsible for collecting and reporting serious adverse events to the study principal investigator, Lilly, and to other participating sites for IRB submission. Each practice must designate an IRB for this study and follow any by-laws regarding the use of an IRB set forth by the terms of

their employment or determined by the institution in which they practice. Investigators must supply their designated IRB with ongoing progress reports for the study and a formal review of each study will be conducted at least every 364 days or more frequently as designated by the IRB. The IRB may suspend, terminate or restrict the study as appropriate.

FER will manage the flow of documents to participating sites and external agencies (including reports of serious adverse events) to facilitate ongoing and timely review of the protocol. FER will monitor the medical and study records of each participant accrued at each site throughout the course of the study. In addition, FER will audit, collect and report data to the study Principle Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAE's) will be reviewed on a real time basis first by the study site PI and subsequently by Dr.Langer.

7.7 Criteria for Study Termination

This study will be considered complete six months after the last patient is enrolled or after 80% of the enrolled patients have progressed, whichever is later. Data generated to this point will be collected and entered into the clinical trial database. Data collected up to this point (after cleaning and locking) will be used to write the clinical study report.

After completion of the trial (as defined in the previous paragraph), data will continue to be collected on all surviving patients who are still under therapy. This data collection will continue until all patients have either progressed or are off study therapy. This post-lock data will be combined with the data in the locked database and stored in a data library separate from the locked database. The clinical study report will not be revised to reflect this additional data.

8. Informed Consent, Ethical Review, and Regulatory Considerations

8.1 Informed Consent

The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing any new information that may be relevant to the patient's willingness to continue his or her participation in the trial in a timely manner.

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, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient's legal representative. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

8.2 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). Any member of the ethical review board who is directly affiliated with this study as an investigator or as site personnel must abstain from the ethical review board's vote on the approval of the protocol. The ethical review board(s) will review the protocol as required.

8.3Regulatory Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. The investigator or designee will promptly submit the protocol to applicable ethical review board(s).

An identification code assigned by the PI or designee to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting adverse events and/or other trial-related data.

9.0 Study Agent Information

9.1 Pemetrexed Disodium

9.1.1 Other Names

Pemetrexed, MTA, LY231515

9.1.2 Classification

Antifolate antimetabolite

9.1.3 Mode of Action

Multitargeted antifolate compound that has been shown to inhibit several enzymes in the folate pathway including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase.

9.1.4 Storage and Stability

The drug product is stable when stored at room temperature. Reconstituting the 500 mg vial contents with 10 mL to 50 mL of sodium chloride injection gives a clear solution with a concentration of 10 mg/mL to 50 mg/mL. The reconstituted formulation is in the pH range of 6.8 to 7.5 and has been shown to be chemically stable for 72 hours at refrigerated or room temperature. After dilution the shelf-life of the product is 24 hours at room temperature. If pemetrexed disodium is reconstituted with sterile water for injection and is stored for up to 24 hours before administration to the patient, it must be refrigerated during this time. LY231514 is not sensitive to light. Vials of LY231514 contain no anti-microbial preservative, and they are single-use vials. Any unused portion of a vial may not be stored for future use, and unused portions of product in a vial must be discarded.

9.1.5 Preparation and administration

The freeze-dried drug product is composed of LY231514 disodium and mannitol in a 1:1 ratio. Sodium hydroxide and/or hydrochloric acid solution may be added during processing to adjust the pH. The vial size is 500 mg. 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 from the 500-mg vial. Vial contents should be inspected for particulate matter before and after the drug product is withdrawn from a vial into a syringe.

The concentrated solution cannot be administered without further dilution. For purposes of clinical administration an appropriate quantity of the contents of the reconstituted vial must be further diluted into an infusion solution of 75 to 125 mL of 0.9% sodium chloride for injection. LY231514 is incompatible in solution with acidic medications or media and must not be mixed or administered simultaneously through the same infusion line. The infusion line should be flushed prior to administration of any concomitant medication. LY231514 is compatible with standard PVC administration sets and IV solution bags.

Administer as an intravenous infusion over 10 minutes (8 to 15).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

9.1.6 Incompatibilities

Do not infuse pemetrexed disodium with other drugs concurrently.

9.1.7 Drug Interaction

Salicylates and NSAIDs should not be given for a 5 day period (2 days before, the day of, and 2 days following administration of pemetrexed disodium) While pemetrexed is structurally related to methotrexate, the actual effect on renal excretion with concurrent NSAIDs and salicylates is not yet characterized.

9.1.8 Side Effects

1. Hematologic: Myelosuppression with anemia, leucopenia, neutropenia and thrombocytopenia. Elevated homocycteine levels increase risk of neutropenic sepsis.
2. Dermatologic: Rash, pruritis, alopecia, skin discoloration.
3. Gastrointestinal: Nausea, vomiting, stomatitis, diarrhea, constipation, anorexia, hematemesis, abdominal pain, melena, dyspepsia, flatulence.
4. Genitourinary: Renal dysfunction, dehydration, hematuria, dysuria, UTI.
5. Hepatic: Hyperbilirubinemia, elevated liver transaminases, jaundice.

6. Cardiac: Tachycardia, vasodilatation, hypotension, hypertension, edema.
7. Neurologic: Dizziness, insomnia, somnolence, blurred vision, headache, back and chest pain, anxiety, paresthesia, malaise, taste perversion, depression, confusion.
8. Allergic: Fever, rigors, allergic reaction.
9. Ocular: Conjunctivitis, eye disorder or pain.
10. Pulmonary: very uncommon but may include: cough, effusions, pneumonitis and fibrosis.
11. Other: Myalgia, sweating, pharyngitis, epistaxis, facial edema, dysphagia, ascites, hiccups, weight loss, hyperglycemia, bone pain, asthenia.

9.1.9 Nursing/Patient Implications

1. When handling, preparing, or administering pemetrexed, follow recommended procedures and guidelines for the safe handling of a cytotoxic agent.
2. Administer antiemetics as indicated.
3. Monitor for hematologic toxicity.
4. Observe for gastrointestinal toxicity (stomatitis, diarrhea, nausea, vomiting).
5. Pemetrexed must be given with folate and vitamin B12 rescue. Educate patient and significant other about importance of compliance with medication schedule.
6. Any acute change in mental status should prompt immediate notification of medical staff.

9.2 Gemcitabine

9.2.1 Other name:

2'-deoxy-2',2' difluorocytidine-monohydrochloride, Gemzar. Gemcitabine is commercially available and supplied as a lyophilized powder in sterile vials containing 200mg or 1g of gemcitabine as the hydrochloride salt (expressed as free base), mannitol and sodium acetate.

9.2.2 Storage

The lyophilized powder should be stored below 30°C. Drug vials will be reconstituted with normal saline added to the vial to make a solution ideally containing 10mg/ml or less. The concentration for 200mg and 1 g vials should be no greater than 40mg/ml.

9.2.3 Administration

The drug will be infused intravenously over 30 minutes. Once the drug has been reconstituted it should be stored at room temperature and used within 24 hours.

9.2.4 Side effects

Allergic: bronchospasm was reported for less then 2% of patients with anaphylactoid reactions rarely reported. Gemcitabine is contraindicated in patients with a known hypersensitivity to this drug.

Cardiovascular: 2% of patients discontinued therapy due to cardiovascular event like myocardial infarction, cerebrovascular accident, arrhythmia and hypertension. Many of these patients had a prior history of cardiovascular disease.

Hematologic: myelosuppression is the principal dose-limiting factor. Dose adjustment for hematologic toxicity are needed but <1% of patients require discontinuation of therapy.

Gastrointestinal: nausea and vomiting are frequent but usually mild or moderate. Diarrhea and stomatitis occur less frequently.

Hepatic: transient elevations of serum transaminase occur in about 2/3 of patients

Renal-Mild proteinuria and hematuria are frequently reported. Clinical findings consistent with the hemolytic uremic syndrome (HUS) were reported in 6 out of 2429 patients (0.25%) receiving gemcitabine in clinical trials. Four patients developed HUS while on gemcitabine therapy, two immediately post-therapy. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Fever: the incidence of fever is 41%. This is in contrast to the incidence of infection 16%. The fever may be present in the absence of infection. It may have associated flu-like symptoms and is usually mild and clinically manageable.

Rash: reported in 1/3. It is typically a macular or finely granular maculo-papular pruritic eruption of mild to moderate severity involving the trunk and extremities.

Pulmonary: dyspnea was reported in 23%, severe dyspnea in 3%. It may be due to underlying lung cancer (40% of study population) or pulmonary manifestations of other malignancies. Dyspnea was occasionally accompanied by bronchospasm (<2% of patients). Rare reports of parenchymal lung toxicity consistent with drug induced pneumonitis have occurred.

Edema: 13%, peripheral edema 20% and generalized edema have been reported. Less than 1% of patients required discontinuation of therapy due edema.

Flu like symptoms. Reported for 19% of patients. Fever, asthenia, headache, cough, chills and myalgia were commonly reported. Fever and asthenia were reported as isolated symptoms. Insomnia, sweating, rhinitis and malaise were reported infrequently.

Infection: reported for 16% of patients. Sepsis has been rarely reported.

Alopecia: Hair loss reported in 15% of patients.

Neurotoxicity: 10% incidence of mild paresthesias and a 1% incidence of severe paresthesia.

9.2.5 Extravasation

Gemcitabine is not a vesicant. 4% had documented injection site related event with no reports of injection site necrosis.

9.2.6 Overdosage

There is no known antidote for overdosage. Myelosuppression, and severe rash were the principal toxicities documented when a single dose as high as 5700mg/m2 was administered by IV infusion over 30min every 2 weeks to several patients in a phase I trial. In the event of overdose the patient should be monitored with blood counts weekly and supportive growth factor as necessary.

9.3 Drug Ordering and Accountability

9.3.1 Pemetrexed and Gemcitabine will both be supplied by Eli Lilly. During each site initiation visit, the drug ordering process and forms will be reviewed and distributed. Drug orders may not be placed until all required regulatory documents have been received by the FER project manager and forwarded and approved by the Lilly representative. Each site is responsible for maintaining current records of product disposition. Records or logs must comply with applicable regulations and guidelines and include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label ID number or batch number
- Dates and initials of person responsible for each site product inventory entry/movement

- Amount dispensed to and wasted per subject including unique subject identifier
- Amount transferred to another are for dispensing or storage
- Non-study disposition (wasted, broken)

FER will provide forms to facilitate inventory control if the staff at the site does not have an established system that meets these requirements or the NCI Investigational Agent Accountability Record can be utilized (available online).

10.0 Bibliography

1. Grindey GB, Shih C, Barnett C, al. e: LY231514, a novel pyrrolopyrimidine antifolate that inhibits thymidylate synthase (TS), Proc Am Assoc Cancer Res, 1992, pp 411. Abstract 2451
2. Shih C, Gossett L, Gates SB, al. e: LY231514 and its polyglutamates exhibit potent inhibition against both human dihydrofolate reductase (DHFR) and thymidylate sythase (TS): multiple folate enzyme inhibition, Ann Oncol, 1996, pp 85. Abstract 289
3. Grem J: Fluorinated pyrimidines, in Chabner B, Collins J (eds): Cancer chemotherapy: principles and practice. Philadelphia (PA), Lippincott, 1990, pp 180-224
4. Schilsky R: Antimetabolites., in Perry M (ed): The chemotherapy source book. Baltimore (MD), Williams & Wilkins, 1992, pp 301-17
5. Schultz R, Andis S, Chen V, al. e: Comparative antitumor activity of the multitargeted antifolate LY231514 and the thymidylate synthase (TS) inhibitor ZD1694, 1996, pp 85. Abstract 290
6. Chen V, Bewley JR, Gossett L, al. e: Activity of LY231514 against several enzymes in the folate-dependent pathways, Proc am Assoc Cancer Res, 1996, pp 381. Abstract 2598
7. Rinaldi D, Burris H, Dorr F, al. e: A phase I evaluation of LY231514, a novel multi-targeted antifolate, administered every 21 days., Proc Am Soc Clin Oncol., 1996, pp 489. Abstract 1559

8. Morgan SL, Baggott JE, Vaughn WH, Young PK, Austin JV, Krumdieck CL, Alarcon GS: The effect of folic acid supplementation on the toxicity of low-dose methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 33:9-18, 1990
9. Mendelsohn LG, Gates SB, Habeck LL, Shackelford KA, Worzalla J, Shih C, Grindey GB: The role of dietary folate in modulation of folate receptor expression, folylpolyglutamate synthetase activity and the efficacy and toxicity of lometrexol. Adv Enzyme Regul 36:365-81, 1996
10. Smith GK, Amyx H, Boytos CM, Duch DS, Ferone R, Wilson HR: Enhanced antitumor activity for the thymidylate synthase inhibitor 1843U89 through decreased host toxicity with oral folic acid. Cancer Res 55:6117-25, 1995
11. Alati T, Worzalla JF, Shih C, Bewley JR, Lewis S, Moran RG, Grindey GB: Augmentation of the therapeutic activity of lometrexol -(6-R)5,10-dideazatetrahydrofolate- by oral folic acid. Cancer Res 56:2331-5, 1996
12. Niyikiza C: LY231514 (MTA) Safety Analysis, 3 December 1999. Submitted to the FDA as Serial Number 95 to IND#40,061. On file., 1999
13. Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, Kish JA, McClure S, VonFeldt E, Williamson SK, et al.: Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J. Clin. Oncol. 10:1245-51, 1992
14. Pivot X, Raymond E, Laguerre B, Degardin M, Cals L, Armand JP, Lefebvre JL, Gedouin D, Ripoche V, Kayitalire L, Niyikiza C, Johnson R, Latz J, Schneider M: Pemetrexed disodium in recurrent locally advanced or metastatic squamous cell carcinoma of the head and neck. Br. J. Cancer 85:649-55, 2001
15. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J. Clin. Oncol. 21:2636-44, 2003
16. Piccirillo JF: Importance of comorbidity in head and neck cancer. Laryngoscope 110:593-602, 2000
17. Hertel L, Kroin J, Misner J, al. e: Synthesis of 2-deoxy-2',2'-difluoro-D-ribose and 2-deoxy-2',2'-difluoro-D-ribofuranosyl nucleosides. J Org Chem 53:2406-9, 1988
18. Hertel LW, Boder GB, Kroin JS, Rinzel SM, Poore GA, Todd GC, Grindey GB: Evaluation of the antitumor activity of gemcitabine (2',2'-difluoro-2'-deoxycytidine). Cancer Res 50:4417-22, 1990
19. Abbruzzese JL, Grunewald R, Weeks EA, Gravel D, Adams T, Nowak B, Mineishi S, Tarassoff P, Satterlee W, Raber MN, et al.: A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol 9:491-8, 1991
20. Fossella F, Lippman S, Tarassoff P, al. e: Phase 1/2 study of gemcitabine, an active agent for advanced non-small cell lung cancer (nsclc), Proc ASCO, 1995, pp A1144
21. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, Trochanowski B, Tarassoff PG: Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 12:29-34, 1994
22. Tonato M: Gemcitabine safety overview, in: gemcitabine, novel combination of efficacy and tolerability., Proc Eur Cont Clin Oncol 7. Satellite Symposium, Jerusalem, Israel, November, 1993, pp 14-6

23. Poplin E, Redman B, Flaherty L, al. e: Difluorodeoxycytidine: a phase I study. Proc Am Assoc Clin Res 30:282, 1989
24. Poplin EA, Corbett T, Flaherty L, Tarasoff P, Redman BG, Valdivieso M, Baker L: Difluorodeoxycytidine (dFdC)--gemcitabine: a phase I study. Invest New Drugs 10:165-70, 1992
25. O'Rourke T, Brown T, Havlin K, al. e: Phase I clinical trial of difluorodeoxycytidine (LY188011) given as an intravenous bolus on five consecutive days. Invest New Drugs 7:380, 1989
26. Grunewald R, Kantarjian H, Du M, Faucher K, Tarassoff P, Plunkett W: Gemcitabine in leukemia: a phase I clinical, plasma, and cellular pharmacology study. J Clin Oncol 10:406-13, 1992
27. Plunkett W: Pharmacology of gemcitabine. Ann Oncol 3:191, 1992
28. Pollera C, Ceribelli A, Crecco M, Zeuli M, Bortini S, Calabresi F: Prolonged infusion of gemcitabine; a preliminary report of a Phase I study. Ann Oncol 44:1819-27, 1992
29. Adjei AA, Erlichman C, Sloan JA, Reid JM, Pitot HC, Goldberg RM, Peethambaram P, Atherton P, Hanson LJ, Alberts SR, Jett J: Phase I and pharmacologic study of sequences of gemcitabine and the multitargeted antifolate agent in patients with advanced solid tumors. J. Clin. Oncol. 18:1748-57, 2000
30. Ettinger DS, Monnerat C, Kelly K, Novello S, Brahmer JR, Readett D, Rusthoven J, Bunn PA, Chevalier TL: Phase II trial of pemetrexed + gemcitabine in patients with advanced non-small cell lung cancer: importance of survival over response. Proc Am Soc Clin Oncol 21:Abstract 1243, 2002
31. Vici P, Foggi P, Capomolla E, Santiccioli S, Cauchi C, Giacinti L, Lopez M: Biweekly paclitaxel/gemcitabine (P/G) as salvage treatment in breast cancer patients (pts): preliminary results. Proc Am Soc Clin Oncol 21:Abstract 2054, 2002
32. Hitt R, Castellano D, Cortes-Funes H, Colomer R: Biweekly Gemcitabine Plus Vinorelbine: A Dose-Finding Phase I Study in Advanced Cancer. Proc Am Soc Clin Oncol 18:Abstract 821, 1999
33. Dudek A, Larson T, Mellskog CE, Bloss LP, Obasaju C: A phase I clinical study of biweekly pemetrexed and gemcitabine in patients with advanced solid tumors. Journal of Clinical Oncology 22:2141, 2004
34. Urba SG, Forastiere AA: Systemic therapy of head and neck cancer: most effective agents, areas of promise. Oncology (Huntington) 3:79-88; discussion, 1989
35. Jacobs C, Lyman G, Velez-Garcia E, Sridhar KS, Knight W, Hochster H, Goodnough LT, Mortimer JE, Einhorn LH, Schacter L: A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J. Clin. Oncol. 10:257-63, 1992
36. Clavel M, Vermorken JB, Cognetti F, Cappelaere P, de Mulder PH, Schornagel JH, Tueni EA, Verweij J, Wildiers J, Clerico M: Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann. Oncol. 5:521-6, 1994

37. Karnofsky DA, Bruchenal JH: The clinical evaluation of chemotherapeutics in cancer, in McLeod CM (ed): Evaluation of chemotherapeutic agents. New York, Columbia University, 1949, pp 191-205
38. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J. Natl. Cancer Inst. 92:205-16, 2000
39. Simon R: Optimal two-stage designs for phase II clinical trials. Control. Clin. Trials 10:1-10, 1989

Protocol Appendix 1.
Folic Acid and Vitamin B_{12} Supplementation

A recent safety assessment of the impact of folic acid and vitamin B_{12} supplementation on the severe toxicities related to pemetrexed therapy has been completed and a report submitted to the FDA (Serial number 323 to IND #40,061 on June 4, 2001). The overall objectives of this report were to assess the impact of folic acid and vitamin B_{12} supplementation on homocysteine levels over time and to compare the incidence of severe toxicities and drug-related deaths associated with pemetrexed therapy between patients with and without folic acid and vitamin B_{12} supplementation. For this analysis, two groups of patients with solid tumors treated with pemetrexed for at least two cycles of therapy and who had a baseline homocysteine concentration obtained were selected for this analysis. The first group included 394 patients who were never supplemented with folic acid and vitamin B_{12} at any time during their therapy with pemetrexed 500 to 600 mg/m^2, while the second group included 196 patients supplemented with vitamin B_{12} and daily folic acid during their treatment with pemetrexed 500 mg/m^2. All toxicities reported were based on the CTC grading scale.

The data showed that folic acid and vitamin B_{12} supplementation caused a statistically significant reduction in plasma homocysteine concentrations over time, from 9.4 μM at baseline to 7.7 μM at Cycle 7. This reduction was observed after one cycle of therapy and was maintained throughout the study.

The analysis assessed cumulative toxicities related to pemetrexed therapy occurring within the first seven cycles of therapy. The analysis focused on those severe hematologic (Grade 4 neutropenia and thrombocytopenia) and nonhematologic (Grade 3/4 infection, diarrhea, and mucositis) toxicities associated with pemetrexed therapy. The incidence of both Grade 4 hematologic and Grade 3/4 nonhematologic toxicities decreased markedly in those patients supplemented with vitamins (Table 4). These data indicate a marked improvement in the incidence of severe toxicities associated with pemetrexed therapy when patients are supplemented with folic acid and vitamin B_{12}.

Table 4. Incidence of Severe Toxicities Related to pemetrexed Therapy in Patients with and without Folic Acid and Vitamin B_{12} Supplementation Occurring within the First 7 Cycles

	Without folic acid/B_{12} supplementation (n=394)	With folic acid/B_{12} supplementation (n=196)	P value*
Grade 4 hematologic and Grade 3/4 nonhematologic toxicities[a]	33%	12%	<0.0001
Grade 4 neutropenia	28%	9%	<0.0001
Grade 4 thrombocytopenia	6%	1%	0.001
Grade 3/4 mucositis	5%	0.5%	0.002
Grade 3/4 diarrhea	5%	4%	NS**
Grade 3/4 infection	3%	1%	NS
Grade 4 neutropenia + Grade 3/4 mucositis	3%	0%	0.002
Grade 4 neutropenia + Grade 3/4 diarrhea	3%	1%	NS
Grade 4 neutropenia +G3/4 infection	1%	1%	NS

*Determined by Chi-Square test.

**Not statistically significant.

Seven of 504 patients (1.4%) supplemented with folic acid and vitamin B_{12} died as a result of toxicities possibly or probably related to pemetrexed therapy compared to 49 of 1169 patients (4.2%) not supplemented with folic acid and vitamin B_{12}. These results indicate that folic acid and vitamin B_{12} supplementation results in a marked improvement in the incidence of pemetrexed-related death.

The analysis confirmed the hypothesis that the administration of daily folic acid and vitamin B_{12} reduces homocysteine and in turn results in a significant reduction of death and toxicity associated with pemetrexed. The results from this analysis support the following conclusions:

- Supplementation with folic acid and vitamin B_{12} causes a statistically significant reduction in homocysteine levels and these levels are maintained while on study as long as the patient continues to take the vitamins.
- Folic acid and vitamin B_{12} supplementation results in a reduction of pemetrexed-related deaths.

- Folic acid and vitamin B_{12} supplementation significantly reduces the number of episodes of Grade 4 hematologic and Grade 3/4 nonhematologic toxicities associated with pemetrexed therapy.
- Folic acid and vitamin B_{12} supplementation acts quickly to protect the patient from the increased risk of developing severe toxicities and from drug-related death. This protection continues throughout study therapy with LY231514.

Protocol Appendix 2.
American Joint Committee on Cancer
Staging Criteria

Protocol Appendix 2
AJCC Staging Criteria for Lip and Oral Cavity tumors

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4 (lip) Tumor invades adjacent structures (e.g., through cortical bone, inferior alveolar nerve, floor of mouth, skin of face)
T4 (oral cavity) Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin. Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4)

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Protocol Appendix 2
AJCC Staging Criteria for Pharynx tumors

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*

Nasopharynx

T1 Tumor confined to the nasopharynx
T2 Tumor extends to soft tissues of oropharynx and/or nasal fossa
  T2a without parapharyngeal extension
  T2b with parapharyngeal extension
T3 Tumor invades bony structures and/or paranasal sinuses
T4 Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit

Oropharynx

T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4 Tumor invades adjacent structures (e.g., pterygoid muscle, mandible, hard palate, deep muscle of tongue, larynx)

Hypopharynx

T1 Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2 Tumor involves more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3 Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4 Tumor invades adjacent structures (e.g., thyroid/cricoid cartilage, carotid artery, soft tissues of neck, prevertebral fascia/muscles, thyroid and/or esophagus)

Regional Lymph Nodes (N): Nasopharynx

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
N2 Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
N3 Metastasis in a lymph node(s)
- N3a greater than 6 cm in dimension
- N3b extension to the supraclavicular fossa

Regional Lymph Nodes (N): Oropharynx and Hypopharynx

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
- N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
- N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping: Nasopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Stage Grouping: Oropharynx, Hypopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Protocol Appendix 2
AJCC Staging Criteria for Larynx tumors

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues
T4 Tumor invades through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid, and/or esophagus

Glottis

T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
  T1a Tumor limited to one vocal cord
  T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation
T4 Tumor invades through the thyroid cartilage and/or to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, pharynx)

Subglottis

T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
T4 Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, esophagus)

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Protocol Appendix 3.
Performance Status Scale

Karnofsky Performance Status

100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of one's needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization indicated although death not imminent.
20	Very sick; hospitalization necessary; active, supportive treatment necessary.
10	Moribund, fatal processes progressing rapidly.
0	Dead

Protocol Appendix 4.
Study Schedule

	BL	During Therapy				PS
Cycle/Visit		Cycles (every 28 days)				
Relative Day in a Cycle		1	8	15	22	
Procedure						
Informed consent (before procedures/tests)	X					
Physical examination	X	X[a]				
Medical history	X					
Blood pressure and pulse measurements	X	X[a]		X		
Body Surface Area calculation	X	X[a]				
Concomitant med. notation	X	X[a,b]				
Performance Status	X	X[a]				
Tumor measurement (palpable)[c]	X				X [c]	
Radiologic tests for tumor measurement [d]	X				X [d]	
Serum pregnancy test (if indicated)	X					
Chemistry[e]	X	X		X		X
Hematology[e]	X	X		X		X
Calculated creatinine clearance[e]	X	X		X		
CTC v3.0 grading	X	X[a]		X[a]		X[h]
Folic acid supplementation[f]	X	X	X	X	X	X
Vitamin B12 injection[g]	X					X
Pemetrexed		X		X		
Gemcitabine		X		X		

Abbreviations: BL = Baseline, PS = Post study is 30 days after the last dose of study drug

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 at every other cycle, starting with the third cycle. **Post-therapy follow-up:** Approximately every 8 weeks for 6 months or until disease progression, 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/or plain x-ray no more than 28 days prior to study enrollment. **On study therapy:** CT or MRI scans or plain x-ray (same method as baseline) are done 0-7 days prior to every other cycle. **Post-therapy follow-up:** Post-therapy radiological measurements – CT or MRI scan or plain x-ray (same method used for on study therapy assessment) – will be repeated approximately every 8 weeks for 6 months or until disease progression, 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 14 days of study enrollment, within 2 days of Day 15 for chemistry and hematology, within 4 days prior to each cycle, and if possible approximately 30 days after the last dose of study therapy. If any result that would justify dose modification is abnormal, lab must be repeated within 24 hours of treatment.

f – Daily beginning 5-7 days prior to first dose of pemetrexed and continuing daily until 3 weeks after the last dose of study therapy. Must have completed 5 doses prior to first dose of pemetrexed. Compliance will be monitored via medical interview as documented in the patient chart and by review of the Patient Daily Diary for Folic Acid and Decadron..

g – Given as an intramuscular injection approximately up to 2 weeks prior to first dose of pemetrexed (may be given on D1 prior to first dose of pemetrexed) and repeated approximately every 2 to 3 cycles (i.e., approximately every 8 weeks) starting with the third cycle until 3 weeks after the last dose of study therapy. The second and subsequent injections may be given $\pm$ 1 week in order to time it for the same day as chemotherapy treatment.

h-Toxicities that are felt to be possibly, probably or definitely related to treatment should be followed at least monthly until resolved.

Protocol Appendix 5.
Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:

- Hemoglobin
- Erythrocyte count (RBC)
- Leukocytes (WBC)
- Platelets
- Neutrophils, (sum of segmented and bands)
- Lymphocytes
- Monocytes

Clinical Chemistry:

- Total bilirubin
- Alkaline phosphatase (AP)
- Alanine aminotransaminase (ALT/SGPT)
- Aspartate aminotransaminase (AST/SGOT)
- Blood urea nitrogen (BUN)
- Serum creatinine
- Calculated creatinine clearance (CrCl)[b]
- Sodium
- Potassium
- Magnesium

Serum Pregnancy Test

a Assayed by local laboratory.

Protocol Appendix 6.
Abbreviations and Definitions

Abbreviations and Definitions

pemetrexed	pemetrexed, LY231514, multitargeted antifolate
ALT	alanine transaminase
ANC	absolute neutrophil count
AP	alkaline phosphatase
AST	aspartate transaminase
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
BUN	blood urea nitrogen
Compliance	Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements and the applicable regulatory requirements.
CR	Complete response
CrCl	creatinine clearance
CSF	colony stimulating factors
CT	computed tomography
CTC	common toxicity criteria
DHFR	dihydrofolate reductase
DLT	dose limiting toxicity
dTMP	deoxythymidine monophosphate
dUMP	deoxyuridine monophosphate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Enroll	See Study Entry Terms
Enter	See Study Entry Terms
FPGS	folylpolyglutamate synthase
GARFT	glycinamide ribonucleotide formyl transferase
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB/ERB	Institutional review board/ethical review board: a board or committee (institutional, regional, or national) composed of medical professional and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical trial are protected.
LBW	lean body weight

LCSS	Lung Cancer Symptoms Scale
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the [patient's/subject's] participation in the clinical trial.
LY231514	pemetrexed, pemetrexed, multitargeted antifolate
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MQA	Lilly Medical Quality Assurance
NS	not statistically significant
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
PD	progressive disease
PR	partial response
RBC	red blood cells (erythrocyte count)
RECIST	Response Evaluation Criteria in Solid Tumors (see Therasse et al. 2000)
Screen	See Study Entry Terms
SD	stable disease
Study Entry Terms	**Enter/Consent** The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives. **Enroll** The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
TS	thymidylate synthase
ULN	upper limit of normal
WBC	white blood cell (leukocyte count)