

## Redacted Protocol for Journal of Clinical Oncology

### **Protocol S124(b) (PARAMOUNT) A Phase 3, Double-Blind, Placebo-Controlled Study of Maintenance Pemetrexed plus Best Supportive Care versus Best Supportive Care Immediately Following Induction Treatment with Pemetrexed + Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer**

Pemetrexed (LY231514)

This is a randomized, double-blind, placebo-controlled Phase 3 study comparing pemetrexed plus best supportive care with placebo plus best supportive care as maintenance therapy in patients with Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or Stage IV non-small cell lung cancer.

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This redacted protocol includes excerpts for the following protocol topics:

- Selection of patients, including both eligibility and ineligibility criteria
- Schema and treatment plan, including administration schedule
- Rules for dose modification
- Measurement of treatment effect including response criteria, definitions of response and survival, and methods of measurement
- Reasons for early cessation of trial therapy
- Objectives and entire statistical section (including endpoints)

## 2. Objectives

### 2.1. Primary Objective

The primary objective of this study is to compare maintenance therapy with pemetrexed plus BSC versus placebo plus BSC, in terms of objective PFS time in patients with Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or IV nonsquamous NSCLC whose disease has not progressed during 4 cycles of pemetrexed and cisplatin induction chemotherapy.

### 2.2. Secondary Objectives

Secondary objectives of this study are to compare the following between randomized treatment arms:

- Time-to-event efficacy endpoint:
  - OS
- Objective tumor response rate
- Patient-reported outcomes using the EuroQol 5-dimensional scale (EQ-5D)
- Resource utilization
- Toxicity.

## 3. Investigational Plan

### 3.1. Summary of Study Design

This is a multicenter, randomized, placebo-controlled, double-blind, Phase 3 study comparing pemetrexed plus BSC with placebo plus BSC as maintenance therapy following first-line treatment with a pemetrexed-cisplatin combination chemotherapy in patients with advanced nonsquamous NSCLC. Figure S124.1 illustrates the study design.

The study will have 4 periods: a baseline period, an unblinded induction treatment period, a blinded maintenance treatment period, and a postdiscontinuation period.

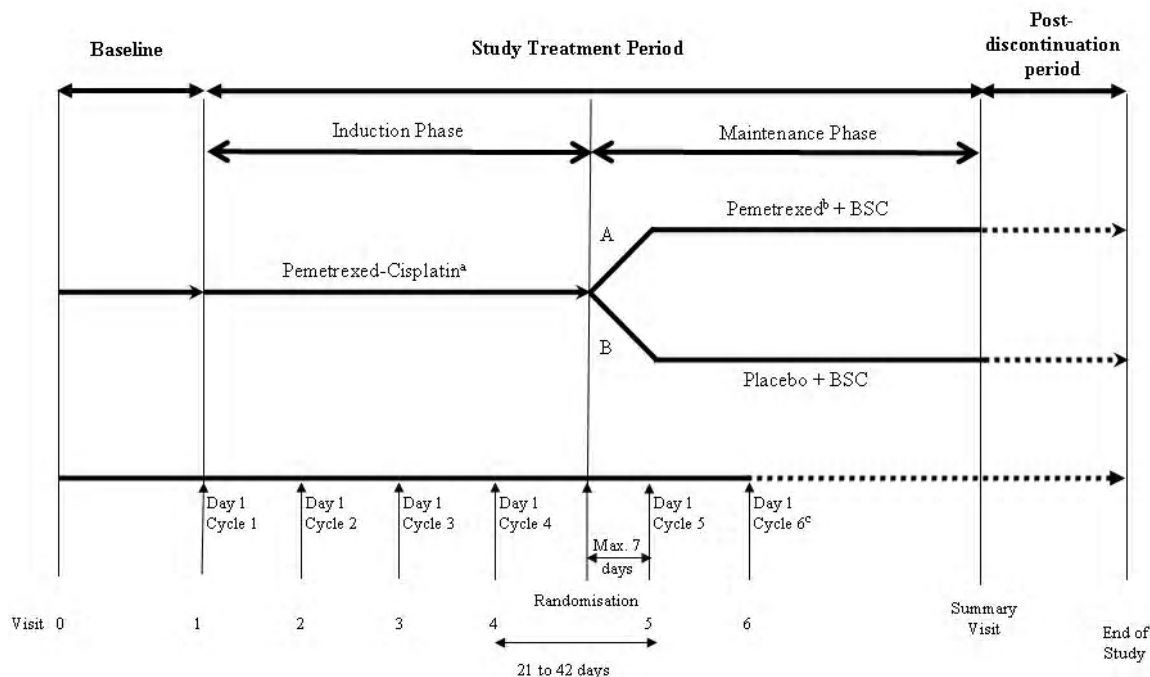
In the induction treatment period, eligible patients will receive 4 cycles of induction chemotherapy with pemetrexed and cisplatin. Patients who have a documented (confirmed or unconfirmed) response of CR, PR, or SD after completion of induction chemotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 will be considered eligible for randomization to maintenance treatment (see Section 4.3). Immediately following the induction treatment period, a minimum of 558 eligible patients will be randomized in a 2:1 ratio to pemetrexed plus BSC maintenance treatment (experimental Arm A, approximately 372 patients) or to placebo plus BSC maintenance treatment (control Arm B, approximately 186 patients). In order to randomize at least 558 eligible patients, it is expected that approximately 900 patients must be enrolled to this study.

Maintenance therapy should start at the time of randomization. If this is not possible, a maximum of 7 days will be allowed from the date of randomization to the start date of maintenance therapy. Maintenance therapy will end when the patient meets 1 of the prespecified reasons for discontinuation, including disease progression (as described in Section 4.4.1). Patients must start maintenance therapy no earlier than 21 days and no later than 42 days from Day 1 of the fourth cycle of induction therapy. During the entire study treatment period, all patients will receive standard folic acid and vitamin B<sub>12</sub> supplementation and prophylactic dexamethasone.

Terms used to describe the study periods are defined below:

- **Baseline:** Time from screening to first dose of induction therapy (or discontinuation, if no treatment is given).
- **Study Treatment:** For randomized patients, study treatment includes both the induction and maintenance treatment periods. For patients not eligible for randomization, study treatment is the induction treatment period.
  - **Induction Treatment Period:** Time from the start of induction treatment to either the date of randomization to maintenance treatment (for randomized patients) or to the date of discontinuation from study treatment (for patients not eligible for randomization).

- **Maintenance Treatment Period:** For randomized patients, the time from the date of randomization to the date of discontinuation from study treatment.
- **Postdiscontinuation Period:** Each patient will have a summary visit at the time of discontinuation from study treatment. The postdiscontinuation period includes the 30-day follow-up and long-term follow-up visits, and will continue until death or the end of study data collection.



Abbreviations: BSC = best supportive care.

<sup>a</sup> Pemetrexed (500 mg/m<sup>2</sup>, Day 1) plus cisplatin (75 mg/m<sup>2</sup>, Day 1).

<sup>b</sup> Pemetrexed (500 mg/m<sup>2</sup>, Day 1). Patients who require a dose reduction of pemetrexed during induction treatment, and who are eligible to receive maintenance treatment, will start blinded maintenance treatment (pemetrexed or placebo) at the reduced dose.

<sup>c</sup> Subsequent cycles during the maintenance phase should follow the same guidelines as Cycle 6. Patients may continue to receive study therapy until 1 of the reasons for discontinuation of study drug is met (see Section 4.4.1).

**Figure S124.1. Illustration of study design for Protocol H3E-EW-S124.**

### 3.1.1. Study Extension

This study will be considered complete following the final analysis for overall survival. All patients who continue to receive study treatment will be unblinded after the data have been validated for the final survival analysis. Following the final analysis, Lilly will determine if an extension phase is appropriate. Lilly will communicate this decision to investigators, and all patients who elect to participate in the extension phase will sign a new informed consent

document. All remaining on-study patients without disease progression will be permitted to transition into the extension phase of the study to continue to receive treatment with open-label pemetrexed until disease progression, death, unacceptable toxicity, patient refusal, or start of any new anticancer treatment, whichever occurs first.

## 4. Study Population

### 4.1. Inclusion Criteria for the Induction Phase

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

- [1] Histological or cytological diagnosis of NSCLC defined as other than predominantly squamous cell histology (squamous cell and/or mixed small cell, non-small cell histology is not permitted).
- [2] Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or Stage IV prior to induction therapy, as defined by the American Joint Committee on Cancer Staging Criteria for Lung Cancer, that is not amenable to curative therapy (Fleming et al. 1997).
- [3] ECOG performance status (PS) of 0 or 1 (Oken et al. 1982).
- [4] Patients must have had no prior systemic chemotherapy for lung cancer (see also Exclusion Criterion [22] below).
- [5] Patients with prior radiation therapy may be eligible for this study if they meet the following guidelines:
  - Previous radiation therapy is allowed to <25% of the bone marrow (Cristy and Eckerman 1987), but should have been limited and must not have included whole pelvis radiation.
  - Patients must have recovered from the toxic effects of the treatment prior to study enrollment (except for alopecia).
  - Prior thoracic radiotherapy must be completed 30 days before study enrollment.
  - Lesions that have been radiated cannot be included as sites of measurable disease unless clear tumor progression has been documented in these lesions since the end of radiation therapy.
  - Palliative extrathoracic radiotherapy to preexisting lesions may continue on study; however, these lesions may not be included as sites of measurable disease.
- [6] At least 1 unidimensionally measurable lesion meeting Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Positron emission tomography (PET) scans and ultrasounds may not be used for tumor measurements.
- [7] Estimated life expectancy of at least 12 weeks.
- [8] Patient compliance and geographic proximity that allow adequate follow up.
- [9] Adequate organ function, including the following:

- Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC)  $\geq 1.5 \times 10^9/L$ , platelets  $\geq 100 \times 10^9/L$ , and hemoglobin  $\geq 9$  g/dL.
- Hepatic: bilirubin  $\leq 1.5$  times the upper limit of normal ( $\times$  ULN); alkaline phosphatase (AP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)  $\leq 3.0 \times$  ULN (AP, AST, and ALT  $\leq 5 \times$  ULN is acceptable if liver has tumor involvement).
- Renal: calculated creatinine clearance (CrCl)  $\geq 45$  mL/min based on the original weight based Cockcroft and Gault formula (Cockcroft and Gault 1976).

[10] Patients must sign an informed consent document (ICD).

[11] Patients must be at least 18 years of age.

[12] For women: Must be surgically sterile, postmenopausal, or compliant with a highly reliable contraceptive method (failure rate  $< 1\%$ ) during and for 6 months after the treatment period; must have a negative serum or urine pregnancy test within 7 days before study enrollment and must not be breast-feeding.

For men: Must be surgically sterile or compliant with a contraceptive regimen during and for 6 months after the treatment period.

## 4.2. Exclusion Criteria for the Induction Phase

Patients will be excluded from the study if they meet **any** of the following criteria:

- [13] 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.
- [14] Have previously completed or withdrawn from this study or any other study investigating pemetrexed.
- [15] Have a serious concomitant systemic disorder (for example, active infection including human immunodeficiency virus) that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol.
- [16] Have a serious cardiac condition, such as myocardial infarction within 6 months, angina, or heart disease, as defined by the New York Heart Association Class III or IV.
- [17] Have had a prior malignancy other than NSCLC, carcinoma in situ of the cervix, or nonmelanoma skin cancer, unless that prior malignancy was diagnosed and definitively treated at least 5 years previously with no subsequent evidence of recurrence. Patients with a history of low-grade (Gleason score  $\leq 6$ ) localized prostate cancer will be eligible even if diagnosed less than 5 years previously.

- [18] Have central nervous system (CNS) metastases (unless the patient has completed successful local therapy for CNS metastases and has been off corticosteroids for at least 4 weeks before starting study therapy). A screening CT scan or magnetic resonance imaging (MRI) before enrollment in the absence of a clinical suspicion of brain metastases is not required.
- [19] Are receiving concurrent administration of any other antitumor therapy.
- [20] Have clinically significant (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.
- [21] Have received a recent (within 30 days of enrollment) or are receiving concurrent yellow fever vaccination.
- [22] Have received prior systemic anticancer therapy for lung cancer (including adjuvant early-stage treatment for NSCLC).
- [23] Are unable to interrupt aspirin or other nonsteroidal anti-inflammatory agents, other than an aspirin dose  $\leq 1.3$  grams per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).
- [24] Are unable or unwilling to take folic acid, vitamin B<sub>12</sub> supplementation, or corticosteroids.

### **4.3. Inclusion Criteria at Randomization (Maintenance Phase)**

After completion of 4 cycles of induction chemotherapy, patients will be evaluated for eligibility to receive maintenance therapy. In order to receive double-blind maintenance therapy, patients must meet the following criteria:

- [25] ECOG PS of 0 or 1.
- [26] Documented radiographic evidence of a tumor response of CR, PR, or SD. Tumor assessment must occur between Cycle 4 (Day 1) of induction therapy and the date of randomization. This response does not have to be confirmed in order for the patient to be randomized (RECIST; Therasse et al. 2000).

### **4.4. Discontinuations**

#### **4.4.1. Discontinuation of Patients**

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient is to be discontinued from the study drug but can be allowed to continue in the study in order to provide the follow-up data needed for the analysis of the entire intention-to-treat population. An exception may be granted in rare circumstances where the patient has a serious or life-threatening condition for which there is no effective alternative therapy and, in the opinion of the investigator, is receiving benefit from study drug. In these rare cases, the investigator must obtain documented approval from Lilly to allow the patient to continue to receive study drug.



In addition, patients will be discontinued from study treatment in the following circumstances:

- The investigator decides that the patient should be withdrawn from study treatment. If this decision is made because of toxicity, a serious AE (SAE), 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.
- The patient or attending physician requests that the patient be withdrawn from study treatment.
- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from study treatment should occur immediately upon introduction of the new agent.
- The investigator or Lilly, for any ethical, medical, or scientific reason, while considering the rights, safety, and well-being of the patient(s), stops the study or stops the patient's participation in the study.
- The patient has evidence of progressive disease (PD).
- 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 has had 2 (Day 1) dose reductions and experiences an AE that would cause a third dose reduction.
- The patient cannot receive study treatment within 42 days of the beginning of the previous cycle, unless continuation is approved by Lilly.

Patients who discontinue the study drug early will have end-of-therapy procedures performed as shown in the Study Schedule of Events.

#### **4.4.2. Discontinuation of Study Sites**

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board of the study site judges it necessary for any reason.

#### **4.4.3. Discontinuation of the Study**

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.

## 5. Treatment

### 5.5. Selection and Timing of Doses

A cycle is defined as an interval of 21 days (a delay of a cycle due to holidays, weekends, and bad weather or other unforeseen circumstances will be permitted and not counted as a protocol violation). The actual doses of pemetrexed and cisplatin administered will be determined by calculating the body surface area at the beginning of each cycle. A  $\pm 5\%$  variance in the calculated total dose will be allowed for ease of dose administration.

Patients will receive 4 cycles of pemetrexed-cisplatin chemotherapy during the induction phase of the treatment period. Patients who achieve a response of CR, PR, or SD after completing 4 cycles of induction chemotherapy and have an ECOG PS of 0 or 1 will be eligible to receive double-blind maintenance therapy. At Cycle 5, eligible patients will be randomly assigned to 1 of 2 double-blind maintenance therapies, as described below:

Experimental Arm A: pemetrexed 500 mg/m<sup>2</sup> administered intravenously on Day 1 every 21 days, plus BSC.

Control (Placebo) Arm B: normal saline (0.9% sodium chloride) administered intravenously on Day 1 every 21 days, plus BSC.

Maintenance therapy should begin at the time of randomization at Cycle 5. If this is not possible, a maximum of 7 days will be allowed from time of randomization to start of maintenance therapy. Patients must start maintenance therapy no earlier than 21 days and no later than 42 days from Cycle 4, Day 1. Maintenance therapy will continue until the patient meets 1 or more of the specified reasons for discontinuation, including disease progression (as described in Section 4.4.1).

Dosage and administration during the induction and maintenance phases of the treatment period is summarized in Table S124.1 and Table S124.2, respectively.

**Table S124.1. Drug Dosage and Administration During the Induction Phase of the Treatment Period (All Patients, Cycles 1 to 4)**

Drug	Dose	Administration
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Pemetrexed	500 mg/m <sup>2</sup>	IV infusion over approximately 10 minutes on Day 1.
Cisplatin	75 mg/m <sup>2</sup>	Cisplatin therapy should be immediately preceded and followed by hydration procedures and administered according to local practice and labels. The protocol permits (but does not require) that cisplatin doses may be calculated up to a maximum BSA of 2.0 m <sup>2</sup> , according to local cisplatin labels. IV infusion approximately 30 minutes after the pemetrexed infusion.

Abbreviations: BSA = body surface area; IV = intravenous.

**Table S124.2. Drug Dosage and Administration During the Maintenance Phase of the Treatment Period (Cycle 5+)**

Treatment Arm <sup>a,b</sup>	Drug	Dose	Administration
Arm A (Pemetrexed plus BSC)	Pemetrexed	500 mg/m <sup>2</sup>	IV infusion over approximately 10 minutes on Day 1.
Arm B (Placebo Plus BSC)	Normal saline	Not applicable	IV infusion over approximately 10 minutes on Day 1 (target volume: 100 mL; acceptable range: 75 to 125 mL)

Abbreviations: BSC = best supportive care; ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous.

- <sup>a</sup> Patients who have received 4 cycles of pemetrexed-cisplatin chemotherapy and do not have clear evidence of progressive disease (either objectively determined or clinical progression) and have an ECOG PS of 0 or 1 will be randomized to receive either pemetrexed (500 mg/m<sup>2</sup> on Day 1 of each 21-day cycle, starting at Cycle 5) plus BSC or placebo plus BSC.
- <sup>b</sup> Patients who require a dose reduction of pemetrexed during induction treatment, and who are eligible to receive maintenance treatment, will start blinded maintenance treatment (pemetrexed or placebo) at the reduced dose.

Table S124.3 summarizes supplementation with folic acid and vitamin B<sub>12</sub> and prophylaxis with dexamethasone for both phases of the treatment period. All randomized patients will be required to take vitamin supplementation and dexamethasone during the maintenance phase of the treatment period to maintain the double-blind design of the study.

**Table S124.3. Supplementation and Prophylactic Therapy During the Induction and Maintenance Phases of the Treatment Period**

Drug	Dose	Administration
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Folic Acid (supplementation)	350-1000 µg	Oral dosage daily: At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
Vitamin B <sub>12</sub> (supplementation)	1000 µg	IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B <sub>12</sub> injections may be given the same day as pemetrexed administration.
Dexamethasone (prophylaxis)	4 mg, orally twice per day (or equivalent)	Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for reasons other than routine rash prophylaxis (e.g., antiemetic prophylaxis).

Abbreviation: IM = intramuscular.

### 5.5.1. Dose Adjustments or Delays for Subsequent Cycles

Treatment may be delayed for up to 42 days to allow a patient sufficient time for recovery from study drug-related toxicity. A patient who cannot be administered the study drug for 42 days from the time of last treatment must be discontinued from the study.

Any patient who requires a dose reduction will continue to receive the reduced dose for the remainder of the study. Any patient who has had 2 dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from study therapy. No dose escalations are allowed in this study. Patients who require a dose reduction of pemetrexed during induction treatment, and who are eligible to receive maintenance treatment, will start blinded maintenance treatment (pemetrexed or placebo) at the reduced dose.

Because the maintenance phase of this study is double-blinded, the investigators will not know the treatment assignments of their patients for the maintenance period. Therefore, it is expected that the investigators will treat all patients as if the patients had received pemetrexed and will adjust doses accordingly.

#### 5.5.1.1. Hematological Toxicity

Dose adjustments at the start of a subsequent course of therapy will be based on platelet and neutrophil counts from the preceding cycle of therapy. The ANC must be  $\geq 1.5 \times 10^9/L$ , and platelets must be  $\geq 100 \times 10^9/L$  before the start of any cycle. Treatment should be delayed to allow sufficient time for recovery. Upon recovery, if treatment is resumed, it must be according to the guidelines provided (Table S124.4). Hematologic toxicities not listed in Table S124.4 do not require dose adjustments.

**Table S124.4. Dose Adjustments for Pemetrexed and Cisplatin Based on Hematologic Values for Preceding Cycle**

Platelets ( $\times 10^9/L$ )		ANC ( $\times 10^9/L$ )	Percentage of Previous Dose <sup>a,b</sup> (Both Drugs)
$\geq 50$	and	$\geq 0.5$	100%

$\geq 50$	and	$< 0.5$	75%
$< 50$	and	Any	75%
$< 50$ with bleeding <sup>c</sup>	and	Any	50%
Any	and	$< 1.0$ plus fever of $\geq 38.5^\circ\text{C}$ <sup>c</sup>	75%
Recurrence of CTCAE Grade 3 or 4 thrombocytopenia after 2 dose reductions	or	Recurrence of CTCAE Grade 3 or 4 neutropenia after 2 dose reductions	Discontinue patient from study

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for AEs.

<sup>a</sup> Dose adjustments for pemetrexed are applicable during both the induction and maintenance treatment periods.

<sup>b</sup> Dose adjustments for cisplatin are only applicable during the induction phase of the treatment period (Cycles 1-4).

<sup>c</sup> Criteria meet the CTCAE version 2.0 definition of  $\geq$ Grade 2 bleeding.

### 5.5.1.2. Creatinine Clearance

CrCl will be based on the original weight based Cockcroft and Gault formula. CrCl must be  $\geq 45$  mL/min prior to the start of any cycle. If a patient's CrCl value has not returned to  $\geq 45$  mL/min within 42 days of last study drug administration, the patient must be discontinued from the study treatment unless continuation is approved by the Lilly clinical research physician.

### 5.5.1.3. Nonhematological Toxicity

In general, for nonhematologic toxicities greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and considered related to study treatment, treatment should be delayed until resolution to less than or equal to the patient's baseline value before resuming treatment. However, an exception may be made for Grade 2 neurotoxicity. The investigator and patient may decide to continue treatment at a reduced dose, with no delay required, as neurotoxicity may not resolve to baseline values. Dose reductions at the start of the subsequent cycle will be based on maximum nonhematologic toxicities from the dose administered in the preceding cycle. Table S124.5 provides the relevant dose adjustments of pemetrexed and cisplatin for nonhematologic toxicities.

**Table S124.5. Dose Adjustments for Pemetrexed and Cisplatin Based on Nonhematologic Toxicities for Preceding Cycle**

CTCAE Grade	Percentage of Previous Dose	
	Pemetrexed <sup>a</sup>	Cisplatin <sup>b</sup>
Grade 3 or 4 nausea or vomiting	100%	100%
Grade 3 or 4 diarrhea or any grade requiring hospitalization	75%	75%
Grade 2 neurotoxicity <sup>c</sup>	100%	50%
Grade 3 or 4 neurotoxicity	Discontinue treatment	Discontinue treatment
Grade 3 or 4 transaminase elevations	75%	75%
Grade 3 or 4 mucositis	50%	100%
Other Grade 3 or 4 nonhematologic CTCAE toxicity	75%	75%
Recurrence of Grade 3 or 4 CTCAE toxicity after treatment at 2 dose reductions	Discontinue treatment	Discontinue treatment

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

- <sup>a</sup> Dose adjustments for pemetrexed are applicable during both the induction and maintenance treatment periods.
- <sup>b</sup> Dose adjustments for cisplatin are only applicable during the induction phase of the treatment period (Cycles 1-4).
- <sup>c</sup> Delay until resolution of toxicity to baseline value is not required for Grade 2 neurotoxicity.

#### **5.5.1.4. Clinically Significant Effusions**

For patients who develop clinically significant pleural or peritoneal effusions (determined on the basis of symptoms or clinical examination) prior to first dose of study drug or during therapy, draining the effusion prior to dosing is required. However, if, in the investigator's opinion, the effusion represents progression of disease, the patient should discontinue therapy and enter the postdiscontinuation period.

#### **5.5.1.5. Insufficient Folic Acid or Vitamin B12 Supplementation**

The first dose of pemetrexed is not to be given until the patient has taken folic acid for at least 5 of the 7 days immediately preceding the first dose of pemetrexed. Subsequent doses of pemetrexed have to be delayed until the patient has taken folic acid for at least 14 of the 21 days before Day 1 of the next cycle.

Patients are to receive an IM injection of vitamin B<sub>12</sub> (1000 µg) in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B<sub>12</sub> injections may be given the same day as pemetrexed administration.

### **6.1. Efficacy Measures**

#### **6.1.1. Timing of Measurements**

##### **6.1.1.1. Baseline and Study Treatment Periods**

Within 4 weeks before the first dose of study drug, baseline tumor measurement(s) will be performed on each patient. Computed tomography (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. The sponsor will collect and store all tumor measurement images on all enrolled patients throughout the study.

The study will not permit ultrasound or PET scans as methods of tumor measurement. The method used at baseline must be used consistently for tumor assessment and will be repeated every other cycle (6 weeks ± 1 week). All patients should have a tumor assessment performed during Cycle 4, prior to being randomized into the maintenance phase, in order to determine eligibility. This tumor assessment will serve as the baseline maintenance assessment, for those patients who are randomized to maintenance treatment.

For patients with CR, PR, or SD in the induction phase, the response does not have to be confirmed in order for the patient to be randomized into the maintenance phase. Following randomization, responses must be confirmed according to RECIST guidelines. **Confirmation of response will occur no less than 4 weeks from the first evidence of response.** Thereafter, a responding patient will be followed every other cycle (6 weeks ± 1 week).

#### **6.1.1.2. Postdiscontinuation Period**

Patients will continue treatment until they require discontinuation of drug for 1 of the reasons cited in Section 4.4 of this document (including disease progression). Each enrolled patient will enter a postdiscontinuation period once study treatment is discontinued.

For those patients who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response (every 6 weeks  $\pm$  1 week) by the same method used at baseline and throughout the study until the patient has objective disease progression based on lesion measurements or study closure. Once the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed up approximately every 90 days ( $\pm$  14 days) until death or study closure.

For patients with a tumor response during maintenance treatment, a confirmation of tumor response by the same method used at baseline and throughout the study must be obtained (if not already done) according to RECIST guidelines.

The date of first documented objective disease progression must be recorded on the eCRF even if it occurs after the patient has started a new therapy. During the postdiscontinuation period, information will be collected regarding date of disease progression, death, and postdiscontinuation anticancer systemic therapy, radiotherapy, or surgical intervention.

#### **6.1.2. Efficacy Criteria for Tumor Response**

During induction treatment, cycle responses will be documented and reported by investigative sites. The response to induction treatment does not have to be confirmed in order for the patient to be randomized; however, a tumor assessment must occur between Cycle 4 (Day 1) of induction therapy and the date of randomization, in order to determine eligibility for randomization. This assessment will serve as the baseline assessment for the maintenance treatment phase, for randomized patients.

An independent review of imaging scans will be performed by Lilly or designee. CT scans will be collected only for the maintenance period, for all randomized patients, including the lesion assessment performed after Cycle 4 of induction to assess eligibility just prior to randomization. These CT scans will be reviewed by an independent panel of radiologists. Tumor responses will be measured and recorded using the RECIST guidelines.

Best response is determined from the sequence of responses assessed. For CR or PR, best response must be confirmed. A second assessment must be performed  $\geq$ 28 days after the first evidence of response. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Best response of SD is defined as disease that does not meet the criteria for CR, PR or PD and has been evaluated at least 1 time, at least 6 weeks after the start of study treatment.

Response to induction therapy will be based on tumor assessments performed at baseline (before the start of induction therapy) and those performed before initiation of maintenance therapy.

For patients randomized into the maintenance phase, the following tumor assessments will be considered:

- **Response to Whole Treatment (Induction and Maintenance):** All tumor assessments performed during the study (until initiation of a new anticancer therapy) will be considered.
- **Response to Maintenance Treatment Only:** The last tumor assessment performed before randomization will be considered as baseline and all subsequent assessments (until initiation of a new anticancer therapy) will be used to assess response to the maintenance therapy.

### **6.1.3. Definition of Efficacy Measures**

A responder to induction therapy is defined as any patient who exhibits a confirmed or unconfirmed CR or PR according to the RECIST guidelines. When assessing response to whole treatment or to maintenance therapy, a responder is defined as any patient who exhibits a confirmed CR or PR according to the RECIST guidelines.

Other definitions are listed below.

- **Objective Progression-Free Survival (PFS) Time:** Objective PFS time is defined as the time from the date of randomization to the first date of objectively determined PD or death from any cause. For patients not known to have died as of the data cut-off date and who do not have objective PD, PFS will be censored at the date of the last objective progression-free disease assessment.
- **Overall Survival (OS) Time:** OS time is defined as the time from the date of randomization to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS will be censored at the last contact date (last contact for patients in postdiscontinuation period = last known alive date in mortality status).

Both PFS and OS will also be summarized and analyzed based on changing the definitions above so as to measure times from the start date of induction therapy. However, the definitions above based on randomization date will be considered primary for purposes of statistical inference within this study.

## **6.2. Patient-reported Outcomes**

Patient-reported outcomes will be measured using a standardized instrument, the EQ-5D. This instrument measures various health outcomes and is applicable to a wide range of health conditions and treatments (EuroQol Group 1990).

The EQ-5D consists of 2 parts. The first part includes 5 descriptive questions relating to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, on which the patient is required to rate his/her health. Each attribute has 3 levels: no problem, some problems, and major problems, thus defining 243 possible health states, to which has been added “unconscious” and “dead” for a total of 245 in all.



The second part of the EQ-5D is a visual analog scale (VAS) that allows patients to rate their present health condition. Possible scores range from 0 (worst imaginable health state) to 100 (best imaginable health state).

The 245 health states defined by the 5-dimensional descriptive system can be converted into a weighted health state index by applying a method described in detail by Dolan (1997). This method permits the measurement of preferences. The possible values for health utility ranges are from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in all dimensions) on a scale where 0 represents death and 1 represents the best possible health state.

As of January 2008, the EQ-5D has been translated and validated into 81 official languages, including French, German, and Spanish (see EuroQol website; <http://www.euroqol.org>). The EQ-5D will only be completed by patients for whom a translation is available in his/her native language.

The EQ-5D, a self-administered health-status questionnaire, will be completed by the patient at the following timepoints:

- At baseline, after consent
- On Day 1 of each cycle of induction therapy. (The Cycle 1 Day 1 assessment does not have to be completed if the baseline assessment is completed within 7 days prior to Day 1 of Cycle 1)
- On Day 1 of each cycle of maintenance therapy
- At the 30-day postdiscontinuation visit

On days that the patient receives chemotherapy (including placebo for those patients randomized to placebo + BSC during maintenance therapy), assessments will be completed prior to treatment administration.

### **6.3. Resource Utilization**

Investigators will be asked to document the use of BSC measures, concomitant medications, transfusions, treatment complications, and treatment-related hospitalization days. Such assessments are to be taken throughout the study until the 30-day postdiscontinuation visit.

## 8. Sample Size and Statistical Methods

### 8.1. Determination of Sample Size

Immediately following the induction treatment period, a minimum of 558 qualified patients will be randomized in a 2:1 ratio to pemetrexed plus BSC maintenance treatment (experimental Arm A, approximately 372 patients) or to placebo plus BSC maintenance treatment (control Arm B, approximately 186 patients). In order to randomize at least 558 qualified patients, it is expected that approximately 900 patients must be treated during the induction treatment period.

Type 1 (alpha) error will be controlled for the analyses of both PFS and OS so as to maintain an overall two-sided alpha level of 0.05. At the time of the PFS analysis, all study outcomes will be analyzed. However, at this time the analysis of OS will be considered preliminary (approximately 18 to 24 months prior to the final, updated analysis of OS). In order to maintain an overall two-sided alpha error probability of 0.05 (controlling both PFS and OS analyses), the following statistical gatekeeping and alpha-spending scheme will be applied:

- The primary statistical test of PFS will be performed using a nominal two-sided alpha level of 0.05.
- A two-sided nominal alpha level of 0.05 will be split between the preliminary and final analyses of OS: a nominal two-sided level of 0.0001 will be spent for the preliminary analysis of OS, leaving a nominal level of 0.0499 to be spent for the final analysis of OS. If the primary test of PFS is statistically significant, then by application of statistical gatekeeping the overall two-sided alpha level will be maintained at 0.05.

The sample size of 558 randomized patients was selected for this study so as to provide 93% statistical power for the final analysis of OS. The sample size of 558 randomized patients was derived assuming the true OS hazard ratio (HR) is 0.70 and assuming 30% censoring in the final analysis of OS. Under these assumptions, the final unadjusted log-rank test of OS will have 93% power to show a statistically significant difference between arms provided that there are 390 events (30% censoring) included in the analysis (Freedman 1982). Therefore, the final analysis of OS should take place only after a minimum of 390 deaths have been confirmed among the randomized patients.

Under the assumption that the true PFS hazard ratio (HR) is 0.65, the primary unadjusted log-rank test of PFS will have 90% power to show a statistically significant difference between arms provided that there are at least 238 events included in the analysis (Freedman 1982). Therefore, the primary analysis of PFS will take place after at least 238 events (52% censoring) of progressive disease or death have been confirmed among randomized patients.

### 8.2. Statistical and Analytical Plans

#### 8.2.1. General Considerations

Efficacy and safety analyses will be performed for all randomized patients, grouped as randomized. Investigator assessments of radiological data will be considered primary for the

analyses of PFS and objective tumor response rate. An independent review of radiological data (lesion measurements based on CT scans) will be conducted and any revision of measurements resulting from the review will be used for sensitivity analyses.

Basic summary analyses will also be performed for nonrandomized patients treated during the induction phase of the study. Analysis of nonrandomized patient data will be considered exploratory.

The interpretation of final study results will be the responsibility of the clinical research physician and statistician. These individuals will also be responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication by Lilly.

Any change to the data analysis methods described in the protocol will require an amendment *only* if it changes a principal feature of the protocol. Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan. Any retrospective or exploratory analyses not defined by the protocol or the statistical analysis plan will be explained in the clinical study report.

This study will be considered complete following final validation and authorization to “lock” the database (after the final survival analysis). With a “locked” final database, the study may be closed and further data collection stopped. The Lilly clinical research physician will notify investigators in the event of study closure and the decision to stop collecting data.

All baseline and efficacy analyses will use the intent-to-treat (randomized) population, as defined below:

- For the induction phase, all patients who receive at least 1 dose of either induction study treatment (pemetrexed or cisplatin)
- For the maintenance phase, all patients who were randomized, and analyzed according to the therapy assigned by the randomization system.

Refer to Section 8.2.10 for the population used for the safety analyses.

### **8.2.2. Patient Disposition**

A detailed description of patient disposition will be provided. It will include:

- Summary of patients entered and enrolled by country
- Total number of patients entered
- Total number of patients enrolled
- Total number of patients randomized
- Summary of reasons for patients entered, but not enrolled
- Total number of patients randomly assigned to treatment by treatment arm

- Total number of patients treated by treatment arm
- Summary of reasons for patients randomly assigned but not treated.

A detailed summary of reasons for patient discontinuation from study treatment will be provided by treatment phase.

A summary of all identified important protocol violations will be provided.

### **8.2.3. Patient Characteristics**

Patient characteristics will include summaries for both the induction period and those randomized to maintenance treatment for the following:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies.

Other patient characteristics will be summarized as deemed appropriate.

### **8.2.4. Concomitant Therapy**

Concomitant medications and BSC measures will be summarized for all patients treated with at least 1 dose of pemetrexed or cisplatin in the induction phase, and for all randomized patients by treatment arm.

### **8.2.5. Treatment Compliance**

Dose omissions, reductions, and delays will be summarized for all treated patients, by treatment phase (induction/maintenance) and per treatment arm during maintenance.

### **8.2.6. Alpha-Controlled Efficacy Analyses**

The analyses of PFS and OS will be analyzed with an overall controlled two-sided alpha level of 0.05. See Section 8.1 for details of alpha allocation.

### **8.2.7. Additional Efficacy Analyses**

For PFS and OS, the following additional analyses will be performed:

- The Kaplan-Meier method will be used to estimate parameters for time-to-event analysis on each treatment group (medians, quartiles, percentages of patients event-free every 3-month interval).
- Hazard ratios will be estimated using the Cox proportional hazards model with assigned treatment as the only covariate, and reported with 2-tailed 95% confidence intervals (CIs).
- Cox regression models with treatment and potential prognostic factors will be used for further exploration of the data.

Tumor response to induction treatment (in all patients treated during the induction phase of the study) will be evaluated considering the radiological assessment performed before the start of induction therapy as baseline for this analysis. This analysis will exclude any radiological assessments performed after randomization to maintenance therapy. Tumor response rate to induction therapy will be calculated as the proportion of these patients who achieve a CR or PR (confirmed or not). Tumor response rate will be reported with a 95% CI (Leemis and Trivedi 1996).

The tumor response to maintenance therapy will be evaluated considering the last radiological assessment performed before randomization as baseline for this analysis. Tumor response rates to maintenance therapy will be calculated as the proportion of randomized patients in each treatment arm who achieve a confirmed CR or PR. Disease control rates to maintenance therapy will be calculated as the proportion of randomized patients in each treatment arm who achieve a confirmed CR, PR, or SD. Tumor response rates and disease control rates will be reported with 95% CIs (Leemis and Trivedi 1996) and will be compared between randomization arms using the Fisher exact test.

Tumor response to whole treatment (induction and maintenance) will be evaluated considering the radiological assessment performed before the start of induction therapy as baseline for this analysis. All radiologic assessments performed after the baseline assessment will be included in this analysis. Tumor response rates to whole treatment will be calculated as the proportion of randomized patients in each treatment arm who achieve a confirmed CR or PR. Tumor response rates to whole treatment will be reported with 95% CIs (Leemis and Trivedi 1996) and will be compared between randomization arms using the Fisher exact test.

Additional analyses may be performed if deemed appropriate and will be further explained in the statistical analysis plan.

### **8.2.8. Patient-reported Outcomes Analyses**

All enrolled patients that have provided baseline and at least 1 subsequent measurement for EQ-5D will be included in the analysis of patient-reported outcomes.

Findings of the EQ-5D will be summarized for all patients enrolled at baseline; at each cycle of treatment during the induction period for all patients eligible to receive study treatment; at each cycle of treatment during the maintenance phase by randomized treatment arms.

Responses for the 3 levels of the 5 dimensions will be summarized. Mean index and VAS scores will be calculated. Frequency distributions, including measures of central tendency and variability (for example, means, medians, and standard deviations), will be calculated for individual items and for the total scale.

The index and VAS scores will be analyzed using a mixed effects analysis of variance model. Of interest are the cycle administration-specific treatment group comparisons (Arms A and B) for each of the items addressing whether treatment group profiles are different over time (from randomization through the last assessment postdiscontinuation).

Other statistical analyses methods may be explored, as deemed appropriate.

### **8.2.9. Resource Utilization Analyses**

All patients treated with study therapy will be included in the analysis of resource utilization.

Resource utilization data (including concomitant medications, BSC measures, treatment-related hospitalization days) will be summarized for all patients enrolled into the induction phase, and for all randomized patients by treatment arm.

### **8.2.10. Safety Analyses**

All patients enrolled in the study (treated with at least 1 dose of pemetrexed or cisplatin during the induction phase) will be evaluated for safety. All of the safety analyses will be performed by treatment phase (induction/maintenance) and by randomization arm for the maintenance phase. All randomized patients will be qualified for the maintenance phase safety analyses.

Safety analyses will include summaries of the incidence of AEs by maximum CTCAE grade (Version 3.0, NCI 2006) that occur during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality. Additionally, the following safety-related outcomes will be summarized:

- study treatment discontinuations due to AEs
- deaths during the study treatment period or within 30 days of the last dose of study treatment
- SAEs during the study treatment period or within 30 days of the last dose of study treatment
- treatment-emergent AEs during the study treatment period or within 30 days of the last dose of study treatment
- hospitalizations and transfusions during the study treatment period or within 30 days of the last dose of study treatment
- select concomitant medications, including growth factors (erythropoietin, G-CSF, granulocyte-macrophage colony-stimulating factor [GM-CSF]), anti-emetics, and antibiotics, during the study treatment period or within 30 days of the last dose of study treatment.

Additional analyses may be performed if deemed appropriate and will be further explained in the statistical analysis plan.

### **8.2.11. Interim Analyses**

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly regulatory scientist will be consulted to determine whether it is necessary to amend the protocol.

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