The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

PointBreak: A Randomized Phase III Study of Pemetrexed plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab versus Paclitaxel plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients with Stage IIIB or IV Nonsquamous Non-Small Cell Lung Cancer

Patel, et al

DOI: 10.1200/JCO.2012.47.9626

Protocol H3E-MC-JMHD(e)
Randomized, Open-Label, Phase 3 Study of Pemetrexed plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab versus Paclitaxel plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients with Stage IIIB or IV Nonsquamous Non-Small Cell Lung Cancer

Pemetrexed (LY231514)

This is a randomized, open-label, Phase 3 study in patients with Stage IIIB or IV nonsquamous non-small cell lung cancer. Approximately 900 patients will be randomized in a 1:1 ratio to receive pemetrexed, carboplatin, and bevacizumab followed by maintenance pemetrexed plus bevacizumab (Arm A) or paclitaxel carboplatin, and bevacizumab followed by maintenance bevacizumab (Arm B).

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol Approved by Lilly: 11 August 2008
Protocol (a) Approved by Lilly: 05 September 2008
Protocol (b) Approved by Lilly: 03 April 2009
Protocol (c) Approved by Lilly: 28 April 2010
Amendment (d) Approved by Lilly: 02 February 2011
Amendment (e) approval date provided below.

Approval Date: 09-Aug-2012 GMT

Randomized, Open-Label, Phase 3 Study of Pemetrexed plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab versus Paclitaxel plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients with Stage IIIB or IV Nonsquamous Non-Small Cell Lung Cancer

Table of Contents

Listing of Tables

Table **Page**

Listing of Figures

Figure **Page**

Table of Contents (concluded)

Appendices

Abbreviations and Definitions

AE	adverse event
Assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some Institutional Review Boards [IRBs]).
AUC	area under the curve
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, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirements.
Blinding/Masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignments. Single-blinding usually refers to the patients being unaware, and double-blinding usually refers to the patients, investigators, monitors, and in some cases, select sponsor personnel being unaware of the treatment assignments.
CI	confidence interval
CNS	central nervous system
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form (sometimes referred to as clinical report form): a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRO	contract research organization

CSF	colony-stimulating factor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate (CR + PR + SD)
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
End of trial	End of trial is the date of the last visit or last scheduled procedure shown in the Extension Period Schedule for the last patient.
Enroll	See Study entry terms
Enter	See Study entry terms
ESA	erythropoiesis-stimulating agent
FACT	Functional Assessment of Cancer Therapy
GFS	glomular filtration rate
HR	hazard ratio
ICD	informed consent document
IDMS	Isotope Dilution Mass Spectrometry
Interim analysis	Any analysis intended to compare treatment groups at any time prior to the formal completion of a trial.
Intent to treat (ITT)	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
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 and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
IVRS	interactive voice response system

Legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical trial.
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OS	overall survival
Patient	A subject with a defined disease.
PFS	progression-free survival
PK	pharmacokinetic/pharmacokinetics
PR	partial response
QOL	quality of life
RECIST	Response Criteria in Solid Tumors
RR	response rate
SAE	serious adverse event
SD	stable disease
study completion	This study will be considered complete after the final analysis of overall survival, after the time of the prespecified number of overall survival events.
Study entry terms	**Screen** The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, x-rays and blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study. **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/Randomize** 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.
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

30-day postdiscontinuation follow-up period	The 30-day postdiscontinuation follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. The 30-day postdiscontinuation follow-up visit occurs at or near the end of the 30-day postdiscontinuation follow-up period (see Figure JMHD.3).
Treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms).
TTPD	time to progressive disease
UPCR	urine protein to creatinine ratio
VEGF	vascular endothelial growth factor

Randomized, Open-Label, Phase 3 Study of Pemetrexed plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab versus Paclitaxel plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients with Stage IIIB or IV Nonsquamous Non-Small Cell Lung Cancer

1. Introduction

1.1. Lung Cancer

Lung cancer is the most common cancer in the world and the leading cause of cancer-related mortality. For 2007, the American Cancer Society (ACS) projected 1.5 million new cases and 1,351,000 deaths worldwide (ACS 2007), despite improvements in lung cancer care that have occurred over the past 2 decades. In 2008, an estimated 215,020 new cases of lung cancer and 161,840 deaths from lung cancer are predicted to occur in the United States (ACS 2008). Approximately 85% of lung cancers are non-small cell (NSCLC; Lustberg and Edelman 2007), and approximately 70% of patients with NSCLC present with inoperable, locally advanced (Stage IIIB) or metastatic (Stage IV) disease (Boulikas and Vougiouka 2004).

1.2. Current Treatment of Advanced Non-Small Cell Lung Cancer

Most patients with inoperable NSCLC are candidates for palliative chemotherapy consisting of standard induction therapy with 4 to 6 cycles of a platinum-based chemotherapy doublet, per American Society of Clinical Oncology (ASCO [Pfister et al. 2004]) and European Society for Medical Oncology (ESMO [D'Addario and Felip 2008]) guidelines.

Recent reviews and meta-analyses of randomized trials in advanced NSCLC have suggested that 4 cycles is the optimal duration of platinum-based first-line treatment, regardless of response to initial therapy; platinum-based chemotherapy beyond 4 cycles was found to improve progression-free survival (PFS) but not overall survival (OS), and led to increased toxicity (Larsen et al. 1995; Smith et al. 2001; Socinski et al. 2002; Lustberg and Edelman 2007; Park et al. 2007; Socinski and Stinchcombe 2007; Soon et al. 2007).

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized study comparing 4 of the platinum-based doublets most commonly used in the United States (cisplatin-paclitaxel [control], cisplatin-gemcitabine, cisplatin-docetaxel, and carboplatin-paclitaxel). The study (ECOG 1594) demonstrated no significant difference among study arms with respect to response rate (RR) or OS (Schiller et al. 2002), and ECOG chose carboplatin-paclitaxel as its reference regimen for future studies.

In 2006, bevacizumab received FDA approval as an initial therapy for advanced NSCLC on the basis of Study ECOG 4599 (Sandler et al. 2006; see Section 1.4.1). Approval was based on

improvement in OS for bevacizumab when combined with carboplatin-paclitaxel, as compared with the platinum doublet alone. This triplet regimen is now recommended by the National Comprehensive Cancer Network (NCCN 2008) for patients with advanced, nonsquamous NSCLC and has become a standard of care in that setting.

Maintenance therapy for advanced NSCLC has also been explored in a large number of studies, although most were powered only for assessment of the entire regimen, and not just the maintenance phase of therapy (Prior et al. 1999; Socinski et al. 2002; Belani et al. 2004, 2005; Herbst et al. 2004; Brodowicz et al. 2006; Davies et al. 2006; Sandler et al. 2006; Manegold et al. 2007). Despite methodological problems, studies with docetaxel (Sekine et al. 2006; Fidias et al. 2007), paclitaxel (Belani et al. 2005), gemcitabine (Brodowicz et al. 2006), and bevacizumab (Sandler et al. 2006) have suggested possible benefit of single-agent treatment beyond the recommended 4 to 6 cycles of platinum-based chemotherapy.

Second-line therapy with agents such as pemetrexed, docetaxel, and erlotinib constitutes a standard of care for patients with advanced NSCLC. Such therapy should be instituted upon documentation of progression in suitable patients (suitability based upon performance status [PS], laboratory values, and need for other treatments). Alternatively, treatment with novel agents on approved clinical trials is also suitable and represents a standard of care. Supportive care alone should be discussed with patients as well, and is most appropriate for those with compromised PS (ECOG > 2).

1.3. Pemetrexed

Pemetrexed, a novel, multitargeted, antifolate antineoplastic agent approved for the first-line treatment of malignant pleural mesothelioma and the second-line treatment of NSCLC, is the chemotherapy agent most recently demonstrated to have activity in the first-line (Scagliotti et al. 2008) and maintenance treatment (Ciuleanu et al. 2008) of NSCLC.

The antitumor activity of pemetrexed likely derives from inhibition of several key folate-requiring enzymes, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) (Shih et al. 1997). This diversity of enzyme targets and the potential to overcome inherent resistance suggest that pemetrexed could have a greater degree and broader scope of antitumor activity than other antifolate therapies, such as methotrexate and 5-fluorouracil. The mechanisms of action and molecular pharmacology of pemetrexed are well characterized (Shih et al. 1998). This allows for correlative research of biomarkers in tumor samples that may be predictive for high clinical benefit from pemetrexed-containing treatment.

The observed side effects of pemetrexed are similar to those of other antifolate therapies. These side effects include myelosuppression (mainly transient neutropenia), oral mucositis, diarrhea, and skin rash. Supplementation with folic acid and vitamin B_{12} reduces the severity and frequency of hematologic and nonhematologic toxicities. Pemetrexed has been investigated in a number of tumor types as a single agent and in combination with other cytotoxic agents. More detailed information about the known benefits and risks of pemetrexed may be found in the investigator's brochure (Lilly 2008).

1.3.1. Single-Agent Pemetrexed in Second-Line NSCLC

Global regulatory approvals of pemetrexed for the second-line treatment of patients with NSCLC were granted on the basis of the pivotal, randomized, open-label, Phase 3 study, H3E-MC-JMEI (JMEI). Patients with Stage III or IV NSCLC received pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 on Day 1 of each 21-day cycle until disease progression. In this study of 571 patients, pemetrexed resulted in clinically similar efficacy outcomes with significantly fewer side effects compared with docetaxel, the established standard of care (Hanna et al. 2004). The RR was 9.1% and 8.8% for pemetrexed and docetaxel respectively, median PFS was 2.9 months in each arm, median OS was 8.3 and 7.9 months for pemetrexed and docetaxel respectively, and the 1-year survival was 29.7% in each arm.

Subsequently, a retrospective subgroup analysis of Study JMEI revealed statistically significant treatment-by-histology interactions for OS ($p = 0.001$) and PFS ($p = 0.004$) (Peterson et al. 2007). In the nonsquamous population, improved survival was demonstrated for patients who received pemetrexed compared with patients who received docetaxel, consistent with the statistically significant treatment-by-histology interaction (adjusted hazard ratio [HR] 0.778; 95% confidence interval [CI]: 0.607 to 0.997; $p = 0.047$; 9.3 months versus 8.0 months). Patients with predominantly squamous cell histology had shorter OS time with pemetrexed compared with docetaxel (adjusted HR 1.563; 95% CI: 1.079 to 2.264; $p = 0.018$; 6.2 months versus 7.4 months). No clinically relevant differences were observed for the safety profile of pemetrexed between the histologic subgroups. Because this was a retrospective analysis, the potential for different treatment results based on NSCLC histology was further evaluated in planned analyses for Studies H3E-MC-JMDB (JMDB) and H3E-MC-JMEN (JMEN) (Sections 1.3.2 and 1.3.3).

1.3.2. Pemetrexed plus Cisplatin in First-Line NSCLC

Data from the multicenter, randomized, open-label, Phase 3 study, JMDB, formed the basis for global applications to regulatory authorities for the initial treatment of patients with locally advanced or metastatic NSCLC (first-line NSCLC). Study JMDB, which compared pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on Day 1 of a 21-day cycle (PC) versus gemcitabine 1250 mg/m^2 on Day 1 and Day 8 plus cisplatin 75 mg/m^2 on Day 1 of a 21-day cycle (GC), met its primary endpoint and demonstrated that OS with PC was noninferior to GC, with significantly fewer side effects (Manegold et al. 2007; Scagliotti et al. 2008).

In the intent-to-treat (ITT) population (all histologies), the 2 arms of the study were equivalent in terms of OS (unadjusted HR 0.93; 95% CI: 0.83 to 1.04; median 10.3 months for both arms), PFS (unadjusted HR 1.04; 95% CI: 0.95 to 1.15; median 4.8 and 5.1 months for the pemetrexed and gemcitabine arms, respectively), and RR (30.6% versus 28.2% for the pemetrexed versus the gemcitabine arm).

Preplanned analyses evaluating the differences in OS with respect to baseline patient and disease characteristics identified a differential effect on survival according to NSCLC histologic subgroups. Overall survival time with PC was statistically superior to GC in patients with nonsquamous histology (adjusted HR 0.844; 95% CI: 0.74 to 0.96; $p = 0.01$ [data on file]). For

patients with squamous histology, OS time with PC was shorter than with GC (adjusted HR 1.229; 95% CI: 1.00 to 1.51; p = 0.050).

The results of Study JMDB are currently under review by the FDA. In April 2008, the European Medicines Agency issued an approval for use of pemetrexed with cisplatin in the initial treatment of NSCLC other than predominantly squamous histology. The previously approved indication for use in second-line NSCLC was amended to include NSCLC with other than predominantly squamous histology only.

1.3.3. Pemetrexed Maintenance Therapy in NSCLC

Pemetrexed was then tested in the maintenance setting in the randomized, double-blind, placebo-controlled, Phase 3 study, JMEN. In this trial, patients received 4 cycles of induction therapy with 1 of 6 standard regimens (gemcitabine, paclitaxel, or docetaxel, with either carboplatin or cisplatin); regimen selection was at the discretion of the investigator. Patients who achieved complete response (CR), partial response (PR), or stable disease (SD) were randomized to maintenance with pemetrexed plus best supportive care (BSC) or placebo plus BSC until progression (Ciuleanu et al. 2008).

Study JMEN demonstrated a significant improvement in PFS following induction chemotherapy for patients receiving pemetrexed maintenance therapy compared with placebo (unadjusted HR 0.60; 95% CI: 0.49 to 0.73; p < 0.00001; 4.04 versus 1.97 months) (data on file). In patients with nonsquamous histology, median PFS for patients receiving pemetrexed versus placebo was 4.4 months versus 1.8 months (unadjusted HR 0.47; 95% CI: 0.37 to 0.60; p < 0.00001). With 55% censoring, preliminary OS following induction chemotherapy in the overall study population was 13.0 months with pemetrexed and 10.6 months with placebo (unadjusted HR 0.798; 95% CI: 0.63 to 1.01; p = 0.06). In the nonsquamous population median OS was 14.4 months for pemetrexed-treated patients and 9.4 months for patients on placebo (unadjusted HR 0.66; 95% CI: 0.49 to 0.88; p = 0.005). In the squamous group, median OS was 9.6 and 11.9 months for pemetrexed and placebo treatment, respectively (unadjusted HR 1.28; 95% CI: 0.85 to 1.93; p = 0.231).

Response to maintenance therapy, analyzed according to Response Criteria in Solid Tumors (RECIST) guidelines (Therasse et al. 2000), was significantly higher for the pemetrexed arm (3.4%; 95% CI: 0.02 to 0.06) compared with the placebo arm (0.5%; 95% CI: 0.00 to 0.03; p = 0.042). Results of the analysis of disease control rate (DCR; CR+PR+SD) also demonstrated a significant improvement for patients receiving pemetrexed (49.1%; 95% CI: 0.44 to 0.54) compared with patients receiving placebo (28.9%; 95% CI: 0.23 to 0.36; p < 0.001).

1.3.4. Pemetrexed plus Carboplatin in NSCLC

The combination of pemetrexed and carboplatin was first tested in Study H3E-MC-JMAU, a Phase 1 mesothelioma study that verified the safety of the combination (Hughes et al. 2002). A 32% RR was noted, with acceptable toxicity.

The Phase 2 studies H3E-MC-JMEK (JMEK) and H3E-MC-JMEZ (JMEZ) examined pemetrexed with carboplatin and vitamin supplementation to determine whether the combination

would maintain the efficacy achieved with pemetrexed plus cisplatin in advanced NSCLC (Manegold et al. 2000; Shepherd et al. 2001).

In Study JMEK, 83 chemonaive patients with Stage IIIB or IV NSCLC were randomized to receive pemetrexed 500 mg/m^2 plus either carboplatin area under the curve (AUC) 6 (41 patients) or oxaliplatin 120 mg/m^2 (42 patients) on Day 1 of a 21-day cycle, for up to 6 cycles of therapy (Scagliotti et al. 2005). In the pemetrexed-carboplatin arm, 12 of the 38 evaluable patients (31.6%) had best overall responses of PR and 17 (44.7%) had best overall responses of SD. Median TTPD was 5.7 months, the 1-year survival rate was 43.9%, and median OS was 10.5 months. Grade 3/4 neutropenia was observed in 10 (25.6%) of 39 patients evaluable for safety. Grade 3/4 thrombocytopenia was reported in 7 (17.9%) patients. Grade 3 events also included anemia and fatigue, each reported in 3 (7.7%) patients, and stomatitis and febrile neutropenia, each reported in 1 (2.6%) patient. One (2.6%) patient experienced Grade 4 infection without neutropenia.

In Study JMEZ, 50 chemonaive patients with Stage IIIB (with effusion) or IV NSCLC received pemetrexed 500 mg/m^2 and carboplatin AUC 6 on Day 1 every 3 weeks for 6 cycles (Zinner et al. 2005). Twelve patients (24%) had PRs, and 25 (50%) had SD. Median TTPD was 5.4 months, the 1-year survival rate was 56%, and median OS was 13.5 months. Grade 3/4 neutropenia was observed in 13 (26%) patients. One (2%) patient had Grade 3 thrombocytopenia, and 1 (2%) patient had Grade 4 anemia. Three (6%) patients experienced Grade 3 nonhematologic side effects (nausea, fatigue, diarrhea, and vomiting).

These Phase 2 trials demonstrated that the combination of pemetrexed with carboplatin is tolerable and that its activity in first-line treatment of advanced-stage NSCLC is comparable with other standard platinum doublets commonly used in clinical practice (Kelly et al. 2001; Scagliotti et al. 2002; Schiller et al. 2002; Fossella et al. 2003). The toxicity with the pemetrexed and carboplatin combination appears to be less than that seen with other standard regimens in first-line NSCLC.

1.4. Bevacizumab

Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. By blocking the endothelial interaction of VEGF and its receptors, bevacizumab serves as an antiangiogenic agent.

Bevacizumab has been studied in more than 5000 patients and in multiple tumor types in Phase 1, 2, and 3 clinical trials. In addition, data are available from 3863 patients enrolled in 2 postmarketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials.

1.4.1. Bevacizumab in NSCLC

In the Genentech-sponsored, randomized, Phase 2 study AVF0757g, bevacizumab was added to the ECOG reference regimen established in Study ECOG 1594 (carboplatin-paclitaxel; see Section 1.2). This Phase 2 study identified a relationship between fatal hemoptysis and central lesions with squamous histology in lung cancer patients treated with bevacizumab (Johnson et al. 2004). Based on these safety data, the subsequent Phase 3 study excluded patients with predominantly squamous cell carcinoma, hemoptysis, or both.

The Phase 3 study (ECOG 4599) randomized patients to either carboplatin-paclitaxel-bevacizumab or carboplatin-paclitaxel-placebo (Sandler et al. 2006). Patients who received 6 cycles of bevacizumab plus chemotherapy without progression continued on single-agent bevacizumab until progression. Median OS was 12.3 months for patients on the bevacizumab plus chemotherapy arm compared with 10.3 months for patients receiving carboplatin plus paclitaxel (HR 0.79; 95% CI: 0.67 to 0.92; $p = 0.003$). One-and 2-year survival rates were 51% and 23% for the Sandler regimen, compared with 44% and 15% for the chemotherapy-only regimen. The RR was 35% (133/381) for patients on bevacizumab and 15% (59/392) for patients on chemotherapy only ($p < 0.001$).

The addition of bevacizumab resulted in modest changes to the expected toxicity profiles of chemotherapy alone (Genentech 2007). A number of safety signals, similar to those found in other bevacizumab studies, such as epistaxis, hypertension, and proteinuria, were identified, the majority of which were of low grade and did not require discontinuation of bevacizumab. Study ECOG 4599 suggested that the addition of a third noncytotoxic agent and/or maintenance therapy with an agent of low toxicity could result in improved outcomes in patients with advanced NSCLC. This study demonstrated that the treatment paradigm for patients with nonsquamous NSCLC (*bevacizumab eligible*) is different than the treatment paradigm for patients with squamous histology NSCLC based on a difference in safety (NCCN 2008).

1.4.2. Phase 2 Studies of Bevacizumab in Combination with Pemetrexed and Carboplatin in NSCLC

In the nonrandomized, Phase 2 study H3E-US-X027, 50 chemonaive patients with Stage IIIB (with pleural effusions) or IV nonsquamous cell NSCLC received up to six 21-day cycles of induction bevacizumab 15 mg/kg in combination with pemetrexed 500 mg/m^2 and carboplatin AUC 6. Patients with CR, PR, or SD continued maintenance treatment with pemetrexed 500 mg/m^2 and bevacizumab 15 mg/kg until progressive disease or unacceptable toxicity. Patients received a median of 6 cycles (induction plus maintenance); 30 (60%) patients completed at least 6 cycles, 9 (18%) patients completed at least 18 cycles, and 7 (14%) patients completed at least 24 cycles of therapy (Patel et al. 2008).

Four patients in Study X027 developed complications of their known diverticular disease (Patel et al. 2007; McKoy et al. 2008). Three of the 4 patients had underlying diverticulosis and developed diverticulitis on study; 2 of these patients developed Grade 3 diverticulitis and 1 developed Grade 4 diverticulitis with bowel perforation. The fourth patient had a known history of diverticulitis and developed an episode of Grade 3 diverticulitis on study. As a result of these

episodes of diverticulitis (Grade 3 in 3 [6%] patients and Grade 4 in 1 [2%] patient), the protocol was amended to exclude patients with prior history of diverticulitis or diverticulosis; no additional episodes of diverticulitis occurred following protocol amendment. Two of the patients with Grade 3 diverticulitis received additional cycles of study therapy and had no additional events (personal communication JD Patel, MD, 11 June 2008).

No hemorrhagic events greater than Grade 3 were reported, and no patients experienced Grade 3/4 hypertension. Grade 3 anemia and Grade 4 thrombocytopenia were each reported in 3 (6%) patients, and Grade 3 leukopenia was reported in 2 (4%) patients. Four (8%) patients experienced Grade 3 fatigue, and Grade 3 proteinuria and Grade 3 arterial thrombosis were each reported in 1 (2%) patient. Grade 3 venous thrombosis was reported in 2 (4%) patients, and Grade 4 was reported in 1 (2%) patient.

Among 49 patients evaluable for response, 1 CR and 23 PRs were observed, for a RR of 49% (95% CI: 35% to 61%). Median time to progression was 7.2 months (31 of 49 patients), and median survival was 14.0 months. In a presentation at the 2008 annual meeting of ASCO, the X027 regimen was noted as meriting further investigation in a Phase 3 study (Hanna 2008).

Dalsania and colleagues (2007) reported preliminary results of another nonrandomized, Phase 2 study in patients with Stage IIIB or IV nonsquamous NSCLC. Initial therapy consists of 21-day cycles of bevacizumab 15 mg/kg, carboplatin AUC 6, and pemetrexed 500 mg/m^2 for up to 6 cycles. Patients with CR, PR, or SD continue on maintenance treatment with single-agent bevacizumab until disease progression. Time to progression is the primary objective, and secondary objectives include RR, OS, and safety.

At the time of analysis, 19 patients were evaluable for response. The preliminary RR of 31.6% was comparable with the 35% RR reported in Study ECOG 4599 (Sandler et al. 2006). Survival data for this study have not yet been reported.

Safety analysis included all 21 enrolled patients. Patients received a median of 6.2 cycles (range, 2 to 23 cycles), and 8 patients proceeded to maintenance bevacizumab. Grade 3/4 toxicities included neutropenia in 7 patients, nausea and vomiting, each in 4 patients, bevacizumab-related allergic reaction in 1 patient, and epistaxis in 1 patient. Five events of Grade 2 proteinuria were also reported. The regimen was not associated with alopecia, neuropathy, arthralgia, or myalgia.

These studies demonstrated that induction therapy with pemetrexed and carboplatin plus bevacizumab followed by maintenance pemetrexed and bevacizumab in patients with advanced nonsquamous NSCLC is feasible, with an acceptable toxicity profile, and merits further investigation in a Phase 3 study.

1.4.3. Phase 2 Study of Bevacizumab in Combination with Pemetrexed, Carboplatin, and Enzastaurin

A randomized, double-blind, Phase 2 study (H6Q-MC-S034 [S034]) was ongoing in patients with Stage IIIB (with or without effusions) or IV nonsquamous NSCLC. Treatment in this study consisted of four 21-day cycles of bevacizumab 15 mg/kg plus pemetrexed 500 mg/m^2 and carboplatin AUC 6, all on Day 1, with daily enzastaurin (1125 mg on Day 1 of Cycle 1; 500 mg

each day after Day 1) or placebo. Patients with CR or PR were to continue with 21-day cycles of bevacizumab 15 mg/kg on Day 1, plus daily enzastaurin 500 mg or placebo, until progressive disease or unacceptable toxicity. Forty of the planned 90 patients have been enrolled, and an interim analysis of safety was performed after 20 patients had completed 1 cycle of treatment.

Three of the first 40 patients enrolled in this study experienced gastrointestinal (GI) toxicities. The first patient, who did not meet eligibility criteria due to perirectal fistula repair four months prior to starting the study, was randomized to the Enzastaurin arm and developed perforated sigmoid diverticulitis with multiple adjacent abscesses. The patient subsequently developed a bowel stricture requiring stent placement and a GI perforation requiring surgical resection. This patient recovered; the investigator felt the severe diverticulitis, stricture (colon), and colonic perforation were related to pemetrexed, carboplatin, and bevacizumab, but unrelated to blinded therapy or protocol procedures. A second patient, randomized to the placebo arm, had a history of diverticulosis and narcotic-related constipation; this patient was treated for severe constipation and fecal impaction. Treatment required admission for oil retention enemas and lactulose. The patient developed worsening abdominal pain and underwent exploratory laparotomy which showed sigmoid colon perforation. The patient underwent a sigmoid resection/Hartman's pouch procedure. The patient subsequently developed sepsis and expired. The investigator assessed the event of sepsis with the outcome of death as possibly related to bevacizumab, pemetrexed, and carboplatin but unrelated to blinded therapy or protocol procedures. The investigator considered the bowel perforation as possibly related to pemetrexed, carboplatin, and bevacizumab; but not related to blinded therapy or to protocol procedures. A third patient, randomized to the Enzastaurin arm, with a history of Crohn's disease, perirectal abscess, and bowel resection (many years previously with no active treatment or problems in the last 3 years) developed two perirectal abscesses on study. Although this was considered an adverse event (AE), but not a serious adverse event (SAE), the patient was discontinued from the study at the investigator's discretion. No new cases of diverticulitis or bowel perforation were seen in this study in patients with no history of diverticular disease. Treatment arm assignment was not considered a factor in these outcomes.

These cases were thoroughly reviewed by the lead investigator of the study, a safety assessment committee, and Lilly Global Patient Safety. Primary recommendations included: better patient selection; increased awareness of GI toxicity and risks by both investigators and patients, with both being well instructed relative to the critical importance of prompt follow up relative to early signs of GI issues; proactive prevention of constipation; prompt and appropriate work-up for patients with abdominal pain using imaging. Sigmoidoscopy and colonoscopy were not recommended because of the increased risk of perforation imposed by instrumentation.

The S034 trial was closed due to futility following an interim analysis conducted after 40 patients were enrolled. The external assessment committee identified no undue safety concerns between the two treatment arms but that there were more toxicities seen in the enzastaurin arm.

1.4.4. Bevacizumab Safety Profile

In the initial Phase 1 and 2 clinical trials, 4 potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events (TEs), and hemorrhage. Additional completed Phase 2 and 3 studies of bevacizumab and spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in Phase 3 trials include congestive heart failure (primarily in metastatic breast cancer), gastrointestinal perforations, wound-healing complications, and arterial TEs (Genentech 2007).

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS; see details below) (Glusker et al. 2006; Ozcan et al. 2006).

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled to ≤ 150/100 mm Hg with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Reversible posterior leukoencephalopathy syndrome: There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker et al. 2006; Ozcan et al. 2006).

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an AE) was up to 38%. The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been Grade 1. Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 was reported in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and

rarely required discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding Phase 2 studies suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinuria will be monitored at every cycle. In patients with Grade 3 proteinuria, bevacizumab should be omitted until resolved to ≤ Grade 2. Bevacizumab should be discontinued for patients with Grade 4 proteinuria.

Thromboembolic (TE) events: Both venous and arterial TE events, ranging in severity from catheter-associated phlebitis to fatal events, have been reported in patients treated with bevacizumab in the CRC trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis): The incidence of ≥ Grade 3 venous TE events in Study ECOG 4599 was higher in the bevacizumab-containing arm compared with the chemotherapy control arm (5.6% versus 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; nonfatal events were reported in the carboplatin/paclitaxel arm. In clinical trials across all indications the overall incidence of venous TE events was 2.8% to 17.3% in the bevacizumab-containing arms compared with 3.2% to 15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of venous TE event compared with chemotherapy alone.

See Table JMHD.5 for management of bevacizumab dosing in patients on full-dose anticoagulants for treatment of Grade 3 or 4 venous thrombosis.

Arterial TE events: An increased incidence of arterial TE events was observed in patients treated with bevacizumab compared with those receiving control treatment. Arterial TE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other arterial TE events. Bevacizumab should be discontinued for patients experiencing any grade of arterial TE events.

In a pooled analysis of data from 5 randomized Phase 2 and 3 trials (in metastatic CRC, locally advanced or metastatic NSCLC, and metastatic breast cancer), the incidence rate of arterial TE events was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. Arterial TE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% of patients with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial TEs in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the 5 randomized

studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Because the number of aspirin users and the number of arterial TEs were relatively small, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of Grade 1/2 or 3/4 bleeding events, and similar data with respect to metastatic CRC patients have been reported (Hambleton et al. 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin are ongoing.

Gastrointestinal (GI) perforation: Patients with metastatic carcinoma may be at increased risk for the development of GI perforation when treated with bevacizumab and chemotherapy. Bevacizumab should be discontinued in patients who develop GI perforation. No causal association between bevacizumab and intra-abdominal inflammatory process or GI perforation has been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab (see Section 5.7.6, Recommended Bowel Program). GI perforation has been reported in trials of CRC, NSCLC, and ovarian, renal cell, pancreatic, and breast cancer and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI track are common (incidence, 1% to 10%) in patients with metastatic CRC, but uncommon (0.1% to 1%) or rare (0.01 to 0.1%) in other indications. In addition, tracheoesophageal, brochopleural, urogenital, and biliary fistulae have been reported uncommonly (0.1% to 1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various time points during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Bevacizumab should be discontinued in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered. (See Section 5.7.6, Recommended Bowel Program.)

Wound-healing complications: Wound-healing complications, such as wound dehiscence, have been reported in patients receiving bevacizumab. In an analysis of pooled data from 2 trials in metastatic CRC, patients undergoing surgery 28 to 60 days before the study treatment with 5-fluorouracil/leucovorin + bevacizumab did not appear to have an increased risk of wound-healing complications compared with patients treated with chemotherapy alone (Scappaticci et al. 2005). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to determine a safe interval after bevacizumab exposure with respect to wound-healing risk in patients receiving elective surgery; however, the estimated half-life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with wound-healing complications requiring medical intervention (bevacizumab package insert, 2008).

If patients receiving bevacizumab require elective major surgery, bevacizumab should be held for 4 to 8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure

should not begin or restart bevacizumab until 4 weeks after that procedure. In the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, chemotherapy should be restarted no earlier than 6 weeks after surgery and bevacizumab should be restarted no earlier than 8 weeks after surgery.

Hemorrhage: Overall, Grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from 8 Phase 1, 2, and 3 clinical trials in multiple tumor types. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage. Bevacizumab should be discontinued in patients with serious hemorrhage (that is, requiring medical intervention) and aggressive medical management should be initiated (bevacizumab package insert, 2008).

Tumor-associated hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related AE in NSCLC studies. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for benefit-risk analysis.

In Study ECOG 4599, in which squamous cell carcinoma was excluded, the rate of any type of Grade ≥ 3 hemorrhage was 1.0% in the carboplatin-paclitaxel arm versus 4.1% in the bevacizumab-carboplatin-paclitaxel arm (Sandler et al. 2006).

GI hemorrhages, including rectal bleeding and melena, have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhage was also seen rarely in other tumor types and locations, including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases and continuous oozing of blood from a thigh sarcoma with necrosis (Gordon et al. 2001).

Mucocutaneous hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20% to 40% of patients treated with bevacizumab. These were most commonly Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention, and did not require any changes in bevacizumab treatment regimen.

Other hemorrhage: Minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding, have also been reported.

Congestive heart failure (CHF): In clinical trials, CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In a Phase 3 study in metastatic breast cancer, 7 (3%) bevacizumab-treated patients experienced CHF, compared with 2 (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240 to 360 mg/m^2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al. 2005).

In a randomized, Phase 3 trial of patients with previously untreated metastatic breast cancer, the incidence of LVEF decrease (defined as Grade 3 or 4) in the paclitaxel-bevacizumab arm was 0.3% versus 0% for the paclitaxel-only arm.

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II, III, or IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase 2 trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decreased to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well (Karp et al. 2004).

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing. Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scan or echocardiogram with a normal LVEF.

More detailed information about the known benefits and risks of bevacizumab may be found in the investigator's brochure (Genentech 2007).

1.5. Rationale for Study JMHD

Studies have demonstrated that pemetrexed is efficacious in the second- and first-line treatment of NSCLC, is superior to gemcitabine in combination with cisplatin for the treatment of nonsquamous NSCLC, and is efficacious in the maintenance setting. Moreover, because of the superior efficacy compared with the gemcitabine doublet in nonsquamous histology NSCLC, the combination of pemetrexed-carboplatin and bevacizumab should now be compared with the standard of care in nonsquamous advanced-stage NSCLC, paclitaxel-carboplatin and bevacizumab. Addition of the targeted-agent bevacizumab is intended to improve patient outcomes without significantly increasing toxicity.

The experimental and control arms for Study JMHD were selected as an appropriate study design to demonstrate superiority of pemetrexed-carboplatin-bevacizumab, with pemetrexed and bevacizumab continued until disease progression (Arm A), compared with paclitaxel-carboplatin-bevacizumab, with bevacizumab continued until disease progression (Arm B).

In Study JMHD, patients with advanced, nonsquamous NSCLC will be randomized to receive first-line treatment for 4 cycles or until progression. Patients who demonstrate CR, PR, or SD will go on to maintenance therapy. This superiority study is a US registration trial.

2. Objectives

2.1. Primary Objective

The primary objective is to compare overall survival (OS) for:

- Arm A: pemetrexed plus carboplatin plus bevacizumab, followed by maintenance bevacizumab plus pemetrexed
- Arm B: paclitaxel plus carboplatin plus bevacizumab, followed by maintenance bevacizumab

in the first-line induction and maintenance therapy for the treatment of patients with Stage IIIB (with pleural effusions) or IV nonsquamous NSCLC.

2.2. Secondary Objectives

The secondary objectives of the study are as follows:

Efficacy:

- to compare the overall response rates (RRs) and the disease control rates (DCRs), assessed according to Response Evaluation Criteria in Solid Tumors (RECIST; Therasse et al. 2000), between the 2 treatment arms
- to compare the following time-to-event efficacy variables between the 2 treatment arms:
  - progression-free survival (PFS)
  - time to progressive disease (TTPD).

Safety:

- to examine the safety and toxicity profile of study treatments, graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 (NCI 2006)
- to compare hospitalizations, transfusions, and concomitant medication use between the 2 treatment arms.

Quality of Life:

- to evaluate differences in patient-reported outcomes (PROs), as assessed by the Functional Assessment of Cancer Therapy-Lung/Neurotoxicity (FACT-L/Ntx) instrument (Cella et al. 1995; Calhoun et al. 2003) between the 2 treatment arms.

Pharmacokinetics:

- to characterize pharmacokinetics (PK) of carboplatin (total and free platinum) and bevacizumab and compare between the 2 treatment arms
- to characterize pemetrexed PK in patients randomized to Arm A.

Translational Research:

- to assess biomarkers relevant to pemetrexed, carboplatin, and bevacizumab
- to assess biomarkers relevant to the disease state
- to assess the correlation between biomarkers and clinical outcome.

3. Investigational Plan

3.1. Summary of Study Design

Study JMHD is a multicenter, randomized, open-label, Phase 3 trial. Eligible patients will be randomized in a 1:1 ratio to 1 of the following treatment arms:

- **Arm A** - Pemetrexed, carboplatin, and bevacizumab followed by pemetrexed and bevacizumab (450 patients)
- **Arm B** - Paclitaxel, carboplatin, and bevacizumab followed by bevacizumab (450 patients).

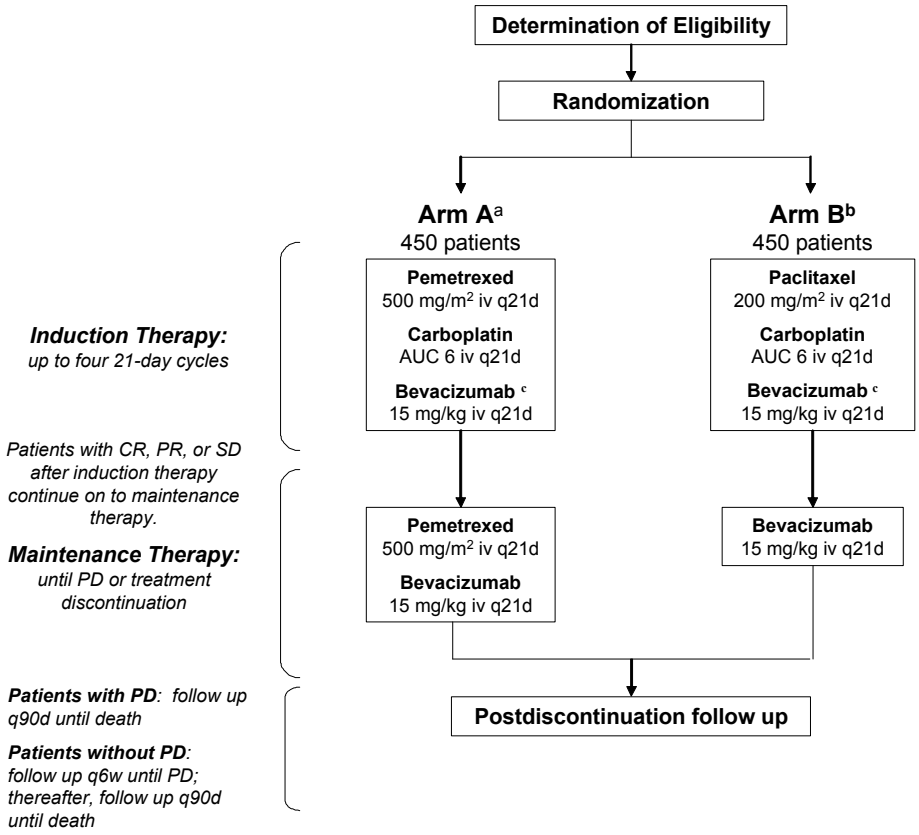
Patients randomized to Arm A will receive folic acid, vitamin B_{12}, and dexamethasone as stated in the pemetrexed label. Before administration of paclitaxel, patients randomized to Arm B will receive premedication (dexamethasone, diphenhydramine, and cimetidine or ranitidine) as recommended in the paclitaxel label.

Blood samples for PK evaluation will be obtained from 20 patients on Arm A and 20 patients on Arm B. Samples will be obtained in Cycle 1, as shown in Protocol Appendix 7.

Randomization will be stratified by the following factors:

- disease stage (IIIB with pleural effusions versus IV)
  (see Exclusion Criterion [13])
- measurable versus nonmeasurable disease
- ECOG performance status (0 versus 1)
- sex (male versus female).

Figure JMHD.1 illustrates the study design.



Abbreviations: AUC = area under the curve; CR = complete response; iv = intravenous; PD = progressive disease; PR = partial response; q21d = every 21 days; q6w = every 6 weeks; q90d = every 90 days; SD = stable disease.

[a] All patients on Arm A should receive standard premedication (folic acid, vitamin B_{12}, and dexamethasone) per the pemetrexed label.

[b] All patients on Arm B should receive standard premedication (dexamethasone, diphenhydramine, and cimetidine or ranitidine) per the paclitaxel label.

[c] The first dose of bevacizumab will be administered over 90 ± 15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 ± 10 minutes. If the 60-minute infusion is well tolerated, subsequent infusions may be delivered over 30 ± 10 minutes.

Figure JMHD.1. Study design.

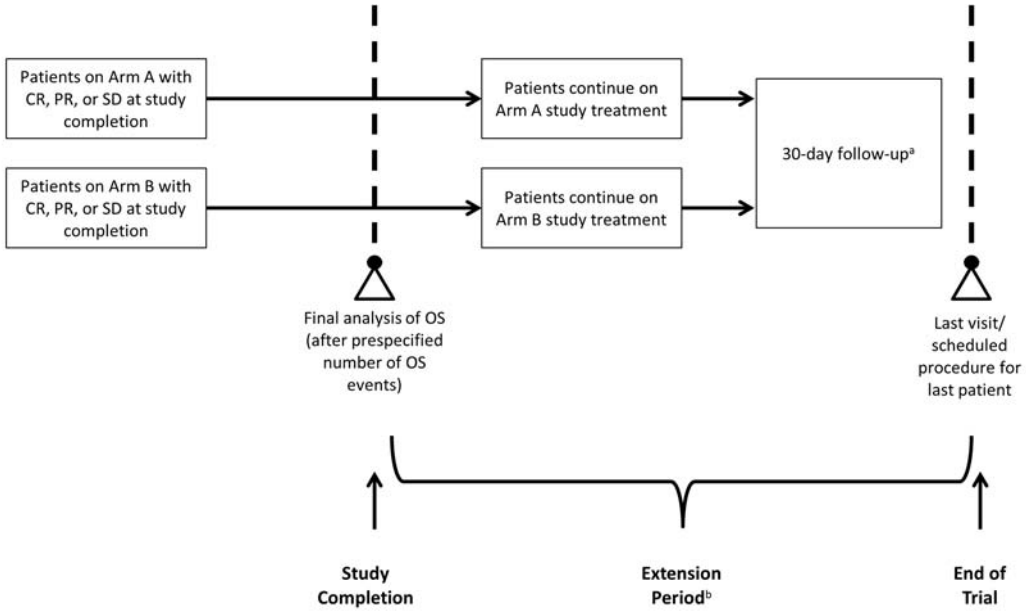
3.1.1. Study Completion and End of Trial

This study will be considered complete following the final analysis of OS, after the prespecified number of OS events.

The term "end of trial" refers to the date of the last visit or last scheduled procedure for the last patient in the extension period (see Appendix 10).

3.1.2. Extension Period

All patients who are still receiving study treatment at the time of study completion (see Section 3.1.1) may continue to receive study treatment in the extension period until one of the criteria for discontinuation is met (see Section 4.3.1). For all patients who continue to receive study treatment during the extension period, a follow-up visit will occur approximately 30 days after discontinuation from study treatment (see Section 6.3.1.2). Figure JMHD.2 provides an illustration of study completion, the extension period, and the end of trial. Lilly or its designee will notify investigators when the extension period begins and ends. Patients must sign a new informed consent document (ICD) before entering the extension period.



[a] See Figure JMHD.3.
[b] Lilly will notify sites when the extension period begins and ends.

Figure JMHD.2. Study completion, extension period, and end of trial.

3.2. Discussion of Design and Control

Study JMHD is a multicenter, randomized, open-label, Phase 3 trial in patients with advanced, nonsquamous NSCLC (Stage IIIB with pleural effusions or Stage IV).

The three Phase 3 studies, JMEI, JMDB, and JMEN, showed consistent evidence suggesting an efficacy advantage for pemetrexed in patients with nonsquamous histology NSCLC (Peterson et al. 2007; Ciuleanu et al. 2008; Scagliotti et al. 2008). Because of this evidence, and because of the relationship between bevacizumab treatment and serious hemorrhagic events in patients with squamous NSCLC (Johnson et al. 2004), patients with squamous cell histology are excluded from Study JMHD.

Eligible patients will be randomized in a 1:1 ratio to 1 of the following treatment arms:

- **Arm A** - Pemetrexed, carboplatin, and bevacizumab followed by pemetrexed and bevacizumab (450 patients)
- **Arm B** - Paclitaxel, carboplatin, and bevacizumab followed by bevacizumab (450 patients).

The study drugs and doses chosen for this study are also the same as those used in Studies X027 (Arm A) and ECOG 4599 (Arm B). The regimens for Arm A and Arm B were selected as an appropriate study design to demonstrate superiority in OS of pemetrexed-carboplatin-bevacizumab compared with paclitaxel-carboplatin-bevacizumab. Treatment will consist of up to 4 cycles of induction therapy followed by maintenance therapy until disease progression or treatment discontinuation. A maximum of 4 cycles of induction therapy was chosen based on recent reviews and meta-analyses showing this as the optimal duration of initial, platinum-based therapy (see Section 1.2).

4. Study Population

4.1. Inclusion Criteria

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

[1] have signed an informed consent document for clinical research.

[2] have a histologic or cytologic diagnosis of advanced, nonsquamous NSCLC (Stage IIIB with pleural effusions or IV disease) that is not amenable to curative therapy. See Appendix 3, American Joint Committee on Cancer Staging Criteria for Non-Small Cell Lung Cancer (Greene et al. 2002). (See Exclusion Criteria [13] and [14].)

[3] have not received any prior systemic chemotherapy, immunotherapy, targeted therapy, or biological therapy, including adjuvant therapy, for any stage of NSCLC.

[4] prior radiation therapy is allowed to < 25% of the bone marrow; however, prior radiation to the whole pelvis is not allowed. Prior radiation therapy must be completed at least 2 weeks prior to Day 1 of Cycle 1. Patients must have recovered from the acute toxic effects prior to Day 1 of Cycle 1. Patients with a prior history of NSCLC who have been treated with radiation therapy to the chest are not eligible. See Exclusion Criterion [15] for guidelines regarding prior radiotherapy for the treatment of brain metastases.

[5] have measurable or nonmeasurable disease as defined by RECIST (Therasse et al. 2000). See Appendix 4.

[6] males and females at least 18 years of age.

[7] have a performance status of 0 or 1 on the ECOG scale (Oken et al. 1982). See Appendix 5.

[8] have adequate organ function as follows:

Bone marrow reserve:

(a) white blood cell count $\geq 3 \times 10^9$/L;

(b) absolute neutrophil count (segmented and bands) $\geq 1.5 \times 10^9$/L;

(c) platelet count $\geq 100 \times 10^9$/L;

(d) hemoglobin ≥ 9.0 g/dL.

Hepatic:

(a) bilirubin $\leq 1.5 \times$ upper limit of normal (ULN);

(b) alkaline phosphatase, alanine transaminase, and aspartate transaminase $\leq$ $2.5 \times$ ULN ($\leq 5 \times$ ULN with liver metastases).

Renal:

(a) serum creatinine ≤ 1.5 × ULN;

(b) calculated creatinine clearance (CrCl) ≥ 45 mL/min based on the original, weight-based Cockcroft and Gault formula (Cockcroft and Gault 1976; see Appendix 6);

(c) urine protein to creatinine ratio (UPCR) < 1. Patients with UPCR ≥ 1 may be enrolled if < 1 g of protein in 24-hour urine collection.

These tests must be performed within 7 days prior to Day 1 of Cycle 1.

[9] male and female patients with reproductive potential must use an approved contraceptive method (for example, intrauterine device, birth control pills, or barrier device) during and for 3 months after discontinuation of study treatment.

[10] women with childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to Day 1 of Cycle 1; local laboratory results must be confirmed by a serum pregnancy test performed by the central laboratory. Patients are considered not of childbearing potential if:

(a) they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or

(b) they are postmenopausal.

[11] have an estimated life expectancy of at least 12 weeks.

[12] are able to comply with study and/or follow-up procedures.

4.2. Exclusion Criteria

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

[13] have clinically significant third-space fluid collections; for example, ascites or pleural effusions that cannot be controlled by drainage or other procedures prior to Day 1 of Cycle 1. Patients with Stage IIIB disease with pleural effusions are eligible if the effusions can be adequately controlled.

[14] have predominantly squamous cell histology NSCLC. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the patient is ineligible.

[15] have known central nervous system (CNS) disease, other than stable, treated brain metastasis. Stable, treated brain metastasis is defined as metastasis having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and post-treatment brain imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]) at baseline. Patients should be off corticosteroids for 1 week (7 days) at the time of the post-treatment brain CT/MRI. Anticonvulsants (stable dose) are allowed. Treatment for brain metastases may include whole brain radiotherapy, radiosurgery (Gamma Knife®, linear particle accelerator, or equivalent), or a combination, as deemed appropriate by the treating physician, and must have been completed > 7 days prior to Day 1 of Cycle 1. During study therapy, patients with stable, treated brain metastasis will be monitored every 2 cycles using the same modality (MRI or CT scan) that was used at baseline. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 8 weeks prior to Day 1 of Cycle 1 will be excluded.

[16] had a major surgical procedure, open biopsy, open pleurodesis, or significant traumatic injury within 28 days prior to Day 1 of Cycle 1 or have an anticipated need for major surgery during the study.

[17] had a core biopsy or other minor surgical procedure, excluding placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy, within 7 days prior to Day 1 of Cycle 1.

[18] have a history of gastrointestinal fistula, perforation, or abscess, inflammatory bowel disease, or diverticulitis.

[19] are currently receiving ongoing treatment with full-dose warfarin or equivalent (that is, unfractionated and/or low molecular weight heparin).

[20] have significant vascular disease (such as, aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1.

[21] have evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).

[22] have a serious cardiac condition, such as myocardial infarction, angina, or heart disease, as defined by the New York Heart Association Class II, III, or IV, within 6 months prior to Day 1 of Cycle 1 (AHA 1994).

[23] have inadequately controlled hypertension (defined as systolic blood pressure > 150 and/or diastolic > 100 mm Hg on antihypertensive medications).

[24] have any prior history of hypertensive crisis or hypertensive encephalopathy.

[25] have a serious, nonhealing wound, active ulcer, or untreated bone fracture.

[26] have another active malignancy, other than superficial basal cell and superficial squamous (skin) cell, or carcinoma in situ of the cervix within the last 5 years.

[27] have received treatment within the last 30 days prior to Day 1 of Cycle 1 with any drug that has not received regulatory approval for any indication at the time of study entry.

[28] have previously received treatment with paclitaxel, carboplatin, pemetrexed, or bevacizumab (Prior intravitreal administration of bevacizumab does not preclude study participation).

[29] are pregnant or breast-feeding.

[30] have a history of stroke or transient ischemic attack within 6 months prior to Day 1 of Cycle 1.

[31] have a known sensitivity to any component of paclitaxel, carboplatin, pemetrexed, or bevacizumab.

[32] have a history of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 3 months prior to randomization.

[33] are unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤ 1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).

[34] are unable or unwilling to take folic acid or vitamin B_{12} supplementation.

[35] are unable to take corticosteroids.

[36] have a serious concomitant systemic disorder (for example, active infection including human immunodeficiency syndrome [HIV]) that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol.

4.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [13] through [25] and [30] through [36] provide for patient safety.

Exclusion Criterion [26] helps in maintaining the specificity of the patient population. Exclusion Criterion [27] eliminates drugs that cannot be mapped to a standard drug dictionary, or for which little data are known and for which it would not be possible to evaluate the potential relationship of AEs or drug interactions. Exclusion Criterion [28] excludes patients who have already received treatment with paclitaxel, carboplatin, pemetrexed, or bevacizumab, as these patients would not likely benefit from re-treatment with these agents. Exclusion Criterion [29] is required because study drugs could have adverse effects on a developing fetus or breast-feeding infant.

4.3. Discontinuations

4.3.1. 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 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 intent-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 the 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, an SAE, or a clinically significant laboratory value, all study drugs are to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Section 6.3, Safety Evaluations.
- 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 that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from study treatment occurs prior to introduction of the new agent.
- The investigator or Lilly, for any reason, stops the study or stops the patient's participation in the study.
- The patient has evidence of progressive disease (see Section 1.2).
- 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 dose reductions and experiences an AE that would cause a third dose reduction.
    - If a study drug is discontinued due to an allergic reaction, the patient should remain on study per protocol with discontinuation of only the offending study drug. See Section 5.5.1.
    - If bevacizumab is discontinued per protocol rules for an AE, the patient should remain on study per protocol with discontinuation of only bevacizumab, see Section 5.5.1.

- The patient cannot receive *any* study treatment within 42 days after the beginning of the previous cycle, unless continuation is approved by Lilly.

4.3.2. 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.

4.3.3. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for sound medical and/or ethical reasons.

5. Treatment

5.1. Treatments Administered

Table JMHD.1 shows the treatment regimen for Arm A.

Table JMHD.1. Treatment Regimen for Arm A

Premedication	Dose	Route	Timing
Folic acid	350-1000 µg	po	QD beginning at least 5-7 days before Cycle 1, Day 1 and continuing until 3 wk after discontinuation of pemetrexed
Vitamin B_{12}	1000 µg	im	q9w beginning the 7-day period before Cycle 1, Day 1 and continuing until 3 wk after discontinuation of pemetrexed
Dexamethasone	4 mg	po	BID the day prior to, the day of, and the day after each infusion of pemetrexed
Prophylactic antiemetics	per local practice		

Study Drug	Dose	Route	Induction Period (Maximum = 4 Cycles)	Maintenance Period (Until PD)
Pemetrexed	500 mg/m^2	iv	over approximately 10 min on Day 1 q21d	over approximately 10 min on Day 1 q21d
Carboplatin	AUC 6[a]	iv	over approximately 30 min after pemetrexed on Day 1 q21d	not applicable
Bevacizumab	15 mg/kg	iv	over 30 – 90 ± 15 min after carboplatin on Day 1 q21d[b]	over 30 – 90 ± 15 min after pemetrexed on Day 1 q21d[b]

Abbreviations: AUC = area under the curve; BID = twice daily; CrCl = creatinine clearance; im = intramuscular; iv = intravenous; min = minute; PD = progressive disease; po = by mouth; q21d = every 21 days; q9w = every 9 weeks; QD = once daily; wk = week.

[a] Carboplatin dose (mg) = target AUC (mg/mL/min) x (CrCl + 25)(mL/min) (Calvert et al. 1989).

[b] See Section 5.2.4.

Table JMHD.2 shows the treatment regimen for Arm B.

Table JMHD.2. Treatment Regimen for Arm B

Premedication[a]	Dose	Route	Induction Period (Maximum = 4 Cycles)	Maintenance Period (Until PD)
Dexamethasone	20 mg	po	approximately 12 and 6 h prior to each infusion of paclitaxel	not applicable
Diphenhydramine (or equivalent)	50 mg	iv	30 – 60 min prior to each infusion of paclitaxel	not applicable
Cimetidine or Ranitidine	300 mg 50 mg	iv	30 – 60 min prior to each infusion of paclitaxel	not applicable
Prophylactic antiemetics	per local practice			

Study Drug	Dose	Route	Induction Period (Maximum = 4 Cycles)	Maintenance Period (Until PD)
Paclitaxel	200 mg/m^2	iv	over approximately 3 h on Day 1 q21d	not applicable
Carboplatin	AUC 6[b]	iv	over approximately 30 min after paclitaxel on Day 1 q21d	not applicable
Bevacizumab	15 mg/kg	iv	over 30 – 90 ± 15 min after carboplatin on Day 1 q21d[c]	over 30 – 90 ± 15 min on Day 1 q21d[c]

Abbreviations: AUC = area under the curve; h = hour; iv = intravenous; min = minute; PD = progressive disease; po = by mouth; q21d = every 21 days.

[a] Recommended premedication per paclitaxel label.

[b] Carboplatin dose (mg) = target AUC (mg/mL/min) x (CrCl + 25)(mL/min) (Calvert et al. 1989).

[c] See Section 5.2.4.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agents to study site personnel and to the patient (or the patient's legal representative), verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the trial.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drugs so that the situation can be assessed.

5.2. Materials and Supplies

5.2.1. Pemetrexed – Arm A

Pemetrexed for injection will be provided by Lilly and is supplied as a sterile, lyophilized powder for intravenous infusion packaged in a single-use glass vial. Each vial contains pemetrexed disodium equivalent to 500 mg of pemetrexed. The freeze-dried drug product is pemetrexed disodium and mannitol in a 1:1 ratio. Sodium hydroxide and/or hydrochloric acid

solution may have been added during processing to adjust the pH. Each vial contains an excess of pemetrexed to facilitate the withdrawal of the label amount. The drug product is stable when stored at controlled room temperature and normal lighting conditions.

Each vial must be reconstituted with sodium chloride (0.9%) solution for injection, without preservative, resulting in a solution containing 10 mg/mL to 50 mg/mL. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.8 and 7.8. Further dilution is required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or a dark green color is observed, do not administer.

The appropriate volume of reconstituted pemetrexed solution should be further diluted to 75 to 125 mL with sodium chloride (0.9%) solution for injection, without preservative. Pemetrexed infusion solutions prepared in this manner are compatible with polyvinyl chloride (PVC) and polyolefin line administration sets and infusion bags.

When prepared as directed, reconstituted and infusion solutions of pemetrexed contain no antimicrobial preservatives. Chemical and physical stability of reconstituted and infusion solutions were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or room temperatures. From a microbiological point of view, the product should be used immediately or within 24 hours following initial reconstitution. Discard any unused portion.

Reconstitution and further dilution prior to intravenous infusion is recommended with sodium chloride (0.9%) solution for injection, without preservative, only. Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's injection and Ringer’s Injection. Coadministration of pemetrexed with other drugs and diluents has not been studied, and therefore, is not recommended.

Clinical trial materials will be labeled according to the country's local regulatory requirements.

5.2.2. Paclitaxel – Arm B

Paclitaxel will be provided by the investigator. Paclitaxel is administered by intravenous infusion over 3 hours per local practice guidelines.

5.2.3. Carboplatin – Arm A and Arm B

Carboplatin will be provided by the investigator. Carboplatin is administered after paclitaxel (Arm B) or pemetrexed (Arm A) by intravenous infusion over 30 minutes with standard antiemetics per local practice guidelines.

Carboplatin dosing, using the Calvert formula, is often based upon a calculated creatinine clearance using serum creatinine as a surrogate for renal function. Several assays are available to measure serum creatinine. In the United States and many parts of the world, most laboratories

use methods that are standardized against reference material in which the creatinine value has been assigned by Isotope Dilution Mass Spectrometry (IDMS). After 31 December 2010, all clinical laboratories in the United States will use creatinine methods standardized relative to the IDMS reference material.

The recalibration of serum creatinine measurements against the IDMS reference material may result in slight differences in reported serum creatinine levels in the low range of normal. If the total carboplatin dose is calculated based on an estimated glomerular filtration rate (GFR) using an IDMS-standardized serum creatinine and the Calvert formula, carboplatin dosing could be higher than if the GFR had been directly measured, and could result in increased toxicity.

At sites where creatinine is determined by a method standardized to the IDMS reference material, the estimated GFR used in the Calvert formula to calculate area under the curve (AUC)-based dosing should not exceed 125 mL/min for patients who have not begun therapy. After 31 December 2010, all US sites should calculate carboplatin doses based upon serum creatinine values that were measured by the IDMS method.

The carboplatin dose will be calculated as the target AUC 6, using the Calvert formula (1989):

Calvert Formula

Total Dose (mg) = (target AUC) × (CrCl + 25)

Maximum carboplatin dose (mg) = target AUC 6 (mg•min/mL) × (125 + 25) = 6 × 150 mL/min = 900 mg

5.2.4. Bevacizumab – Arm A and Arm B

Bevacizumab will be provided by the manufacturer, and distributed to investigators by Lilly. Bevacizumab is supplied as a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous infusion. Bevacizumab may be supplied in 5-mL (100-mg) and 20-mL (400-mg) glass vials containing 4 or 16 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are suitable for single use only.

Upon receipt of the study drug, vials are to be refrigerated at 2°C to 8°C (36°F to 46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Bevacizumab will be diluted in a total volume of 100 mL of 0.9% sodium chloride injection, USP. Administration will be as a continuous intravenous infusion. Anaphylaxis precautions should be observed during study drug administration (see Section 5.5.1.5). It is not necessary to correct dosing based on ideal weight.

The initial dose will be delivered over 90 ± 15 minutes. If the first infusion is tolerated without infusion-associated AEs (fever and/or chills), the second infusion may be delivered over 60 ± 10

minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ± 10 minutes.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 patient may not be used for any other patient. Once bevacizumab has been added to a bag of sterile saline, the solution must be administered within 8 hours.

5.2.5. Premedication for Arm A

5.2.5.1. Folic Acid

Investigators will obtain folic acid in 1 of the following forms, with preference in order from Option 1 to Option 3:

1) 350 to 600 μg folic acid
2) a multivitamin containing folic acid in the range of 350 to 600 μg (acceptable only if Option 1 is not available)
3) a dose of folic acid between 600 and 1000 μg (acceptable only if neither Option 1 nor Option 2 is available).

For purposes of this study, folic acid must be given at least 5 to 7 days before Cycle 1, Day 1 and continuing daily until 3 weeks after discontinuation of pemetrexed.

5.2.5.2. Vitamin B12

Vitamin B_{12} will be prescribed by the investigator and administered as a 1000-μg intramuscular injection. A vitamin B_{12} injection must be administered in the 7-day period prior to Cycle 1, Day 1 and should be repeated approximately every 9 weeks until 3 weeks after discontinuation of pemetrexed.

5.2.5.3. Dexamethasone

Dexamethasone 4 mg (or an equivalent corticosteroid and dose) will be given orally twice per day on the day before, the day of, and the day after each dose of pemetrexed.

5.2.6. Premedication for Arm B

Study site personnel will administer premedication as indicated in the paclitaxel label. Such premedication may consist of: (1) dexamethasone 20 mg taken by mouth approximately 12 and 6 hours prior to paclitaxel, (2) diphenhydramine (or its equivalent) 50 mg administered intravenously 30 to 60 minutes prior to paclitaxel, and (3) cimetidine (300 mg) or ranitidine (50 mg) administered intravenously 30 to 60 minutes prior to paclitaxel.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to Arm A or Arm B at the baseline visit (Visit 0). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive voice response system (IVRS) at a central location. Randomization will be stratified by the following factors:

- disease stage (IIIB with pleural effusions versus IV) (see Exclusion Criterion [13])
- measurable versus nonmeasurable disease
- ECOG performance status (0 versus 1)
- sex (male versus female).

5.4. Rationale for Selection of Doses in the Study

The doses of paclitaxel, pemetrexed, carboplatin, and bevacizumab used in this study are the doses approved in the United States for patients with NSCLC.

5.5. Selection and Timing of Doses

Patients will be randomly assigned to Arm A or Arm B (see Section 3.1). Study drug will be administered as shown in Section 5.1.

5.5.1. Dose Adjustments and Cycle Delays

All toxicities will be graded according to CTCAE guidelines (Version 3.0; NCI 2006). 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 discontinued from all study treatment.

Discontinuation of study drug typically requires withdrawal from the study. If an AE occurs with bevacizumab, bevacizumab may be discontinued as outlined in Section 5.5.1.5, and the other study drugs continued. In addition, paclitaxel may be discontinued for Grade 3 or 4 neurotoxicity and the other study drugs continued (see Table JMHD.4). The only other situation allowing discontinuation of study drugs other than bevacizumab that allows a patient to stay on study therapy is an allergic reaction, in which case the patient should remain on study per protocol with discontinuation of only the offending study drug.

5.5.1.1. Carboplatin Toxicity and Dose Reductions

For patients who have started therapy regardless of method of serum creatinine measurement who:

- have already received >900 mg carboplatin, and who are not experiencing Grade 3/4 toxicity that an investigator would reasonably attribute to carboplatin, that patient should continue on his/her current dose of carboplatin.
- have experienced Grade 3/4 toxicity attributed to carboplatin, that patient should have all study drugs reduced per protocol.
    - If this dose reduction does not result in a carboplatin dose <900 mg, the carboplatin dose should be further reduced to 900 mg.
- have already undergone a dose reduction and the carboplatin dose remains >900 mg, and that patient has already received subsequent treatment at this lower dose without Grade 3/4 toxicity, that patient should continue on his/her current dose of carboplatin.

5.5.1.2. Hematologic Toxicity

At the start of each cycle, ANC must be $\geq 1.5 \times 10^9$/L and platelet count must be $\geq 100 \times 10^9$/L. Treatment should be delayed for up to 42 days to allow sufficient time for recovery.

Upon recovery, dose adjustments at the start of a subsequent cycle will be based on the lowest platelet and neutrophil values from the previous cycle (see Table JMHD.3).

Table JMHD.3. Dose Adjustments Based on Lowest Hematologic Values from the Previous Cycle

Lowest Hematologic Value from the Previous Cycle		Adjust Dose to Percentage of Previous Dose			
Platelets (× 10^9/L)	**ANC (× 10^9/L)**	**Pemetrexed (Arm A)**	**Paclitaxel (Arm B)**	**Carboplatin[a] (Arms A and B)**	**Bevacizumab (Arms A and B)**
≥ 50 *and*	≥ 0.5	100%	100%	100%	See Section 5.5.1.5
≥ 50 *and*	< 0.5	75%	75%	75%	
< 50 without bleeding *and*	Any	75%	75%	75%	
< 50 with Grade ≥ 2 bleeding from any site *and*	Any	50%	50%	50%	
any *and*	< 1.0 + fever ≥ 38.5°C (101°F)	75%	75%	75%	

Abbreviations: ANC = absolute neutrophil count; AUC = area under the curve; CTCAE = Common Terminology Criteria for Adverse Events (Version 3.0; NCI 2006).

[a] Adjust carboplatin dose to the specified percentage of the previous AUC. Refer to Section 5.5.1.1 for additional dose reduction guidelines.

5.5.1.3. Creatinine Clearance

Creatinine clearance will be estimated using the original, weight-based Cockcroft and Gault formula (1976; see Appendix 6) or measured using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA) to determine glomerular filtration rate (GFR). The method of CrCl assessment used at baseline should be used throughout the study. Enrollment and dosing decisions based on CrCl may be made using locally determined clinical laboratory results (calculated using the original, weight-based Cockcroft and Gault formula). The serum creatinine must be assayed at the same local lab each time for that patient. If a local lab is being used to monitor a patient's renal function, the central laboratory sample still must be drawn for safety analysis. See Section 5.2.3 for details regarding the measurement of serum creatinine to calculate the carboplatin dose.

Creatinine clearance should be ≥ 45 mL/min before the start of any cycle. The cycle may be delayed for up to 42 days to allow the patient time to recover from the toxicity. If CrCl has not returned to ≥ 45 mL/min within 42 days after the previous dose, the patient must be discontinued from all study drugs unless continuation is approved by the Lilly clinical research physician.

5.5.1.4. Nonhematologic Toxicity

For Grade 3 or 4 nonhematologic toxicities, treatment should be delayed until resolution to less than or equal to the patient's baseline value. Dose reductions at the start of the subsequent cycle will be based on nonhematologic toxicities from the dose administered in the preceding cycle.

Table JMHD.4 provides the relevant dose adjustments for nonhematologic toxicities.

Table JMHD.4. Dose Adjustments Based on Nonhematologic Toxicities from the Preceding Cycle

		Adjust Dose to Percentage of Previous Dose			
Event	**CTCAE Grade**	**Pemetrexed (Arm A)**	**Paclitaxel (Arm B)**	**Carboplatin[a] (Arms A and B)**	**Bevacizumab (Arms A and B)**
Diarrhea	3 or 4[c]	75%	75%	100%	See Section 5.5.1.5
Mucositis	3 or 4	50%[b]	100%	100%	
Nausea or vomiting	3 or 4	100%	100%	100%	
Neurotoxicity – motor or sensory	2	100%	80%	100%	
	3 or 4	75%	discontinue paclitaxel	75%	
Transaminase elevation	3	75%	75%	75%	
	4	discontinue pemetrexed	discontinue paclitaxel	discontinue carboplatin	
Other nonhematologic CTCAE[d]	3 or 4	75%	75%	75%	

Abbreviations: AUC = area under the curve; CTCAE = Common Terminology Criteria for Adverse Events (Version 3; NCI 2006).

[a] Adjust carboplatin dose to the specified percentage of the previous AUC. Refer to Section 5.5.1.1 for additional dose reduction guidelines.

[b] See guidelines for leucovorin rescue (Section 5.7.3).

[c] Or any grade of diarrhea requiring hospitalization.

[d] If deemed appropriate by the treating physician.

5.5.1.5. Treatment Delays due to Insufficient Folic Acid or Vitamin B12 Supplementation – Arm A

For patients receiving pemetrexed (Arm A), do not start Cycle 1 until both of the following requirements are met:

1. The patient has taken folic acid for at least 5 days immediately preceding the first dose of pemetrexed.
2. The patient has received a vitamin B_{12} injection once within 7 days immediately preceding the first dose of pemetrexed.

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

5.5.1.6. Bevacizumab – Arm A and Arm B

There are no reductions in the bevacizumab dose. If AEs that require omitting bevacizumab occur, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Omission of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its omission results in slow elimination over several months. There is no available antidote for bevacizumab.

Patients should be clinically assessed for toxicity before, during, and after each infusion of bevacizumab. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be permanently discontinued, however the patient may remain on study.

Infusion reaction: Infusion of bevacizumab should be interrupted for patients who develop dyspnea or clinically significant hypotension. Patients who experience CTCAE (Version 3.0) Grade 3 or 4 allergic reaction/hypersensitivity, or adult respiratory distress syndrome, or any grade bronchospasm will be discontinued from bevacizumab treatment.

If a patient experiences an infusion-associated AE, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 ± 10 minutes as long as the patient continues to be premedicated. If a patient experiences an infusion-associated AE with the 60-minute infusion, all subsequent doses should be given over 90 ± 15 minutes. Similarly, if a patient experiences an infusion-associated AE with the 30-minute infusion, all subsequent doses should be given over 60 ± 10 minutes. Infusion time should not be extended beyond 90 ± 15 minutes.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table JMHD.5.

Regardless of the reason for omitting bevacizumab treatment, the maximum allowable length of bevacizumab treatment interruption is 42 days.

Table JMHD.5. Bevacizumab Dose Management due to Adverse Events

Event[a]	Action to be Taken
Hypertension	
Grade 3	If not controlled to ≤ 150/100 mm Hg with medication, discontinue bevacizumab
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab
Hemorrhage	
Pulmonary or CNS hemorrhage	
Grade 1	For patients who are also receiving full-dose anticoagulation, discontinue bevacizumab For all other patients, omit bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of bevacizumab therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4	Discontinue bevacizumab
Nonpulmonary / non-CNS hemorrhage	
Grade 3	Omit bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of bevacizumab therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4	Discontinue bevacizumab

(continued)

Table JMHD.5. Bevacizumab Dose Management due to Adverse Events (continued)

Event[a]	Action to be Taken
Venous thrombosis	
Grade 3 or 4	Omit bevacizumab. If the planned duration of full-dose anticoagulation is < 2 weeks, omit bevacizumab until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) if the patient is on warfarin. LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Arterial thromboembolic event (New onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab
Congestive heart failure (left ventricular systolic dysfunction)	
Grade 3	Omit bevacizumab until resolution to Grade ≤ 1
Grade 4	Discontinue bevacizumab
Proteinuria	
Grade 3 (UPCR > 3.5; 24-hour urine collection > 3.5 g; or urine dipstick 4+)	Omit bevacizumab until ≤ Grade 2, as determined by (a) UPCR ≤ 3.5; (b) 24-hour collection ≤ 3.5 g; or (c) urine dipstick 2+ to 3+
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab
GI perforation	Discontinue bevacizumab
Diverticulitis	Omit bevacizumab and begin appropriate treatment. The investigator must obtain documented approval from Lilly to allow the patient to continue on study therapy.
Fistula	
Any grade tracheoesophageal fistula	Discontinue bevacizumab
Grade 4 fistula	Discontinue bevacizumab

(continued)

Table JMHD.5. Bevacizumab Dose Management due to Adverse Events (concluded)

Event[a]	Action to be Taken
Bowel obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention
Grade 2	Omit bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3 or 4	Omit bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at investigator's discretion.
Wound dehiscence	
Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab
Reversible posterior leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab
Other unspecified bevacizumab-related adverse events	
Grade 3	Omit bevacizumab until recovery to Grade ≤ 1
Grade 4	Discontinue bevacizumab

Abbreviations: CNS = central nervous system; GI = gastrointestinal; INR = international normalized ratio; LMWH = low molecular weight heparin; MRI = magnetic resonance imaging; UPCR = urine protein to creatinine ratio.

[a] Events are graded according to Common Terminology Criteria for Adverse Events version 3.0 (NCI 2006).

Source: Bevacizumab protocol template 01 Nov 2007 (Table 1).

5.6. Blinding

This is an open-label study. Each patient will be aware of his or her own assigned treatment group. At each investigative site, all staff involved in treating and caring for study patients will have full knowledge of treatment assignments for the patients under their care.

For the accumulated aggregate database, treatment assignment will not be included, and other parameters that can disclose treatment assignment will be scrambled. Therefore, the sponsor and all investigative sites will remain blinded to treatment group assignments for the aggregate database until the database lock for the final analysis.

Four planned interim analyses will be conducted for this study (see Section 8.2.12). Only the Statistical Analysis Center (SAC) and Data Monitoring Committee (DMC), both external to Lilly, will have access to unblinded or partially unblinded interim data for these formal interim analyses, unless an internal review is needed in order for Lilly to make an informed decision based on a DMC recommendation to stop or modify the study. In that case, the individuals involved in the internal review may also view the unblinded or partially unblinded interim data. Study sites will not receive any information about interim data unless investigators need to know this information for the safety of their patients.

5.7. Concomitant Therapy

Patients are allowed to receive full supportive care therapies concomitantly during the study. No other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation therapy, surgery for cancer, or experimental medications 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.

5.7.1. Clinically Significant Effusions

If a patient develops clinically significant pleural or peritoneal effusions (as determined on the basis of symptoms or clinical examination) prior to the first dose of study treatment or during therapy, draining the effusion prior to dosing is required. However, if the investigator determines that the effusion represents disease progression, the patient should be discontinued from study treatment.

5.7.2. Colony-Stimulating Factors

Routine use of colony-stimulating factors (CSFs) is not permitted. American Society of Clinical Oncology guidelines for use of CSFs should be followed (Smith et al. 2006).

5.7.2.1. Use of Erythropoiesis-Stimulating Agents

According to NCCN guidelines (Rodgers et al. 2008), erythropoiesis-stimulating agents (ESAs) are not indicated for treatment of cancer-related anemia in patients with solid tumors. Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia for a hemoglobin < 10 g/dL after the patient has been counseled about the risks and benefits of ESA use.

Because recommendations on the use of ESAs are rapidly evolving, investigators should frequently refer to the NCCN, ASCO, and/or Centers for Medicare and Medicaid Services web sites for the latest guidelines.

5.7.3. Leucovorin

Leucovorin is allowed: (1) for treatment of CTCAE Grade 4 leukopenia or Grade 4 neutropenia lasting more than 3 days, beginning on the third day of Grade 4 myelosuppression; or (2) immediately, for treatment of Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis.

The following doses and schedules are recommended for intravenous use:

- leucovorin 100 mg/m^2 intravenously once, followed by
- leucovorin 50 mg/m^2 intravenously every 6 hours for 8 days.

Appropriate doses of the oral formulation may also be used at the investigator's discretion.

5.7.4. Nonsteroidal Anti-Inflammatory Drugs

Patients taking NSAIDs or salicylates will not take the NSAID or salicylate (other than an aspirin dose ≤ 1.3 grams per day) for 2 days before, the day of, and 2 days after receiving pemetrexed. Patients taking NSAIDs or salicylates with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAIDs or salicylates for 5 days before, the day of, and 2 days after pemetrexed.

5.7.5. Therapy for Diarrhea

In the event of CTCAE Grade 3 or 4 diarrhea, doses of pemetrexed and paclitaxel should be adjusted as shown in Table JMHD.4, and the following supportive measures are allowed: hydration, octreotide, and antidiarrheals. Bevacizumab may be given without interruption unless the investigator considers the diarrhea to also be related to bevacizumab.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe (Grade 3 or 4) neutropenia, 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.

5.7.6. Recommended Bowel Program

Diverticular disease occurs when intralumenal pressure increases in the bowel. The most common part of the bowel affected is the sigmoid colon. Diverticulitis occurs when diverticuli become inflamed or infected, a situation that is more likely to occur if a patient is constipated. Constipation in patients with advanced-stage lung cancer is common because many of these patients require narcotic therapy for pain management of metastatic sites. To decrease the risk of constipation, especially in patients with diverticulosis, a bowel program is recommended for all patients with any evidence of constipation.

Patients with diverticulosis are more likely to develop diverticulitis when severely constipated or impacted because of the increase in intralumenal pressure. Enemas and manual disimpaction may further increase intralumenal pressure. This may increase the risk of abscess, perforation, and fistula independent of chemotherapy. Because bevacizumab is associated with a risk of bowel perforation, prevention and proactive management of constipation may increase patient safety.

The following measures are recommended:

- diet high in fiber and water. Fiber may be obtained in the diet and through products such as Benefiber®, Metamucil®, or Citrucel®.
- stool softeners.

If the above measures are not adequate to maintain a daily bowel movement, additional measures to increase bowel movements to at least every other day may include:

- milk of magnesia
- lactulose

- magnesium citrate.

5.7.7. Therapy for Febrile Neutropenia

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

5.8. Treatment Compliance

All study drugs will be administered intravenously at the investigational sites. As a result, patient compliance is ensured.

For patients on Arm A:

- In the period before the first dose of study therapy, compliance with folic acid supplementation is required and should be documented by the investigative site personnel.
- Vitamin B_{12} supplementation will be administered as an intramuscular injection at the investigational sites. As a result, patient compliance is ensured.

Sections 5.2.5.1 and 5.2.5.2 provide definitions of sufficient folic acid and vitamin B_{12} therapy, respectively.

6. Efficacy and Health Outcome Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Appendix 1) and the Extension Period Schedule (Appendix 10).

6.1. Efficacy Measures

Efficacy assessments are performed until study completion. During the extension period, investigators are responsible for performing any procedures and tests needed for the appropriate care of the patient; however, the results of efficacy assessments performed during the extension period will not be reported on the case report form (CRF).

Sites will assess tumor response in patients by using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Therasse et al. 2000; Appendix 4).

Baseline tumor measurements will be performed within 4 weeks before enrollment. Computed tomography including spiral CT, scans and MRI are the preferred methods of measurement, but chest x-ray is acceptable for clearly defined lesions surrounded by aerated lung. In addition, a physical examination will be performed within 2 weeks before enrollment for measurement of palpable tumor lesions. Ultrasound and positron emission tomography scans are not permitted as methods of tumor measurement.

The same method used at baseline, covering the same anatomy, must be used consistently for tumor assessment throughout the study. During study therapy, tumor assessment will be repeated every 2 cycles (± 2 weeks). For responding patients, response must be confirmed as described in Section 6.1.1.1.

If a patient has PD, he or she will be discontinued from study therapy. If a patient discontinues from study therapy and has not had disease progression, tumor measurements will also be performed at the 30-day postdiscontinuation follow-up visit (see Figure JMHD.3) and every 6 weeks (± 2 weeks) thereafter. Once the patient has objective disease progression, the patient will be followed every 90 days (± 14 days).

Until study completion, the following postdiscontinuation data will be reported on the CRF: the date of disease progression; documentation of any anticancer treatment patient has received, including the dates of any postdiscontinuation systemic therapy, radiotherapy, or surgical intervention; and the date of death. For patients who discontinue from study therapy before study completion, postdiscontinuation follow up will continue until the earliest of the following events: death, lost to follow up, or study completion.

6.1.1. Efficacy Criteria for Tumor Response

Tumor responses will be measured and recorded by using RECIST guidelines (Therasse et al. 2000; Appendix 4). During the extension period, patients should be assessed according to good clinical practice requirements to ensure continued eligibility to receive study treatment.

6.1.1.1. Best Response

Best response is determined from the sequence of cycle responses assessed. For complete response (CR) or partial response (PR), best response must be confirmed. A second assessment should be performed 28 to 42 days after the first documentation of response. Thereafter, a responding patient will be followed every 6 weeks (± 2 weeks) per the Study Schedule (Appendix 1). 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 baseline assessment.

6.1.2. Definition of Efficacy Measures

The following definitions for time-to-event measures will apply:

Overall survival (OS): Duration is measured from the date of randomization to the date of death from any cause. If a patient has not died at the time of the data inclusion cutoff date for the analysis, OS will be censored at the last date the patient was known by the treating physician to still be alive.

Progression-free survival (PFS): Duration is measured from the date of randomization to the date of objective progression of disease or the date of death from any cause, whichever is earlier. For patients who receive subsequent systemic anticancer therapy (after discontinuation from the study chemotherapy) prior to objective progression or death, PFS will be censored at the date of the last objective progression-free disease assessment prior to starting the subsequent systemic anticancer therapy. For patients not known to have died as of the data inclusion cutoff date and who do not have objective progressive disease, PFS will be censored at the date of the last objective progression-free disease assessment prior to the cutoff date or the date of initiation of subsequent systemic anticancer therapy, whichever is earlier.

Time to progressive disease (TTPD): Time is measured from the date of randomization to the first date of objective progression of disease. For patients who receive subsequent systemic anticancer therapy (after discontinuation from the study chemotherapy) prior to objective progression, TTPD will be censored at the date of the last objective progression-free disease assessment prior to starting this subsequent systemic anticancer therapy. For patients not known to have had objective progression of disease as of the data-inclusion cutoff date for a particular analysis, or who have died without objective progression of disease, TTPD will be censored at the date of the last objective progression-free disease assessment prior to that cutoff date or the date of initiation of subsequent systemic anticancer therapy, whichever is earlier.

6.2. Health Outcome Measures

Previous studies have demonstrated the potential for increased toxicity when treatment regimens that combine multiple chemotherapeutic agents are used. It therefore becomes important to include PRO measures as endpoints in Phase 3 trials where combination therapies are used, especially in the advanced NSCLC setting, where treatment is only palliative. In Study JMHD,

toxicities will be assessed using CTCAE (Version 3.0 [NCI 2006]) and through the use of patient-administered FACT questionnaires (see Appendix 8).

The FACT questionnaires used in this study are designed to capture the patient's assessment of his or her overall QOL, patient-reported side effects, and disease- and treatment-related symptoms. PRO instruments that mainly capture the effect of treatment on disease-related symptoms will not be effective in assessing treatment-related side effects. Thus, multiple instruments should be used, especially because patients can simultaneously report both an improvement of disease-related symptoms and a worsening of treatment-related side effects. Use of FACT questionnaires will enable assessment of the differences between treatment arms with respect to overall QOL and changes in QOL brought about by symptom worsening/alleviation and treatment toxicity.

Study JMHD will use the FACT-General (FACT-G) questionnaire, plus the lung cancer and neurotoxicity subscales. Collectively, the instruments used in this study are referred to as the *FACT-L/Ntx* questionnaire.

Speculated differences in the safety profiles of the 2 treatment arms include the incidence and severity of peripheral neuropathy, febrile neutropenia, fatigue, and nausea. The FACT-L/Ntx will provide supplemental assessment of these toxicities from the patient's perspective and explore the relationship of the toxicity to the PRO. This is especially important for peripheral neuropathy (a common side effect of taxane therapy), as it has been shown to be under-reported when assessed using CTCAE compared with patient-reported measurement (Morton et al. 2005). Fatigue and nausea (common side effects of pemetrexed therapy) will be captured via CTCAE assessment and the FACT physical well-being subscale.

6.2.1. FACT-G

The FACT-G is a reliable and valid instrument used to measure QOL in patients with cancer (Cella at al. 1993). The 27-item questionnaire is organized into subscales, each designed to assess a QOL domain:

- physical well-being (PWB) – 7 items
- social/family well-being (SWB) – 7 items
- emotional well-being (EWB) – 6 items
- functional well-being (FWB) – 7 items.

6.2.2. FACT-Lung

The FACT-Lung (FACT-L) is a reliable and valid instrument consisting of the FACT-G and a 9-item lung cancer subscale (LCS) and is appropriate for both small cell lung cancer and NSCLC (Cella et al. 1995).

Results of the FACT-L can be reported as:

- scores for the 5 individual subscales (PWB, SWB, EWB, FWB, and LCS)

- total FACT-L - the sum of the scores of all 5 subscales (total FACT-L = PWB + SWB + EWB + FWB + LCS)
- Trial Outcome Index-Lung (TOI-L) – the sum of the PWB and FWB subscales plus the LCS (TOI-L = PWB + FWB + LCS).

6.2.3. FACT/GOG-Ntx

The FACT/GOG-Ntx consists of an 11-item neurotoxicity subscale (Ntx) developed in collaboration with the Gynecologic Oncology Group (GOG) for use in patients with neurotoxicity. This instrument possesses strong psychometric properties and is both reliable and valid (Calhoun et al. 2003).

Results of the FACT/GOG-Ntx can be reported as:

- scores for the 5 individual subscales (PWB, SWB, EWB, FWB, and NTX)
- total FACT/GOG-Ntx - the sum of the scores of all 5 subscales (total FACT-T = PWB + SWB + EWB + FWB + NTX)
- Ntx Trial Outcome Index (TOI-Ntx) - the sum of the PWB and FWB subscales plus the NTX (TOI-Ntx = PWB + FWB + NTX).

6.2.4. FACT-L/Ntx Timing and Scoring

Collection of all FACT-L/Ntx data will end at study completion (see Section 3.1.1).

FACT-L/Ntx questionnaires will be completed only by randomized patients for whom a validated translation is available in a language in which the completer is fluent. Each patient should complete a questionnaire once at each of the following time points:

- at baseline (before randomization)
- before each cycle, except Cycle 1
- upon discontinuation from all study-drug treatment
- during the postdiscontinuation follow-up visit approximately 30 days after the last dose of study drug (see Figure JMHD.3).

For each item, the patient makes a selection from a 5-point rating scale, where 0 equals “not at all” and 4 equals “very much.”

Patients should fill out the questionnaires at the beginning of each visit, before any extensive contact and consultation with the clinician/study investigator. Consultation with the clinician may bias the patient’s perceptions about his or her health-related QOL and thus affect FACT-L/Ntx assessment.

For questionnaires completed at the beginning of a cycle, the patient’s answers should be based on his or her response to treatment in the preceding cycle. For example, the questionnaire completed at the beginning of Cycle 2 describes the patient’s response during Cycle 1 and would be labeled as *Cycle 1 QOL*.

Study JMHD will use the TOI-L and the TOI-Ntx for analyses. The TOI, which measures the physical aspects of QOL, is often used as a single clinical trial outcome index and is considered to be the outcome measure that is most sensitive to change when assessing anticancer therapies (Cella et al. 1995).

The FACT-L/Ntx will be scored as recommended by the developers. At least 50% of the items within the subscale must be completed for a score to be calculated. For the FACT-L/Ntx and the TOI, all component subscales must be scored and at least 80% of all items must be completed. Each subscale and composite score will be considered valid based on these criteria. For all FACT scales and symptom indices, higher scores indicate better QOL.

6.3. Safety Evaluations

Sites will perform safety evaluations as described in this section and the Study Schedule (Appendix 1) until study completion. During the extension period, investigators remain responsible for performing any procedures and tests needed for the appropriate care of the patient; however, only data regarding study drug administration, AEs, and SAEs will be reported on the CRF.

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

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

Physical exams, documentation of concomitant medications, ECOG performance status, CTCAE grading, and blood chemistry will be performed at the beginning of each cycle during induction and maintenance therapy; additional chemistry values may be collected per local practice or at the investigator's discretion. Hematology will be performed weekly during induction therapy. During maintenance therapy, hematology will be performed at the beginning of each cycle; additional hematology values may be collected during maintenance therapy per local practice or at the investigator's discretion. PT/INR will be performed as clinically indicated. Specific details are included in the Study Schedule (Appendix 1).

At baseline, all patients will be assessed by physical examination and brain imaging (CT scan or MRI) to determine eligibility. Randomized patients with stable brain metastasis will be monitored every 2 cycles using the same imaging modality that was used at baseline.

Hypertension will be monitored through routine evaluation of blood pressure before each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Proteinuria will be monitored by UPCR or dipstick at every cycle.

Gastrointestinal toxicities will be monitored through interval history with specific targeted questions (see Appendix 9) and physical examination. Patients with evidence of GI toxicity should be more thoroughly evaluated by CT or MRI scans and/or by a gastroenterologist to assess for diverticulitis, abscess, fistula, or perforation.

If patients receiving bevacizumab require elective major surgery, bevacizumab should be held for 4 to 8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure. In the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, chemotherapy should be restarted no earlier than 6 weeks after surgery and bevacizumab should be restarted no earlier than 8 weeks after surgery.

The investigator remains responsible for following, through an appropriate health care option, AEs 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.

6.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to a drug or drug delivery system.

Lack of drug effect is not an AE in clinical trials because the purpose of the clinical trial is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to study drug or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

During the study, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

After the informed consent document is signed, all AEs related to protocol procedures are reported to Lilly or its designee via CRF.

All AEs occurring after the patient receives the first dose of study drug must be reported to Lilly or its designee via CRF.

Study site personnel will record any daily dosage that exceeds the maximum dosage in the protocol or in the relevant reference safety document (for example, clinical dosage section for humans in the investigator brochure), whichever is greater, via CRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug, and/or drug delivery system via CRF.

Events leading to the clinical outcome of death due to disease progression will be included as part of the safety and efficacy analyses for this study and will not be reported to Lilly or its

designee as AEs via CRF unless the investigator believes the event may have been caused by the study drug or drug delivery system.

Any clinically significant findings from laboratory tests or vital sign measurements that result in a diagnosis should be reported to Lilly or its designee using the CRF.

6.3.1.1. Serious Adverse Events

SAE collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

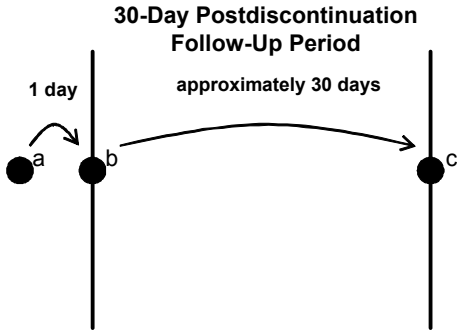
Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. An SAE is any adverse event from this study that results in one of the following outcomes:

- death (excluding death due to progression of study disease, unless related to study treatment)
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.3.1.2. Postdiscontinuation Safety Follow-Up Assessments

For all patients, a follow-up visit will occur approximately 30 days after discontinuation from study treatment. The 30-day postdiscontinuation follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. The 30-day postdiscontinuation follow-up visit occurs at or near the end of the 30-day postdiscontinuation follow-up period (see Figure JMHD.3).



[a] The date the patient and the investigator agree to discontinue the patient from all study treatment. (Also referred to as the Summary Date.)

[b] Day 1 of the 30-day postdiscontinuation follow-up period.

[c] The 30-day follow-up visit, approximately Day 30 of the 30-day postdiscontinuation follow-up period.

Figure JMHD.3. 30-day follow-up period.

For patients who discontinue from study treatment prior to study completion, evaluation at the 30-day postdiscontinuation follow-up visit will include:

- FACT-L/Ntx assessments
- chemistry and hematology assessments
- CTCAE grade (Version 3.0, NCI 2006) (if delayed toxicity related to study drugs is observed, the patient must be assessed approximately every 30 days until toxicity resolves or is stabilized)
- report of postdiscontinuation AEs, including the following:
  - any AEs, regardless of relatedness to study treatment or protocol procedure, that occurred after discontinuation of study treatment
  - any residual AEs
  - documentation of date of death, if death has occurred
  - key concomitant medications including G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF), ESAs, antibiotics, and any nonstudy vitamin supplementation
  - study drug-related or adverse event-related hospitalizations
  - transfusions.

After the 30-day postdiscontinuation visit, only SAEs thought to be related to study drug or protocol procedures should be reported immediately to Lilly or its designee via the designated transmission method and recorded on the CRF. For these events, the patient must be followed every 30 days until the event has resolved, stabilized, or until the initiation of a new anticancer systemic therapy.

For patients who discontinue from study treatment during the extension period, postdiscontinuation follow-up procedures will be performed as shown in the Extension Period Schedule (Appendix 10).

6.3.2. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures and will review trends, laboratory analytes, and AEs at periodic intervals.

6.3.3. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee
- determining when a drug/drug delivery system is to be returned for investigation.

6.4. Sample Collection and Testing

Appendix 2 lists the specific tests performed until study completion. During the extension period, investigators are responsible for performing any procedures and tests needed for the appropriate care of the patient; however, the results of the procedures and tests will not be reported on the CRF.

6.4.1. Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the Study Schedule (Appendix 1). Standard laboratory tests, including chemistry, hematology, and urinalysis, will be performed. A pregnancy test will be performed if applicable. Other clinical laboratory tests will be analyzed by a central or local laboratory. Appendix 2 lists the specific tests that will be performed for this study.

Investigators must document their review of each laboratory report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

6.4.2. Samples for Drug Concentration Measurements Pharmacokinetics

Blood samples (4 mL for each drug at each time point) for PK assessment will be collected in 20 patients in Arm A and 20 patients in Arm B. Details of the sampling instructions and the schedule for blood draws are listed in Appendix 7. Plasma samples will be assayed for bevacizumab, pemetrexed, and carboplatin (total platinum and free platinum) using validated analytical methods.

The times for sampling blood are nominal times; the actual sampling time should be accurately recorded for use in the analyses. Bioanalytical samples collected to measure study drug concentration will be retained for a maximum of 1 year following the last patient visit for the study.

A total of 35 blood samples per patient will be collected in Arm A (total blood volume approximately 140 mL). A total of 23 blood samples per patient will be collected in Arm B (total blood volume approximately 92 mL).

6.4.3. Stored Samples for Translational Research

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to pemetrexed, carboplatin, and bevacizumab and to the disease state. The study will also analyze the correlation between biomarkers and clinical outcome. All sites are required to participate in this translational research, with the exception of sites where local regulations prohibit this activity. Patient participation in this portion of the study is optional. Patients will provide consent by signing the translational research portion of the informed consent document (ICD). Patients will not receive the translational research results.

The following samples will be collected for translational research:

- Pretreatment paraffin-embedded tissue will be collected from the tissue sample taken to make the initial histologic diagnosis of cancer. The tissue will be used for research aimed at identifying markers capable of predicting clinical outcome to treatment with pemetrexed, carboplatin, and bevacizumab.
- A pretreatment plasma sample will be taken to investigate any additional markers of interest based on future trial information related to bevacizumab response.
- Whole blood-derived DNA will also be stored for genetic analyses of single nucleotide polymorphisms (SNPs) or other DNA changes.

Samples will be collected at the times specified in the Study Schedule (Appendix 1).

Tissue samples will be collected for immunohistochemical and gene expression analyses, including but not limited to:

- Thymidylate synthase (TS): TS is a direct enzyme target of pemetrexed and plays an essential role in DNA synthesis. Evidence suggests that high levels of TS may represent a resistance state to folates.
- Thyroid transcription factor 1 (TTF-1): TTF-1 is a known marker for lung histology and a transcription factor that is important in lung development and function. Recent evidence (Kendall et al. 2007; Weir et al. 2007) suggests a role as an amplified oncogene in lung cancer.
- Folate receptor-alpha (FR-α): FR-α is a membrane transporter of folates and may contribute to concentration of pemetrexed into the tumor cell. FR-α levels may be varying in different lung histologies present in NSCLC.
- Folylpolyglutamyl synthetase (FPGS): FPGS is an enzyme responsible for polyglutamation of pemetrexed. This results in higher affinity binding of pemetrexed to both the folate-dependent enzymes TS and glycinamide ribonucleotide formyltransferase (GARFT).
- Excision-repair cross-complementing rodent repair deficiency 1 (ERCC1): ERCC1 is a DNA repair enzyme thought to play a role in sensitivity to platinum agents. High ERCC1 levels may represent an ability for the tumor to repair cleavage induced by platinum agents and thus, a marker of resistance.

Other markers of interest may be examined, based on information evolving at the time the laboratory assessments are done. For example, antiangiogenesis markers such as adhesion proteins and circulating VEGF may be investigated. Taken collectively, these evaluations may assist in understanding the biology of lung cancer in this group of patients and their response to therapy.

Stored samples will retain the patient identifier (for example, trial patient numbers) and therefore will not be stored indefinitely. Samples will be stored for a maximum of 5 years after the last patient visit for the study; any sample remaining at that time will be destroyed. Samples will be stored in the United States.

6.4.3.1. Collection Procedures for Translational Research

At the baseline visit (Visit 0), approximately 10 mL of blood for DNA and approximately 5 mL of blood for plasma will be collected by venipuncture.

Supplies required for the collection and shipment of the patients' stored samples will be supplied by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

A small amount of preserved tissue previously taken to make the initial histologic diagnosis of cancer will be obtained for immunohistochemical and gene expression analysis. The tissue is currently preserved in formalin. The size of the sample will be approximately 3 to 5 mm.

6.5. Appropriateness of Measurements

All efficacy and safety assessments used in this study are appropriate for an oncology study. Overall survival is an appropriate primary endpoint in a randomized Phase 3 study. Progression-free survival, objective response rate, and PROs are acceptable secondary endpoints and are clinically relevant in patients with Stage IIIB or IV NSCLC. The FACT-L/Ntx (Cella et al. 1995; Calhoun et al. 2003) is a reliable and valid instrument used to assess quality of life and side effects of treatment in patients with cancer. The CTCAE (Version 3.0, NCI 2006) is an acknowledged method used to evaluate AEs in oncology trials.

7. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate.
- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and use standard computer edits to detect errors in data collection.
- verify the quality of the data.

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

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ethical review boards (ERBs) with direct access to original source documents.

7.1. Data Entry and Computerized Systems

An electronic data capture system will be used in this trial. Some or all of a patient's data (for example, a rating scale, daily dosing schedule, patient diary, event diary) may be directly entered into the system on a CRF (for example, personal desk assistant [PDA], or by means of IVRS) at the time that the information is obtained. In these instances where there is no prior written or electronic record of the data, the CRF (for example, PDA, or by means of IVRS) will serve as the source document.

Case report form (CRF) data collected by the contract research organization (CRO) will be encoded by the CRO and stored electronically in the CRO's database system. Validated data will subsequently be transferred to the sponsor's data warehouse, using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the CRF will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

8. Sample Size and Statistical Methods

8.1. Determination of Sample Size

The primary objective is to compare first-line treatment with pemetrexed, carboplatin, and bevacizumab followed by pemetrexed plus bevacizumab (Arm A) versus paclitaxel, carboplatin, bevacizumab followed by bevacizumab (Arm B), in terms of OS in patients with Stage IIIB (with pleural effusions) or IV NSCLC.

The study will enroll approximately 900 patients (450 per arm), with the final analysis of OS to be performed after 676 deaths have occurred. Assuming an HR of 0.80, this sample size yields at least 80% statistical power to detect superiority of the pemetrexed-combination arm over the paclitaxel-combination arm with the use of a 1-sided log-rank test and a type I error of 0.025 (Freedman 1982). If the true median OS for the paclitaxel-combination arm (Arm B) is 12.3 months (Sandler et al. 2006), then the HR of 0.8 amounts to an approximately 3-month improvement in median OS for the pemetrexed-combination arm (Arm A), under assumption of exponential survival distribution. Assuming approximately 5% screening failure, the study will enter approximately 950 patients.

Pharmacokinetics of total and free platinum (both derived from carboplatin) will be characterized in Arm A and Arm B to evaluate whether pemetrexed has any effect on carboplatin disposition. For comparing free-platinum PK with or without pemetrexed, PK sampling will be conducted in 20 patients in each of these 2 arms. A sample size of 20 patients per arm with at least 18 completers will have at least 90% power that the 90% CI of the ratio of AUC of free platinum for Arm A/Arm B (that is, with pemetrexed/no pemetrexed) will fall within (0.7, 1.43). A completer is defined as a patient who completes the dose administration and PK sampling in Cycle 1 as per the PK sampling schedule (see Appendix 7). This sample size of 18 completers will also provide at least 60% power that the 90% CI of the ratio of AUC for total platinum for Arm A/Arm B will fall within the limits of (0.7, 1.43). These calculations are based on the assumption of log-normal distribution, a true mean ratio of 1 (for both free and total platinum AUC), and an estimate of intersubject variability of approximately 26.2% (free platinum) and 42.9% (total platinum) reported in a published study (Obasaju et al. 1996).

Bevacizumab PK will also be characterized in both groups of patients to determine if pemetrexed has any effect on bevacizumab PK. A sample size of 18 completers will provide approximately 70% power for the 90% CI of the ratio of bevacizumab AUC for Arm A/Arm B to fall within the limits of (0.7, 1.43). These calculations are based on the assumption of log-normal distribution, a true mean ratio of 1, and an estimate of intersubject variability of approximately 39.7% (AUC) from observed bevacizumab data in a published study (Herbst et al. 2005).

8.2. Statistical and Analytical Plans

8.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company. The interpretation of study results will be the responsibility of the Lilly clinical research physician

(CRP) and the statistician. The Lilly CRP and the statistician will also be responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication. Additional independent review of the data may be conducted if deemed appropriate.

Efficacy analyses will be conducted according to the ITT principle with patients grouped as assigned to treatment. Safety analyses will include all enrolled patients receiving at least 1 dose of any of study drugs, grouped as treated.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, all tests of interactions will be conducted at a 2-sided level of 0.10, and all confidence intervals will be given at a 2-sided 95% level, unless otherwise stated.

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. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

8.2.2. Patient Disposition

A detailed description of patient disposition will include a summary of the following:

- all patients entered and enrolled: overall, by treatment arm, and by country
- reasons for patients entered, but not enrolled
- all enrolled patients treated with study drug, by treatment arm
- reasons patients enrolled, but not treated with study drug
- reasons patients discontinued study drug treatment
- all important protocol violations.

8.2.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- patient demographics
- baseline disease characteristics
- preexisting conditions
- prior therapies.

Other patient characteristics will be summarized as deemed appropriate.

8.2.4. Concomitant Therapy

Concomitant medication will be summarized for all randomized patients per treatment arm.

8.2.5. Treatment Compliance

The number of dose omissions, reductions, and delays, and the number of cycles received will be summarized for all treated patients per treatment arm. Summarizations will be performed for the induction period, the maintenance period, and for the combination of the induction and maintenance periods.

8.2.6. Primary Outcome and Methodology

The primary outcome measure for this trial is OS. All randomized patients, according to the ITT principle, will be included in the analysis of OS. The primary analysis will be the comparison of OS between Arm A and Arm B using a 1-sided log-rank test at a significance level of 0.025 (or equivalently, at a 2-sided significance level of 0.05). Kaplan-Meier (K-M) estimation (Kaplan and Meier 1958), including generating K-M curves, quartiles, and interval estimation using 95% confidence intervals, will also be performed.

The supportive analysis of the primary outcome will include a Cox (1972) regression model to estimate treatment HR after adjusting for the following potential prognostic variables:

- disease stage (IIIB with pleural effusions versus IV)
- age (≤ 70 versus > 70 years)
- sex (male versus female)
- ethnic origin (Caucasian versus non-Caucasian)
- basis for pathologic diagnosis (histopathological versus cytological)
- measurable versus nonmeasurable disease
- previously treated brain metastasis (yes versus no)
- smoking status (ever versus never)
- histologic subtype (adenocarcinoma versus large cell versus other).

Analyses may exclude any cofactor (listed above) from the Cox models for 1 or more of the following reasons:

1. if the number of patients representing 1 level of that variable is insufficient
2. if data collected on that variable are insufficiently complete
3. if that cofactor was consistently found to have no prognostic impact ($p > 0.1$).

8.2.7. Secondary Efficacy Analyses

The secondary efficacy endpoints are RR, DCR, and time-to-event variables PFS and TTPD. All randomized patients, according to the ITT principle, will be included in the analysis of these endpoints. For each of the time-to-event endpoints, the following analyses will be performed:

- Kaplan-Meier estimation, including generating K-M curves, quartiles, and interval estimation using 95% confidence intervals

- log-rank test
- Cox regression model adjusting for the potential prognostic variables listed in Section 8.2.6.

The RR and DCR will be compared between Arm A and Arm B using the Fisher exact test. A 95% confidence interval for the response rate of each arm will be calculated using an exact method. The RR will be estimated by dividing the total number of confirmed CRs and PRs by the total number of patients randomized. The DCR will be estimated by dividing the total number of confirmed CRs, PRs, and SDs by the total number of patients randomized.

8.2.7.1. Time-to-Event Analyses for Patients Who Receive Maintenance Therapy

The analyses listed above for the time-to-event endpoints OS, PFS, and TTPD will also be performed for patients who receive maintenance therapy (that is, excluding patients who do not receive maintenance therapy).

8.2.7.2. Sensitivity Analysis for PFS and TTPD

In the primary definitions of PFS and TTPD (Section 6.1.2), patients who receive postdiscontinuation systemic anticancer therapy are censored as a way to control confounding antitumor effect of the subsequent anticancer therapy. As a sensitivity analysis, the above analyses of PFS and TTPD will also be performed when this censoring is not considered. That is, the following definitions for PFS and TTPD will be used to assess the robustness of the PFS and TTPD analyses.

Progression-free survival (PFS): Duration is measured from the date of randomization to the date of objective progression of disease or the date of death from any cause, whichever is earlier. For patients not known to have died as of the data inclusion cutoff date and who do not have objective progressive disease, PFS will be censored at the date of the last objective progression-free disease assessment prior to the cutoff date.

Time to progressive disease (TTPD): Time is measured from the date of randomization to the first date of objective progression of disease. For patients not known to have had objective progression of disease as of the data-inclusion cutoff date for a particular analysis, or who has died without objective progression of disease, TTPD will be censored at the date of the last objective progression-free disease assessment prior to the cutoff date.

8.2.8. Pharmacokinetic/Pharmacodynamic Analyses

8.2.8.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameters will be computed using noncompartmental methods of analysis using WinNonlin® Professional Edition on a computer that meets or exceeds the minimum system requirements for this program. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by Lilly Global Pharmacokinetic management.

Pharmacokinetic parameters to be determined by noncompartmental PK analysis based on plasma concentration versus time data for total platinum and free platinum include: $AUC_{0-\infty}$, C_{max}, CL, V_{ss}, and $t_{1/2}$. For bevacizumab, the PK parameters that will be determined include $AUC_{0-\infty}$, C_{max}, and CL. If data do not allow full characterization, then the analysis may be restricted to descriptive evaluation using graphical comparison between Arm A and Arm B.

Pharmacokinetic evaluation of plasma concentration versus time data for pemetrexed may be limited to descriptive evaluation (that is, overlay plot) to verify consistency with reference pemetrexed PK results. In addition, nonlinear mixed effect modeling method (NONMEM®) will be utilized to fit the plasma concentrations of pemetrexed to the best PK model, relying upon PK data and analyses from previous studies. The PK parameters to be estimated include the plasma CL, V, AUC, and $t_{1/2}$.

8.2.8.2. Pharmacokinetic Statistical Inference

Free platinum, total platinum, and bevacizumab $AUC_{0-\infty}$ (or partial AUC based on plasma concentration time-profile) and C_{max} will be log-transformed and analyzed using a mixed-effects model allowing for the fixed effect of treatment (such as: carboplatin with [Arm A] or without pemetrexed [Arm B], or bevacizumab with [Arm A] or without pemetrexed [Arm B]) and the random effect of patient.

Least squares means will be calculated for carboplatin and bevacizumab AUC in Arm A and in Arm B, as well as the mean differences between both treatments (with or without pemetrexed). The residual variance from the analysis of variance (ANOVA) will be used to calculate the 90% confidence intervals for the differences between treatments. These values will be back transformed to give point estimates and 90% confidence interval for the ratios of the treatments. For these calculations, Arm B (absence of pemetrexed) will be taken as the reference. If the 90% confidence interval for the ratio of AUCs is contained between 0.7 and 1.43, then it could be concluded that no statistically significant drug-drug interaction exists between carboplatin and pemetrexed or between bevacizumab and pemetrexed.

Variance components for the interpatient (between) and intrapatient (within) variability in C_{max} and AUC will be obtained through the linear mixed-effects model. These variances will be expressed as coefficients of variation. The procedure MIXED in the statistical package SAS® will be utilized in running the ANOVA models and in estimating the variance components.

8.2.9. Health Outcome Analyses

The objective of the PRO assessment in this study is to compare clinically meaningful changes in patient-reported toxicity effects and lung cancer symptoms over time using the neurotoxicity and lung cancer subscales of the FACT-L/Ntx. Clinically important difference thresholds will be used to define the proportion of patients that improve, remain stable, or worsen.

The QOL scores will be summed at baseline and for each visit in order to calculate changes from baseline mean scores. These data will be compared between the 2 treatment arms. The scores will include:

- FACT-L total and subscale scores and TOI-L
- FACT/GOG-Ntx total and subscale scores and TOI-Ntx.

Other exploratory analyses may be performed, including longitudinal modeling (for example, repeated measures models and the impact of covariates) and subgroup analysis (for example, age ≤ 70 versus > 70, and subgroups based on ECOG performance status, tumor response status, PFS, and OS).

As a part of analyses, the following definitions apply:

- A patient will be considered as having improved health-related QOL, functioning, symptoms, and health status if the change in the scores of the FACT-L/Ntx and specific subscales rise by at least a clinically meaningful change where established and/or 0.5 standard deviation.
- A patient will be considered as having worse health-related QOL, functioning, symptoms, and health status if the change in the scores of the FACT-L/Ntx and specific subscales fall by at least a clinically meaningful change where established and/or 0.5 standard deviation.
- A patient will be considered as having no change in health-related QOL, functioning, symptoms, and health status if the patient does not fall into either category above.

The appropriate standard deviation will be estimated from the baseline total and subscale scores of all patients (Juniper et al. 1994). Estimates of clinical meaningful change for classification of individuals are shown in Table JMHD.6. Different values will be used for between-group comparisons (Cella et al. 2002a, 2002b). Distribution- and patient-based global rating of change methods will be used for determination of clinically meaningful change for the social/family subscale, which has not yet been established. Further analyses to explore clinically meaningful change may be performed (Wyrwich et al. 1999; Fairclough 2002).

Table JMHD.6. Definition of Clinically Meaningful Change FACT Instruments

Instrument	Scale/Subscale	Clinically Meaningful Change	Reference
FACT-G	PWB	3 points	Cella et al. 2002b
	FWB	3 points	Cella et al. 2002b
	EWB	3 points	Cella et al. 2002b
	SWB	not yet established	
FACT-L	LCS	3 points	Cella et al. 2002a
	Total FACT-L	10 points	Personal communication (D Cella 2002)
	TOI-L	6 points	Cella et al. 2002a
FACT/GOG-Ntx	Ntx subscale	3 points	Cella et al. 2003

Abbreviations: EWB = emotional well-being; FWB = functional well-being; FACT = Functional Assessment of Cancer Therapy; G = general; GOG = Gynecologic Oncology Group; L = lung; LCS = lung cancer subscale; Ntx = neurotoxicity; PWB = physical well-being; SWB = social/family well-being; TOI-L = Trial Outcome Index-Lung.

If at least 50% of items within a subscale are completed, each missing item will be imputed by the average of the completed items; if more than 50% of items within a subscale are missing, the score of the subscale will be treated as missing (Cella 1997). The total FACT-L, total FACT/GOG-Ntx, and the TOIs will be scored only if at least 80% of the items that make up these composite scores are completed and at least 50% of the items are completed within each subscale. If these 2 conditions are satisfied, each missing item within each subscale will be imputed by the average of the completed items within the subscale. Otherwise, the total FACT-L, total FACT/GOG-Ntx, and TOI scores will be treated as missing (Fairclough and Cella 1996).

8.2.10. Safety Analyses

The safety evaluation will include all randomized patients who receive at least 1 dose of any study drug. Safety analyses will include summaries of the following, grouped by actual treatment:

- maximum CTCAE grades for laboratory and nonlaboratory AEs
- treatment-emergent adverse events (TEAEs), by severity and investigator-determined relatedness to study drug
- adverse events causing discontinuation from the study, regardless of causality and by investigator-determined relatedness to study drug
- SAEs, regardless of causality and by investigator-determined relatedness to study drug
- hospitalizations during the study treatment period or during the 30-day postdiscontinuation follow-up period

- blood transfusions during the study treatment period or during the 30-day postdiscontinuation follow-up period
- deaths during the study treatment period or during the 30-day postdiscontinuation follow-up period
- concomitant medications during the study treatment period or during the 30-day postdiscontinuation follow-up period (for example, erythropoiesis stimulating agents, growth factors, antibiotics, antiseizure agents, antidepressants, and analgesics).

The incidences of the above AEs will be compared between Arm A and Arm B using the Fisher exact test.

8.2.11. Subgroup Analyses

8.2.11.1. Efficacy Subgroup Analyses

Subgroup analyses of time-to-event endpoints OS, PFS, and TTPD will be performed for each potential prognostic factor listed in Section 8.2.6. For each factor, the treatment-by-subgroup interaction will be tested at the 0.10 level of significance using Cox regression model containing treatment, the factor, and treatment by the factor interaction in the model. Then, subsequent log-rank test, Kaplan-Meier estimate, and Cox regression model will be performed to estimate and compare treatment effect in each subgroup category.

Subgroup analyses of RR and DCR will also be performed for each potential prognostic factor listed in Section 8.2.6. For each factor, the treatment-by-subgroup interaction will be tested at the 0.10 level of significance using logistic regression model containing treatment, the factor, and treatment by the factor interaction in the model. Then, subsequent Fisher exact test will be performed to compare treatment difference in each subgroup category.

8.2.11.2. Safety Subgroup Analyses

If deemed appropriate, subgroup analyses of selected AEs may be performed for each potential prognostic factor listed in Section 8.2.6. For each factor, the treatment-by-subgroup interaction will be tested at the 0.10 level of significance using logistic regression model containing treatment, the factor, and treatment by the factor interaction in the model. Then, subsequent Fisher exact test will be performed to compare treatment difference in each subgroup category.

8.2.12. Interim Analyses

Four planned interim analyses will be conducted for this study.

1. The first interim analysis will be conducted for safety and futility after 250 patients have been enrolled into the study. The data cutoff date for inclusion in the interim analysis is the date when the 250th patient has completed 4 cycles of treatment or has been followed up for 3 months since enrollment if this patient is discontinued before 4 cycles of treatment. All visits completed prior to this data cutoff date will be validated for inclusion in the interim database.

2. The second interim analysis will be conducted for safety when 500 patients have been enrolled into the study. The data cutoff date for inclusion in this interim analysis is the date when the 500th patient has completed 1 cycle of treatment. All visits completed prior to this data cutoff date will be validated for inclusion in the interim database.
3. The third interim analysis will be conducted for safety when 750 patients have been enrolled into the study. The data cutoff date for inclusion in this interim analysis is the date when the 750th patient has completed 1 cycle of treatment. All visits completed prior to this data cutoff date will be validated for inclusion in the interim database.
4. The fourth and final interim analysis will be conducted for safety after all planned 900 patients have been enrolled into the study. The data cutoff date for inclusion in this interim analysis is the date when the last patient has completed 1 cycle of treatment. All visits completed prior to this data cutoff date will be validated for inclusion in the interim database.

During each interim lock and analysis period except the fourth interim analysis, patient enrollment will continue but will not be included in that interim analysis.

An external DMC will be formed and will be responsible for evaluating interim results. Only the DMC is authorized to review completely unblinded interim efficacy and safety analyses. The DMC will be responsible for making recommendations as to whether continuing study treatment and enrollment is scientifically and ethically appropriate. A list of the planned interim analyses will be included in the DMC charter. A separate interim statistical analysis plan (iSAP) will be created after DMC charter approval to contain mocked tables, figures, and listings (mTFLs) for the planned interim analyses as well as detailed treatment unblinding. This iSAP will be a living document containing planned as well as any additional interim analyses DMC may request prior to interim lock.

8.2.12.1. Stopping Guidance for Safety

There will be no pre-specified rules for stopping the trial due to safety concerns. DMC members will review unblinded safety data at each interim to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.

8.2.12.2. Stopping Guidance for Futility at the First Interim

Futility for the first interim analysis will be determined in terms of PFS because the number of deaths is likely to be too low to yield a meaningful analysis on OS. The futility rule will be based on conditional power, which is the probability of observing significant results at the final analysis under alternative hypothesis assumption, given data at the interim. Because the alternative hypothesis at final analysis is based on the HR for OS, a corresponding alternative hypothesis in terms of HR for PFS is needed in order to calculate the conditional power in terms of PFS. It is believed that if the pemetrexed-combination arm (Arm A) can reduce the risk of death by 20% (that is, the alternative HR 0.8 for OS), then it should reduce risk of progression by at least 10%. Therefore, the conditional power will be calculated under the alternative hypothesis of HR 0.9 for PFS.

As guidance, if the conditional power is less than 12% (for illustrative purpose, this corresponds to the PFS HR > 1.21 under a Cox PH model), then the trial would be considered futile. This futility analysis will not affect overall alpha level and hence no alpha adjustment is needed for this interim analysis.

The futility threshold value of 12% was determined by a simulation study. In the simulation, the exponential PFS data with median PFS time of 6.2 months for the paclitaxel-combination arm (Arm B; Sandler et al. 2006) and median PFS time of 6.9 months for the pemetrexed-combination arm (Arm A) are generated according to the alternative hypothesis of HR 0.9. If 250 patients can be enrolled in the first 11 months and all 900 patients can be enrolled in 24 months, and that the interim analysis will be performed 3 months after the enrollment of 250 patients, then the conditional power falls below 12% in 5% of 1000 simulations. Similar simulation results can be obtained if enrollment of 900 patients takes up to 30 months.

Because the stopping guidance for this interim analysis was based on a simulation, which was based on a number of assumptions (such as exponential PFS, accrual time, and alternative hypothesis of HR 0.9 for PFS) that may well be violated by the actual trial enrollment and the observed data, the stopping guidance should be viewed as only guidance, not the absolute rules, and they may be updated in a separate iSAP prior to an interim datalock if deemed necessary.

8.2.13. Translational Research

The distributions of biomarkers with continuous measures, such as gene or protein expression, will be described for the total patient population and by treatment arm. Summary statistics will include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures, such as genotype locus or IHC-staining-assessed protein expression, will be summarized in frequency tables for the total population and by treatment arm.

Associations between clinical endpoints (OS, PFS, TTPD, RR, and DCR) and markers will be evaluated using data from patients who have a reported value for the marker measure of interest. Markers and their interaction with treatment will be assessed on an individual basis; that is, a given marker will be analyzed separately. Discrete measures, such as IHC–staining-assessed protein expression or marker genotype, will be assessed by including these measures as a class effect in the appropriate analytical models. Continuous measures, such as relative gene expression levels, will be dichotomized into low- and high-value groups at the point that best associates these groups with the particular clinical outcome.

Patients will be ordered according to the value of the appropriate measure of marker expression and divided into low- and high-expression subgroups, beginning at the 25th quartile. This grouping, along with its interaction with treatment, will be included as a class effect in the analytical model (for example, Cox regression of time-to-event endpoints). The model will be fit in an iterative fashion by forming groups at each point from the 25% to the 75% cut point of the population. The Wald chi-square statistics for the interaction term from each analysis will be compared, and the maximum value will be used to test the ability of a marker to identify differences in treatment impact on clinical outcome. Because this test statistic is the maximum from a set of values, a direct comparison with the one-degree-of-freedom chi-square distribution

is not appropriate. The probability of the maximum chi-square value will be assessed using an asymptotic cumulative distribution function formula described by Miller and Siegmund (1982).

9. Informed Consent, Ethical Review, and Regulatory Considerations

9.1. 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 in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICD 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 or legal representative. This includes obtaining the appropriate signatures and dates on the ICD prior to the performance of any protocol procedures and prior to the administration of study drug.

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

9.2. Ethical Review

Lilly must agree with all ICDs before they are submitted to the ethical review boards (ERBs) and are used at investigative sites. All informed consent documents must be compliant with the International Conference on Harmonisation (ICH) guideline on good clinical practice (GCP). Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations and performed in accordance with a written process approved by Lilly.

Documentation of ERB approval of the protocol and the ICD must be provided to Lilly *before* the study may begin at the investigative sites. The ERBs will review the protocol as required.

Any member of an ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

The ERBs should be provided with the following:

- the current investigator's brochure or package labeling and updates during the course of the study
- informed consent document
- relevant curricula vitae.

9.3. Regulatory 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, head of the medical institution, or designee will promptly submit the protocol to applicable ERBs.

Pemetrexed is being studied in the United States under a US Investigational New Drug (IND) application. The US IND number is 40,061.

All or some of the obligations of the sponsor will be assigned to a CRO.

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

9.3.1. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

9.3.2. Protocol Signatures

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

9.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator chosen by Lilly will serve as the clinical study report coordinating investigator.

The sponsor’s responsible medical officer will sign the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10. References

[ACS] American Cancer Society. 2007. Global cancer facts and figures 2007. Available at: http://www.cancer.org/downloads/STT/Global_Cancer_Facts_and_Figures_2007_rev.pdf. Accessed 14 February 2008.

[ACS] American Cancer Society. 2008. Cancer Facts and Figures 2008. Available at: http://www.cancer.org/docroot/STT/stt_0.asp. Accessed 21 February 2008.

[AHA] American Heart Association. 1994. 1994 Revisions to classification of functional capacity and objective assessment of patients with diseases of the heart. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1712. Accessed 25 February 2008.

Belani CP, Larocca RV, Rinaldi DA, Tester WJ, Gable PS, Perry MC. 2004. A multicenter, phase III randomized trial for stage IIIB/IV NSCLC of weekly paclitaxel and carboplatin vs. standard paclitaxel and carboplatin given every three weeks, followed by weekly paclitaxel. J Clin Oncol 22(14 S):621s. Abstract 7017.

Belani CP, Perry MC, La Rocca RV, Rinaldi D, Gable PS, Tester WJ. 2005. Maintenance therapy (MT) with weekly paclitaxel improves outcome for advanced non-small cell lung cancer (NSCLC) patients. J Clin Oncol 23(16 Suppl):656s. Abstract 7143.

Bevacizumab [package insert]. 2008. South San Francisco, CA: Genentech, Inc.

Boulikas T, Vougiouka M. 2004. Recent clinical trials using cisplatin, carboplatin and their combination chemotherapy drugs (review). Oncol Rep 11(3):559-595.

Brodowicz T, Krzakowski M, Zwitter M, Tzekova V, Ramlau R, Ghilezan N, Ciuleanu T, Cucevic B, Gyurkovits K, Ulsperger E, Jassem J, Grgic M, Saip P, Szilasi M, Wiltschke C, Wagnerova M, Oskina N, Soldatenkova V, Zielinski C, Wenczl M; Central European Cooperative Oncology Group CECOG. 2006. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 52(2):155-163.

Calhoun EA, Welshman EE, Chang CH, Lurain JR, Fishman DA, Hunt TL, Cella D. 2003. Psychometric evaluation of the Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. Int J Gynecol Cancer 13(6):741-748.

Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E. 1989. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7(11):1748-1756.

Cella D. 1997. Manual of the Functional Assessment of Chronic Illness Therapy (FACIT), Version 4. Center on Outcomes, Research and Education (CORE). Evanston Northwestern Healthcare and Northwestern University.

Cella D, Eton DT, Fairclough DL, Bonomi P, Heyes AE, Silberman C, Wolf MK, Johnson DH. 2002a. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. J Clin Epidemiol 55(3):285-295.

Cella D, Hahn EA, Dineen K. 2002b. Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. Qual Life Res 11(3):207-221.

Cella D, Peterman A, Hudgens S, Webster K, Socinski MA. 2003. Measuring the side effects of taxane therapy in oncology: the functional assessment of cancer therapy-taxane (FACT-Taxane). Cancer 98(4):822-831.

Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. 1995. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 12(3):199-220.

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, Eckberg K, Lloyd S, Purl S, Blendowski C, Goodman M, Barnicle M, Stewart I, McHale M, Bonomi P, Kaplan E, Taylor S IV, Thomas CR Jr, Harris J. 1993. The Functional Assessment of Cancer Therapy (FACT) scale: development and validation of the general measure. J Clin Oncol 11(3):570-579.

Ciuleanu TE, Brodowicz T, Belani CP, Kim J, Krzakowski M, Laack E, Wu Y, Peterson P, Adachi S, Zielinski CC. 2008. Maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC: a phase III study [abstract]. In: Proc Am Soc Clin Oncol 44th annual meeting program; 2008 May 30 to June 3; Chicago. J Clin Oncol 26. Abstract 8011.

Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. Nephron 16(1):31-41.

Cox DR. 1972. Regression models and life-tables. J Royal Stat Soc Ser B 74(2):187-220.

D'Addario G, Felip E. 2008. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 19(Suppl 2):ii39-ii40.

Dalsania CJ, Hageboutros A, Harris E, Krieger K, Vora C, Stevenson JP. 2007. Phase II trial of bevacizumab plus pemetrexed and carboplatin in previously untreated advanced nonsquamous non-small cell lung cancer. In: Proc 8th International Lung Cancer Conf; 2007 Jun 27-30; Maui. Danvers (MA): CIG Media Group, LP. p 444. Abstract 02.

Davies AM, Chansky K, Lau DH, Leigh BR, Gaspar LE, Weiss GR, Wozniak AJ, Crowley JJ, Gandara DR; SWOG S9712. 2006. Phase II study of consolidation paclitaxel after concurrent chemoradiation in poor-risk stage III non-small-cell lung cancer: SWOG S9712. J Clin Oncol 24(33):5242-5246.

Fairclough DL. 2002. Design and analysis of quality of life studies in clinical trials. Boca Raton (FL): Chapman & Hall/CRC Press LLC. 328 p.

Fairclough DL, Cella DF. 1996. Functional Assessment of Cancer Therapy (FACT-G): non-response to individual questions. Qual Life Res 5(3):321-329.

Fidias P, Dakhil S, Lyss A, Loesch D, Waterhouse D, Cunneen J, Chen R, Treat J, Obasaju C, Schiller J. 2007. Phase III study of immediate versus delayed docetaxel after induction therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer: updated report with survival. J Clin Oncol 25(18 S):388s. Abstract 7516.

Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Belani C. 2003. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 Study Group. J Clin Oncol 21(16):3016-3024.

Freedman LS. 1982. Tables of the number of patients required in clinical trials using the logrank test. Stat Med 1(2):121-129.

Genentech. November 2007. Investigator's brochure for Ro 4876646 Avastin® (bevacizumab).

Glusker P, Recht L, Lane B. 2006. Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med 354(9):980-982.

Gordon MS, Margolin K, Talpaz M, Sledge GW Jr, Holmgren E, Benjamin R, Stalter S, Shak S, Adelman DC. 2001. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol 19(3):843-850.

Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller, DG, Morrow M, eds. American Joint Committee on Cancer. 2002. AJCC cancer staging manual. 6th ed. New York, NY: Springer.

Hambleton J, Skillings J, Kabbinavar F, Bergsland E, Holmgren E, Holden SN, Hurwitz H, Scappaticci F. 2005. Safety of low-dose aspirin (ASA) in a pooled analysis of 3 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol 23(16S):259s. Abstract 3554.

Hanna N. Metastatic lung cancer. Poster presented at: Annual Meeting of the American Society of Clinical Oncology; 2008; Chicago.

Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, Gatzemeier U, Tsao TC, Pless M, Muller T, Lim HL, Desch C, Szondy K, Gervais R, Shaharyar, Manegold C, Paul S, Paoletti P, Einhorn L, Bunn PA Jr. 2004. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22(9):1589-1597.

Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, Scagliotti G, Rosell R, Oliff I, Reeves JA, Wolf MK, Krebs AD, Averbuch SD, Ochs JS, Grous J, Fandi A, Johnson DH. 2004. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. J Clin Oncol 22(5):785-794.

Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, Kris MG, Tran HT, Klein P, Li X, Ramies D, Johnson DH, Miller VA; TRIBUTE Investigator Group. 2005. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 23(25):5892-5899.

Hughes A, Calvert P, Azzabi A, Plummer R, Johnson R, Rusthoven J, Griffin M, Fishwick K, Boddy AV, Verrill M, Calvert H. 2002. Phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma. J Clin Oncol 20(16):3533-3544.

Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF 3rd, Gaudreault J, Damico LA, Holmgren E, Kabbinavar F. 2004. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 22(11):2184-2191.

Juniper EF, Guyatt GH, Willan A, Griffith LE. 1994. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 47(1):81-87.

Kaplan EL, Meier P. 1958. Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481.

Karp JE, Gojo I, Pili R, Gocke CD, Greer J, Guo CF, Qian D, Morris L, Tidwell M, Chen H, Zwiebel J. 2004. Targeting vascular endothelial growth factor for relapsed and refractory adult acute myelogenous leukemias: Therapy with sequential 1-beta-D-arabinofuranosylcytosine, mitoxantrone, and bevacizumab. Clin Cancer Res 10(11):3577-3585.

Kelly K, Crowley J, Bunn PA Jr, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara DR. 2001. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 19(13):3210-3218.

Kendall J, Liu Q, Bakleh A, Krasnitz A, Nguyen KC, Lakshmi B, Gerald WL, Powers S, Mu D. 2007. Oncogenic cooperation and coamplification of developmental transcription factor genes in lung cancer. Proc Natl Acad Sci U S A 104(42):16663-16668.

Larsen H, Sorensen JB, Nielsen AL, Dombernowsky P, Hansen HH. 1995. Evaluation of the optimal duration of chemotherapy in phase II trials for inoperable non-small-cell lung cancer (NSCLC). Ann Oncol 6(10):993-997.

[Lilly] Eli Lilly and Company. May 2008. Investigator's brochure for pemetrexed.

Lustberg MB, Edelman MJ. 2007. Optimal duration of chemotherapy in advanced non-small cell lung cancer. Curr Treat Options Oncol 8(1):38-46.

Manegold C, Digumarti R, Zukin M, de Marinis F, Mellemgaard A, Gandara D, Simms L, Kaiser C, Blatter J, Gatzemeier U. 2007. Phase III study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Eur J Cancer 6(Suppl 5):9. Abstract 1BA.

Manegold C, Gatzemeier U, von Pawel J, Pirker R, Malayeri R, Blatter J, Krejcy K. 2000. Front-line treatment of advanced non-small-cell lung cancer with MTA (LY231514, pemetrexed disodium, ALIMTA) and cisplatin: a multicenter phase II trial. Ann Oncol 11(4):435-440.

McKoy JM, Patel J, Courtney DM, Bolden R, Bennett CL. 2008. Bevacizumab-associated diverticulitis. Community Oncology 5(1):31-32.

Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS. 2005. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 23(4):792-729.

Miller R, Siegmund D. 1982. Maximally selected chi-square statistics. Biometrics 38:1011-1016.

Morton RF, Sloan JA, Grothey A, Sargent DJ, McLeod H, Green EM, Fuchs C, Ramanthan RK, Williamson SK, Goldberg RM. 2005. A comparison of simple single-item measures and the common toxicity criteria in detecting the onset of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer. J Clin Oncol 23(16 Suppl 1). Abstract 8087.

[NCCN] National Comprehensive Cancer Network. 2008. NCCN clinical practice guidelines in oncology: non-small cell lung cancer. Available at: http://www.nccn.org/Registration/login/login.aspx. Accessed 23 June 2008.

[NCI] National Cancer Institute. 2006. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Available at: http://ctep.cancer.gov/reporting/ctc_v30.html. Accessed 25 February 2008.

Obasaju CK, Johnson SW, Rogatko A, Kilpatrick D, Brennan JM, Hamilton TC, Ozols RF, O'Dwyer PJ, Gallo JM. 1996. Evaluation of carboplatin pharmacokinetics in the absence and presence of paclitaxel. Clin Cancer Res 2(3):549-552.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5(6):649-655.

Ozcan C, Wong SJ, Hari P. 2006. Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med 354(9):981-982.

Park JO, Kim SW, Ahn JS, Suh C, Lee JS, Jang JS, Cho EK, Yang SH, Choi JH, Heo DS, Park SY, Shin SW, Ahn MJ, Lee JS, Yun YH, Lee JW, Park K. 2007. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non small-cell lung cancer. J Clin Oncol 25(33):5233-5239.

Patel JD, Hensing TA, Rademaker A, Hart E, Obasaju C, Treat JA, Milton D, Bonomi P. 2008. Phase II trial of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for advanced non-squamous non-small cell lung cancer. Poster presented at: Annual Meeting of the American Society of Clinical Oncology; 2008; Chicago.

Patel JD, Hensing TA, Villafor V, Hart E, Bonomi P. 2007. Pemetrexed and carboplatin plus bevacizumab for advanced non-squamous non-small cell lung cancer (NSCLC): preliminary results. J Clin Oncol 25(18S). Abstract 7601.

Peterson P, Park K, Fossella F, Gatzemeier U, John W, Scagliotti G. 2007. Is pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs cisplatin in previously treated patients with advanced non-small cell lung cancer (NSCLC). 12th World Conference on Lung Cancer. J Thoracic Oncol 2(8 Suppl 4):S851.

Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR. 2004. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 22(2):330-353.

Prior C, Oroszy S, Oberaigner W, Ambrosch G, Mohn-Staudner A, Pfeifer W, Pirker R, Huber H. 1999. Advanced non-small-cell lung cancer: adjunctive interferon gamma in induction and maintenance therapy. J Cancer Res Clin Oncol 125(1):42-46.

Rodgers GM, Becker PS, Bennett CL, Cella D, Chanan-Khan A, Chesney C, Cleeland C, Coccia PF, Djulbegovic B, Garst JL, Gilreath JA, Kraut EH, Lin WC, Matulonis U, Millenson M, Reinke D, Rosenthal J, Sabbatini P, Schwartz RN, Stein RS, Vij R. 2008. Cancer- and chemotherapy-induced anemia. J Natl Compr Canc Netw 6(6):536-564.

Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. 2006. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. N Engl J Med 355(24):2542-2550.

Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Di Costanzo F, Frontini L, Tonato M; Italian Lung Cancer Project. 2002. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 20(21):4285-4291.

Scagliotti GV, Kortsik C, Dark GG, Price A, Manegold C, Rosell R, O'Brien M, Peterson PM, Castellano D, Selvaggi G, Novello S, Blatter J, Kayitalire L, Crino L, Paz-Ares L. 2005. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase II trial. Clin Cancer Res 11(2 Pt 1):690-696.

Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP, Gandara D. 2008. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 26(21):3543-3551.

Scappaticci FA, Fehrenbacher L, Cartwright T, Hainsworth JD, Heim W, Berlin J, Kabbinavar F, Novotny W, Sarkar S, Hurwitz H. 2005. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol 91(3):173-180.

Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu, Johnson DH; Eastern Cooperative Oncology Group. 2002. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346(2):92-98.

Sekine I, Nokihara H, Sumi M, Saijo N, Nishiwaki Y, Ishikura S, Mori K, Tsukiyama I, Tamura T. 2006. Docetaxel consolidation therapy following cisplatin, vinorelbine, and concurrent thoracic radiotherapy in patients with unresectable stage III non-small cell lung cancer. J Thorac Oncol 1(8):810-815.

Shepherd FA, Dancey J, Arnold A, Neville A, Rusthoven J, Johnson RD, Fisher B, Eisenhauer E. 2001. Phase II study of pemetrexed disodium, a multitargeted antifolate, and cisplatin as first-line therapy in patients with advanced nonsmall cell lung carcinoma: a study of the National Cancer Institute of Canada Clinical Trials Group. Cancer 92(3):595–600.

Shih C, Chen VJ, Gossett LS, Gates SB, MacKellar WC, Habeck LL, Shackelford KA, Mendelsohn LG, Soose DJ, Patel VF, Andis SL, Bewley JR, Rayl EA, Moroson BA, Beardsley GP, Kohler W, Ratnam M, Schultz RM. 1997. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 57(6):1116-1123.

Shih C, Habeck LL, Mendelsohn LG, Chen VJ, Schultz RM. 1998. Multiple folate enzyme inhibition: mechanism of a novel pyrrolopyrimidine-based antifolate LY231514 (MTA). Adv Enzyme Regul 38:135-152.

Smith IE, O'Brien MER, Talbot DC, Nicolson MC, Mansi JL, Hickish TF, Norton A, Ashley S. 2001. Duration of chemotherapy in advanced non-small-cell lung cancer: a randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. J Clin Oncol 19(5):1336-1343.

Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri GD, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. 2006. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 24(19):3187-3205.

Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R, Unger P, Lee J, Lee JH, Tynan M, Moore M, Kies MS. 2002. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 20(5):1335-1343.

Socinski MA, Stinchcombe TE. 2007. Duration of first-line chemotherapy in advanced non small-cell lung cancer: less is more in the era of effective subsequent therapies. J Clin Oncol 25(33):5155-5157.

Soon YY, Askie L, Stockler M, Boyer M. 2007. Optimal duration of chemotherapy for advanced non-small cell lung cancer: a systematic review and meta-analysis [abstract]. In: Proc World Conf Lung Cancer 12th annual meeting program; 2007 Sep 2-6; Seoul. J Thorac Oncol 2(8 Suppl 4):S450-S451. Abstract PD4-2-1.

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. 2000. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92(3):205-216.

Weir BA, Woo MS, Getz G, Perner S, Ding L, Beroukhim R, Lin WM, Province MA, Kraja A, Johnson LA, Shah K, Sato M, Thomas RK, Barletta JA, Borecki IB, Broderick S, Chang AC, Chiang DY, Chirieac LR, Cho J, Fujii Y, Gazdar AF, Giordano T, Greulich H, Hanna M, Johnson BE, Kris MG, Lash A, Lin L, Lindeman N, Mardis ER, McPherson JD, Minna JD, Morgan MB, Nadel M, Orringer MB, Osborne JR, Ozenberger B, Ramos AH, Robinson J, Roth JA, Rusch V, Sasaki H, Shepherd F, Sougnez C, Spitz MR, Tsao MS, Twomey D, Verhaak RG, Weinstock GM, Wheeler DA, Winckler W, Yoshizawa A, Yu S, Zakowski MF, Zhang Q, Beer DG, Wistuba II, Watson MA, Garraway LA, Ladanyi M, Travis WD, Pao W, Rubin MA, Gabriel SB, Gibbs RA, Varmus HE, Wilson RK, Lander ES, Meyerson M. 2007. Characterizing the cancer genome in lung adenocarcinoma. Nature 450(7171):893-898.

Wyrwich KW, Tierney WM, Wolinsky FD. 1999. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. J Clin Epidemiol 52(9):861-873.

Zinner RG, Fossella FV, Gladish GW, Glisson BS, Blumenschein GR Jr, Papadimitrakopoulou VA, Pisters KM, Kim ES, Oh YW, Peeples BO, Ye Z, Curiel RE, Obasaju CK, Hong WK, Herbst RS. 2005. Phase II study of pemetrexed in combination with carboplatin in the first-line treatment of advanced nonsmall cell lung cancer. Cancer 104(11):2449-2456.

Appendix 1. Study Schedule

Protocol Attachment JMHD.1. Study Schedule

	Baseline[a]	Induction Therapy 21-Day Cycles				Maintenance Therapy 21-Day Cycles				Postdiscontinuation Follow-Up Period	
Cycle Number	**0**	**1**	**2**	**3**	**4**	**501**	**502**	**503**	**504[b]**	**30-day FU[c]**	**Long-Term FU**
Procedure											
ICD (prior to any procedures or tests)	x										
Medical history	x										
Physical exam[d,e]	x	x	x	x	x	x	x	x	x	x	
Interval history[f]		x	x	x	x	x	x	x	x	x	x
BSA calculation[e]	x	x	x	x	x	x	x	x	x		
Concomitant medications[e,g]	x	x	x	x	x	x	x	x	x	x	
ECOG performance status[e]	x		x	x	x	x	x	x	x	x	
CTCAE grading[e,h]	x	x	x	x	x	x	x	x	x	x	x
FACT-L/Ntx[e,i]	x		x	x	x	x	x	x	x	x	
Tumor assessment (RECIST)[b,e,j]	x		x		x		x		x	x	x
Laboratory/diagnostic tests											
Brain MRI or CT scan[k]	x		x		x		x		x	x	x
Hematology[e,l]	x	x	x	x	x	x	x	x	x	x	
Chemistry[e,m]	x		x	x	x	x	x	x	x	x	
Calculated CrCl[e,m]	x		x	x	x	x	x	x	x		
PK blood sampling[n]		x									
UPCR or urine dipstick (and 24-hour urine protein, if indicated)[e,o]	x		x	x	x	x	x	x	x		
Pregnancy test (if indicated)[p]	x										
PT/INR (if indicated)[e,q]	x										
Translational research											
Whole blood and plasma[r]	x										
FFPE tissue[s]	x										
Shipment of FFPE tissue[t]	x										

(continued)

Protocol Attachment JMHD.1. Study Schedule (continued)

	Baseline[a]	Induction Therapy 21-Day Cycles				Maintenance Therapy 21-Day Cycles				Postdiscontinuation Follow-Up Period	
Cycle Number	**0**	**1**	**2**	**3**	**4**	**501**	**502**	**503**	**504[b]**	**30-day FU[c]**	**Long-Term FU**
Premedication – Arm A											
Folic acid[u]	x	x	x	x	x	x	x	x	x		
Vitamin B_{12}[v]	x										
Dexamethasone[w]	x	x	x	x	x	x	x	x	x		
Premedication – Arm B[x]		x	x	x	x						
Study drugs[y]											
Pemetrexed – Arm A[z]		x	x	x	x	x	x	x	x		
Carboplatin – Arms A and B[aa]		x	x	x	x						
Bevacizumab – Arms A and B[ab]		x	x	x	x	x	x	x	x		
Paclitaxel – Arm B[ac]		x	x	x	x						

Abbreviations: AUC = area under the curve; BID = twice per day; BSA = body surface area; C1D1 = Cycle 1, Day 1; CrCl = creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; FACT-L/Ntx = Functional Assessment of Cancer Therapy-Lung/Neurotoxicity; FFPE = formalin fixed, paraffin embedded; FU = follow up; ICD = informed consent document; im = intramuscular; iv = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetics; po = by mouth; PT/INR = prothrombin time/international normalized ratio; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; UPCR = urine protein to creatinine ratio.

a Baseline: 0 to 14 days prior to C1D1, unless otherwise noted.

b For patients continuing maintenance therapy beyond Cycle 504: (1) Perform tumor assessment at even-numbered cycles (for example, at Cycles 510 and 512). (2) Administer other procedures, tests, premedication, and study drug at each additional cycle as shown for Cycle 504.

c The 30-day postdiscontinuation follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. The 30-day postdiscontinuation follow-up visit occurs at or near the end of the 30-day postdiscontinuation follow-up period (see Figure JMHD.3).

d Physical examination should include measurement of height (baseline only), weight, body temperature, blood pressure, and pulse rate.

e During study therapy, perform prior to administration of study drug. Sites must recalculate the patient's BSA **at every treatment visit**.

f Interval history should include questions monitoring for gastrointestinal toxicity and neurotoxicity (see Protocol Attachment JMHD.9).

(continued)

Protocol Attachment JMHD.1. Study Schedule (continued)

g Include (1) all vitamins and key medications other than study premedication and study drugs, and (2) number and type of transfusions.

h Grading using CTCAE (Version 3.0) at baseline, before each cycle, and at the 30-day FU visit. At baseline, assess and classify any preexisting laboratory and/or clinical abnormalities.

i Patient should complete FACT-L/Ntx questionnaires (see Protocol Attachment JMHD.8):
(1) Once at baseline, up to 7 days prior to C1D1. (2) At the end of each cycle, prior to administration of study drug at the next cycle. (3) At the time of discontinuation. (4) At the 30-day follow-up visit.

j Perform radiologic and physical assessment of tumors per RECIST guidelines (see Protocol Attachment JMHD.4). Measurements should be recorded in metric notation by use of a ruler or calipers. Throughout the study, radiologic assessment must be performed using the same imaging modality, covering the same anatomy, as used at the baseline assessment. Conventional or spiral CT or MRI is preferred. Chest x-ray is acceptable for clearly defined lesions that are surrounded by aerated lung.
Response confirmation: Responses must be confirmed. Confirmation should be performed 28 to 48 days after the initial response documentation and repeated every 6 weeks ± 2 weeks.
Timing of tumor assessment: (1) At baseline: radiologic assessment no more than 28 days prior to C1D1; physical assessment within 14 days prior to C1D1. (2) During study therapy: every 6 weeks ± 2 weeks. For example, assessment two weeks following C2D1, C4D1, etc. (3) At the 30-day FU visit. (4) For patients who discontinue from study therapy for reasons other than disease progression: every 6 weeks ± 2 weeks, until disease progression.

k At baseline, perform physical examination and brain imaging (CT scan or MRI) in all patients to determine eligibility. Beginning at Cycle 2, randomized patients who have stable treated brain metastasis should be monitored every 2 cycles and during the postdiscontinuation follow-up period using the same imaging modality that was used at baseline. Stable treated brain metastasis is defined as metastasis having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (CT or MRI) at baseline.

l Hematology should be performed as follows:
(1) Baseline - within 14 days prior to C1D1.
(2) Cycle 1 - on Days 8 and 15 (± 1 day).
(3) Cycles 2, 3, and 4 - (a) within 3 days prior to Day 1 of each cycle and (b) on Days 8 and 15 (± 1 day) of each cycle.
(4) Maintenance therapy - within 3 days prior to Day 1 of each cycle; additional hematology values may be collected during maintenance therapy per local practice guidelines or at the investigator's discretion.
(5) At the 30-day follow-up visit.
Investigators must document their review of each laboratory report.

(continued)

Protocol Attachment JMHD.1. Study Schedule (continued)

[m] Perform baseline tests within 14 days prior to C1D1. During study therapy, perform within 3 days prior to Day 1 of each cycle. Perform chemistry at the 30-day FU visit (calculated CrCl is not required at the 30-day FU visit). Additional chemistry values may be collected per local practice guidelines. Investigators must document their review of each laboratory report.

[n] Perform PK plasma sampling as shown in Protocol Attachment JMHD.7.

[o] (1) At baseline, perform UPCR within 14 days prior to C1D1. If UPCR is ≥ 1, perform 24-hour urine collection. Patient may be enrolled if < 1 g of protein in a 24-hour urine collection. (2) Beginning at Cycle 2, perform UPCR or urine dipstick at each cycle. If patients enrolled with UPCR ≥ 1 at baseline, it is not required to repeat the 24-hour urine collection in these patients on subsequent cycles, unless urine protein increases from the baseline value.

[p] Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to C1D1. Patients are considered not of childbearing potential if: (a) they are surgically sterile (that is, have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or (b) they are postmenopausal. Patients may be entered and enrolled on the basis of a local serum or urine pregnancy test; however, local laboratory results must be confirmed by a serum pregnancy test performed by the central laboratory.

[q] PT/INR should be measured within 14 days prior to C1D1 for patients on subtherapeutic anticoagulation therapy. For patients beginning anticoagulation therapy while on study, PT/INR should be measured as clinically indicated.

[r] For patients participating in translational research: Obtain approximately 10 mL of blood for DNA and approximately 5 mL of blood for plasma. Samples must be collected at baseline before the patient receives any study treatment.

[s] For patients participating in translational research: A sample of FFPE pretreatment tumor tissue should be taken from the original diagnostic tumor specimen and prepared according to instructions provided in the central laboratory manual.

[t] Prepare FFPE tissue sample and ship to the central laboratory no later than 4 weeks after randomization (that is, by the time of the Cycle 2 clinic visit).

[u] Folic acid – Arm A: 350-1000 μg taken po QD, beginning at least 5 to 7 days before C1D1, and continuing daily until 3 weeks after the last pemetrexed dose.

[v] Vitamin B_{12} – Arm A: 1000 μg im given in the 7-day period prior to C1D1 and repeated approximately every 9 weeks until 3 weeks after the last pemetrexed dose.

[w] Dexamethasone – Arm A: 4 mg taken po BID the day prior to, the day of, and the day after each dose of pemetrexed.

[x] Arm B only – During induction therapy, administer premedication as indicated in the paclitaxel label. Such premedication may consist of: (1) dexamethasone 20 mg po administered approximately 12 and 6 hours prior to paclitaxel, (2) diphenhydramine (or its equivalent) 50 mg iv administered 30 to 60 minutes prior to paclitaxel, and (3) cimetidine (300 mg) or ranitidine (50 mg) iv administered 30 to 60 minutes prior to paclitaxel.

(continued)

Protocol Attachment JMHD.1. Study Schedule (concluded)

[y] Study drug may be administered ± 3 days from scheduled Day 1 of current cycle (Day 22 from prior cycle) only due to unavoidable scheduling conflicts. Day 1 is the day that the dose is actually administered, and all study drugs should be administered on the same day. Note that Day 1 may be delayed >3 days due to protocol defined cycle delays to allow for recovery from toxicity (see Sections 5.5.1.1, 5.5.1.2, and 5.5.1.3). If bevacizumab is omitted from a cycle due to toxicity, the other drugs should be administered on Day 1 ± 3 days (see Section 5.5.1.5).

[z] Pemetrexed – Arm A: 500 mg/m^2 iv administered over 10 minutes on Day 1 of each cycle.

[aa] Carboplatin AUC 6 (Calvert formula) iv administered over 30 minutes on Day 1 of each cycle.
Arm A: During induction therapy, administer carboplatin after pemetrexed on Day 1 of each cycle.
Arm B: During induction therapy, administer carboplatin after paclitaxel on Day 1 of each cycle.

[ab] Bevacizumab 15 mg/kg iv over 30 to 90 minutes, after carboplatin on Day 1 of each cycle. See Section 5.2.4 for bevacizumab administration guidelines.
Arm A: During induction therapy, administer bevacizumab after carboplatin. During maintenance therapy, administer bevacizumab after pemetrexed.
Arm B: During induction therapy, administer bevacizumab after carboplatin.

[ac] Paclitaxel – Arm B only: 200 mg/m^2 administered iv over 3 hours on Day 1 of each cycle.

Appendix 2. Clinical Laboratory Tests

Protocol Attachment JMHD.2. Clinical Laboratory Tests

Hematology Hemoglobin Hematocrit WBC Neutrophils (sum of segmented and bands) Platelets **Coagulation** PT/INR (if indicated) **Urinalysis** UPCR or urine dipstick[a] 24-hour urine collection (if indicated)[b]	– **Hematology, coagulation, and urinalysis:** performed by a local laboratory
Pregnancy Test (women) Serum or urine	– **Pregnancy test:** required for women of childbearing potential. Patients may be enrolled on the basis of a local serum or urine pregnancy test; however, local laboratory results must be confirmed by a serum pregnancy test performed by the central laboratory
Clinical Chemistry Total bilirubin Alkaline phosphatase ALT AST Serum creatinine[c] Calculated CrCl BUN Calcium Glucose Total protein Serum magnesium Serum potassium	– **Clinical chemistry:** results from a local laboratory may be used for enrollment or dosing decisions; however, tests must also be performed by the central laboratory

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; CrCl = creatinine clearance; PT/INR = prothrombin time/international normalized ratio; UPCR = urine protein to creatinine ratio; WBC = white blood cell count (leukocytes).

a UPCR is required at baseline; urine dipstick may be used thereafter.

b If baseline UPCR is ≥ 1, perform 24-hour urine collection. Patient may be enrolled if < 1 g of protein in 24-hour urine collection.

c The site should follow guidance in Section 5.2.3 regarding capping the carboplatin dose.

Appendix 3. American Joint Committee on Cancer (AJCC) TNM Staging System for Lung Cancer

Protocol Attachment JMHD.3. AJCC TNM Staging System for Lung Cancer

Primary Tumor (T)	
TX	Primary tumor can not be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm diameter, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T2	Tumor with any of the following features of size or extent: > 3 cm diameter; involves main bronchus, ≥ 2 cm or more distal to the carina; invades visceral pleura; or associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.

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

Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present.

(continued)

Protocol Attachment JMHD.3. AJCC TNM Staging System for Lung Cancer (concluded)

Stage Grouping of TNM Subsets

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T1	N1	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T1-3	N2	M0
	T3	N1	M0
IIIB	Any T	N3	M0
	T4	Any N	M0
IV	Any T	Any N	M1

Abbreviation: Tis = carcinoma in situ.
Source: Greene et al. 2002.

Appendix 4. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines

Protocol Attachment JMHD.4. RECIST Guidelines

Measurability of Tumor Lesions at Baseline:
Measurable lesions: Lesions that can be accurately measured in at least 1 dimension as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan (longest diameter to be recorded).

Nonmeasurable lesions: All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly nonmeasurable lesions. Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Documentation of "Target" and "Nontarget" Lesions at Baseline:
All tumor measurements will be recorded in centimeters using a ruler or calipers. All baseline evaluations should be performed as close as possible to the start of treatment but never more than 28 days before beginning treatment.

Target: All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

Nontarget: All other lesions (or sites of disease) including small lesions (longest diameter < 20 mm with conventional CT scan, < 10 mm with spiral CT scan) and other non-measurable lesions should be identified as nontarget lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence of absence of each should be noted throughout follow up.

Method of Measurement:
The same method of measurement and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up. Computed tomography (CT), or magnetic resonance imaging (MRI), should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Chest X-ray is acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan or MRI is preferred.

Protocol Attachment JMHD.4. RECIST Guidelines (continued)

Clinical lesions will only be considered measurable when they are superficial (for example, skin nodules, or palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Timing of Subsequent Tumor Assessments:
Radiological and physical assessments will be routinely reviewed as specified in the Study Schedule (Protocol Attachment JMHD.1). All areas of disease must be re-evaluated at each subsequent assessment. The same technique used at baseline must be used. Chest x-rays are acceptable for a subsequent assessment if used at baseline, however CT scan or MRI is preferred.

If the patient's disease has responded to therapy, the investigator must confirm the response. It is recommended that confirmation of response occur ≥ 28 days and ≤ 42 days after the first evidence of response using the same radiological technique as at baseline. The baseline sum of longest diameters of target lesions will be used as reference for confirmation of response.

Both measurable and nonmeasurable lesions should be evaluated at each restaging to determine whether they have completely resolved or persisted, or whether new lesions have appeared.

Response Criteria:
Patients will be assessed using the following criteria:

- **Complete response (CR):** Disappearance of all tumor lesions.
- **Partial response (PR):** Either a) at least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LDs or b) complete disappearance of target lesions, with persistence (but not worsening) of 1 or more nontarget lesions. In either case, no new lesions may have appeared.
- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.
- **Progressive disease (PD):** At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.
- **Unknown:** Progression has not been documented and 1 or more target or nontarget sites have not been assessed.

Protocol Attachment JMHD.4. RECIST Guidelines (concluded)

Overall Cycle Responses for All Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

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

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
Source: Therasse et al. 2000.

Appendix 5. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Protocol Attachment JMHD.5. ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al. 1982.

Appendix 6. Calculated Creatinine Clearance

Protocol Attachment JMHD.6. Calculated Creatinine Clearance

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

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Men

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^a}) \times (\mathbf{wt^b}) \times \mathbf{1.0}}{\mathbf{72} \times \textbf{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^a}) \times (\mathbf{wt^b}) \times \mathbf{1.0}}{\mathbf{0.81} \times \textbf{serum creatinine (μmol/L)}}$$

[a] Age in years.
[b] Weight (wt) in kilograms.
Source: Cockcroft and Gault 1976.

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Women

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^a}) \times (\mathbf{wt^b}) \times \mathbf{0.85}}{\mathbf{72} \times \textbf{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^a}) \times (\mathbf{wt^b}) \times \mathbf{0.85}}{\mathbf{0.81} \times \textbf{serum creatinine (μmol/L)}}$$

[a] Age in years.
[b] Weight (wt) in kilograms.
Source: Cockcroft and Gault 1976.

Appendix 7. Pharmacokinetic Sampling Instructions

Protocol Attachment JMHD.7. Pharmacokinetic Sampling Instructions

Blood samples will be collected for the measurement of pemetrexed, bevacizumab, and platinum (total platinum and free platinum) concentrations in plasma. Blood samples for pharmacokinetic (PK) analysis will be obtained during Cycle 1.

It is essential that the following dosing information be collected and reported: the exact infusion start and stop times (actual clock readings), date of infusion, body surface area, and dose administered. Samples are to be collected at the times specified below. The exact time of collection of each venous blood sample will be based on the same clock used to record infusion times. Accurate recording of the actual sample collection times is essential.

It is essential that every PK blood sample be withdrawn from an arm vein not in direct contact with the drug infusion solution. If a heparin lock is used, the first milliliter (1 mL) of blood withdrawn from the venous catheter will be discarded prior to each sample collection to avoid dilution of the blood sample with the solution in the catheter. Thereafter, approximately 4 mL of heparinized blood will be collected for each drug at the specified time points. The samples will be processed, stored, and shipped according to the instructions supplied in the central laboratory manual.

It is essential that samples are collected immediately prior to the end of the drug infusions (< 1 min before the end of the infusion) in order to obtain plasma concentrations to evaluate maximum systemic exposure.

Each blood sample will be collected at the times specified below to facilitate evaluation of these data by standard PK analysis methods. Pharmacokinetic parameters to be determined based on plasma concentration versus time data include: $AUC_{(0-\infty)}$, C_{max}, CL, and V_{ss}.

Protocol Attachment JMHD.7. Pharmacokinetic Sampling Instructions (continued)

Blood Sampling Collection Times - Arm A[a]

Sample	Day	Collection Time	Collection Time Relative to Pemetrexed Infusion	Measurement		
				Pemetrexed[b]	Carboplatin[c]	Bevacizumab[d]
1	1	9 - 10 min	(< 1 min prior to end of pemetrexed infusion)	x		
	1	10-min saline flush				
2	1	20 min	20 min after start of pemetrexed infusion **(immediately before start of carboplatin infusion)**	x	x	
3	1	35 min	35 min after start of pemetrexed infusion **(midway through carboplatin infusion)**	x	x	
4	1	50 min	50 min after start of pemetrexed infusion **(< 1 min prior to end of carboplatin infusion)**	x	x	
	1	10-min saline flush				
5	1	60 min	60 min after start of pemetrexed infusion **(immediately before start of bevacizumab infusion)**	x	x	x

Protocol Attachment JMHD.7. Pharmacokinetic Sampling Instructions (continued)

Blood Sampling Collection Times - Arm A (concluded)[a]

Sample	Day	Collection Time	Collection Time Relative to Pemetrexed Infusion	Measurement		
				Pemetrexed[b]	Carboplatin[c]	Bevacizumab[d]
6	1	105 min (1 hr 45 min)	105 min after start of pemetrexed infusion **(midway through bevacizumab infusion)**	x	x	x
7	1	150 min (2 hr 30 min)	150 min after start of pemetrexed infusion **(< 1 min prior to end of bevacizumab infusion)**	x	x	x
8	1	4 hr	4 hr after start of pemetrexed infusion	x	x	x
9	1	6 hr	6 hr after start of pemetrexed infusion	x	x	x
10	1	8 hr	8 hr after start of pemetrexed infusion	x	x	x
11	2	20 - 28 hr	24 hr after start of pemetrexed infusion	x	x	x
12	3	44 - 52 hr	48 hr after start of pemetrexed infusion		x	x
13	4	66 - 78 hr	72 hr after start of pemetrexed infusion		x	x
14	8	188 - 196 hr	7 days after start of pemetrexed infusion			x
15	15	355 – 365 hr	14 days after start of pemetrexed infusion			x
16	C2D1		Just prior to Cycle 2 bevacizumab infusion			x

Abbreviations: C2D1 = Cycle2, Day 1; hr = hour; min = minute.

[a] This schedule assumes a 10-minute pemetrexed infusion, carboplatin given as a 30-minute intravenous infusion starting 10 minutes after the end of the pemetrexed infusion, and bevacizumab given as a 90-minute infusion starting 10 minutes after end of carboplatin infusion.

[b] Plasma pemetrexed concentration.

[c] Plasma total platinum concentration and free-platinum concentration.

[d] Plasma bevacizumab concentration.

Protocol Attachment JMHD.7. Pharmacokinetic Sampling Instructions (concluded)

Blood Sampling Collection Times - Arm B[a]

Sample	Day	Collection Time	Collection Time Relative to Carboplatin Infusion	Measurement	
				Carboplatin[b]	Bevacizumab[c]
1	1	15 min	15 min after start of carboplatin infusion (midway through carboplatin infusion)	x	
2	1	30 min	30 min after start of carboplatin infusion **(< 1 min prior to end of carboplatin infusion)**	x	
	1	10-min saline flush			
3	1	40 min	40 min after start of carboplatin infusion **(immediately before start of bevacizumab infusion)**	x	x
4	1	85 min	85 min after start of carboplatin infusion (midway through bevacizumab infusion)	x	x
5	1	130 min (2 hr 10 min)	130 min after start of carboplatin infusion **(< 1 min prior to end of bevacizumab infusion)**	x	x
6	1	4 hr	4 hr after start of carboplatin infusion	x	x
7	1	6 hr	6 hr after start of carboplatin infusion	x	x
8	1	8 hr	8 hr after start of carboplatin infusion	x	x
9	2	20 - 28 hr	24 hr after start of carboplatin infusion	x	x
10	3	44 - 52 hr	48 hr after start of carboplatin infusion	x	x
11	4	66 - 78 hr	72 hr after start of carboplatin infusion	x	x
12	8	188 – 196 hr	7 days after start of carboplatin infusion		x
13	15	355 – 365 hr	14 days after start of carboplatin infusion		x
14	C2D1		Just prior to Cycle 2 bevacizumab infusion		x

Abbreviations: C2D1 = Cycle 2, Day 1; hr = hour; min = minute.

[a] This schedule assumes carboplatin given as a 30-minute intravenous infusion; bevacizumab given as a 90-minute infusion starting 30 minutes after end of carboplatin infusion.

[b] Plasma total platinum concentration and free-platinum concentration.

[c] Plasma bevacizumab concentration.

Appendix 8. FACT-L/Ntx Instrument

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS (1)	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS (2)	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

Appendix 9. Interval History

Protocol Attachment JMHD.9. Interval History

To specifically elicit any symptoms of GI toxicity, the patients should be asked at each interval history about symptoms of constipation, abdominal pain, fever, diarrhea, or rectal bleeding.

To specifically elicit any symptoms of neurotoxicity, the patients should be asked at each interval history about symptoms of paresthesias, pareses, dysesthesias, and neuropathic pain.

Answers to these questions are to be documented in the patient's medical record. Positive responses should be appropriately evaluated.

Appendix 10. Protocol JMHD Extension Period Schedule of Events

Protocol Appendix JMHD.10. Extension Period Schedule

Data regarding study drug administration, AEs, and SAEs will be collected on the CRF as shown in the Extension Period Schedule. Investigators remain responsible for performing any procedures and tests needed for the appropriate care of the patient.

	Maintenance Therapy 21-Day Cycles	Postdiscontinuation Follow-Up Period
Cycle Number	**All Cycles**	**30-day FU[a]**
Procedure		
ICD (prior to any procedures or tests)	**x**	
CTCAE grading[b]	**x**	**x**
AE collection	**x**	**x**
SAE collection	**x**	**x**
Study drugs[c]		
Pemetrexed – Arm A[d]	**x**	
Bevacizumab – Arms A and B[e]	**x**	

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; FU = follow up; iv = intravenous; ICD = informed consent document; SAE = serious adverse event.

[a] The 30-day postdiscontinuation follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. The 30-day postdiscontinuation follow-up visit occurs at or near the end of the 30-day postdiscontinuation follow-up period (see Figure JMHD.3).

[b] During study therapy, perform before each cycle.

[c] Study drug may be administered ± 3 days from scheduled Day 1 of current cycle (Day 22 from prior cycle) only due to unavoidable scheduling conflicts. Day 1 is the day that the dose is actually administered, and all study drugs should be administered on the same day. Note that Day 1 may be delayed >3 days due to protocol-defined cycle delays to allow for recovery from toxicity (see Sections 5.5.1.2, 5.5.1.3, and 5.5.1.4). If bevacizumab is omitted from a cycle due to toxicity, pemetrexed should be administered on Day 1 ± 3 days (see Section 5.5.1.5).

[d] Pemetrexed – Arm A: 500 mg/m^2 iv administered over 10 minutes on Day 1 of each cycle.

[e] Bevacizumab 15 mg/kg iv over 30 to 90 minutes on Day 1 of each cycle. See Section 5.2.4 for bevacizumab administration guidelines. Arm A: Administer bevacizumab after pemetrexed.

Appendix 11. Protocol Amendment H3E-MC-JMHD(e) Summary

Overview

Protocol H3E-MC-JMHD (Randomized, Open-Label, Phase 3 Study of Pemetrexed plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab versus Paclitaxel plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients with Stage IIIB or IV Nonsquamous Non-Small Cell Lung Cancer) has been amended. The new protocol is indicated by amendment (e) and will be used to conduct the study in place of any preceding version of the protocol.

The purpose of this protocol amendment was to clarify protocol procedures to be performed during the study's extension period.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Abbreviations and Definitions

End of ~~study (trial)~~	End of ~~study (~~trial~~)~~ is the date of the last visit or last scheduled procedure shown in the Extension Period Schedule for the last patient.~~will occur when data collection for the study is completed (see Section 8.2.14 for further details about criteria for study termination).~~
study completion	This study will be considered complete after the final analysis of overall survival, after the time of the prespecified number of overall survival events.
30-day postdiscontinuation follow-up period	The 30-day postdiscontinuation follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. The 30-day postdiscontinuation follow-up visit occurs at or near the end of the 30-day postdiscontinuation follow-up period (see Figure JMHD.~~2~~3).

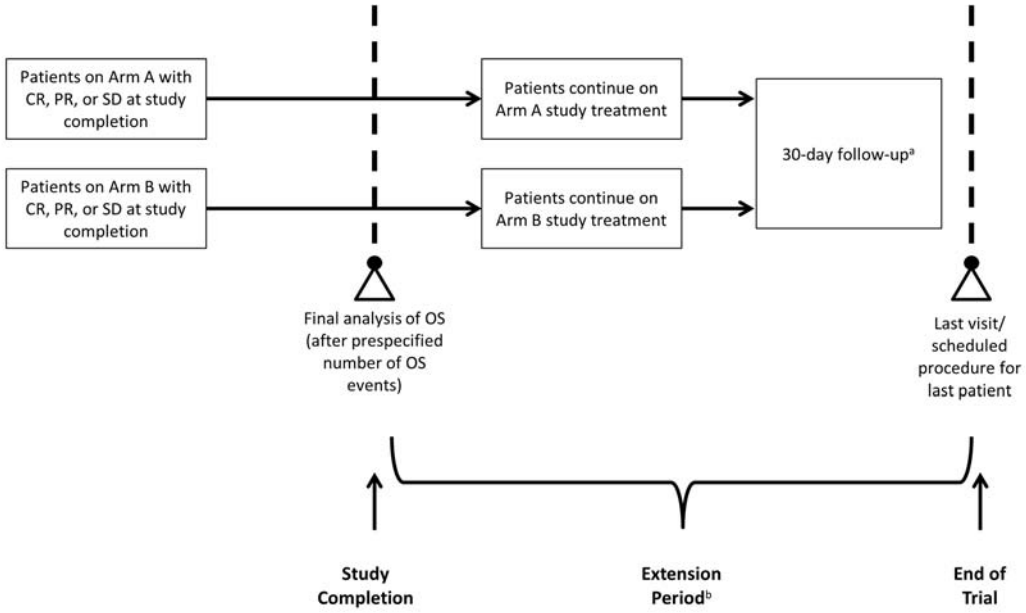
3.1.1. Study Completion and End of Trial

This study will be considered complete following the final analysis of OS, after the prespecified number of OS events.

The term "end of trial" refers to the date of the last visit or last scheduled procedure for the last patient in the extension period (see Appendix 10).

3.1.2. Extension Period

All patients who are still receiving study treatment at the time of study completion (see Section 3.1.1) may continue to receive study treatment in the extension period until one of the criteria for discontinuation is met (see Section 4.3.1). For all patients who continue to receive study treatment during the extension period, a follow-up visit will occur approximately 30 days after discontinuation from study treatment (see Section 6.3.1.2). Figure JMHD.2 provides an illustration of study completion, the extension period, and the end of trial. Lilly or its designee will notify investigators when the extension period begins and ends. Patients must sign a new informed consent document (ICD) before entering the extension period.



[a] See Figure JMHD.3.
[b] Lilly will notify sites when the extension period begins and ends.

Figure JMHD.2. Study completion, extension period, and end of trial.

4.3.1. Discontinuation of Patients

- ~~Patients who discontinue from *all* study treatment will have postdiscontinuation follow-up procedures performed as shown in the Study Schedule (Appendix 1).~~

5.1. Treatments Administered

The investigator or his/her designee is responsible for explaining the correct use of the investigational agents to study site personnel and to the patient (or the patient's legal representative), verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the ~~study~~trial.

6. Efficacy and Health Outcome Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Appendix 1) and the Extension Period Schedule (Appendix 10).

6.1. Efficacy Measures

Efficacy assessments are performed until study completion. During the extension period, investigators are responsible for performing any procedures and tests needed for the appropriate care of the patient; however, the results of efficacy assessments performed during the extension period will not be reported on the case report form (CRF).

If a patient has PD, he or she will be discontinued from study therapy. If a patient discontinues from study therapy and has not had disease progression, tumor measurements will also be performed at the 30-day postdiscontinuation follow-up visit (see Figure JMHD.3~~Figure JMHD.2~~) and every 6 weeks (± 2 weeks) thereafter. Once the patient has objective disease progression, the patient will be followed every 90 days (± 14 days).

Until study completion, the following p~~P~~ostdiscontinuation data ~~to be collected~~ will be reported on the CRF: ~~include~~ the date of disease progression; documentation of any anticancer treatment patient has received, including the dates of any postdiscontinuation systemic therapy, radiotherapy, or surgical intervention; and the date of death. For patients who discontinue from study therapy before study completion, p~~P~~ostdiscontinuation follow up will continue until the earliest of the following events: death, lost to follow up, or study ~~closure~~ completion.~~(Section 8.2.14. Refer to Section for Extension Period requirements.~~

6.1.1. Efficacy Criteria for Tumor Response

Tumor responses will be measured and recorded by using RECIST guidelines (Therasse et al. 2000; Appendix 4). During the extension period, patients should be assessed according to good clinical practice requirements to ensure continued eligibility to receive study treatment.

6.2.4. FACT-L/Ntx Timing and Scoring

Collection of all FACT-L/Ntx data will end at study completion (see Section 3.1.1).

FACT-L/Ntx questionnaires will be completed only by randomized patients for whom a validated translation is available in a language in which the completer is fluent. Each patient should complete a questionnaire once at each of the following time points:

- at baseline (before randomization)
- before each cycle, except Cycle 1
- upon discontinuation from all study-drug treatment
- during the postdiscontinuation follow-up visit approximately 30 days after the last dose of study drug (see Figure JMHD.3~~Figure JMHD.2~~).

6.3. Safety Evaluations

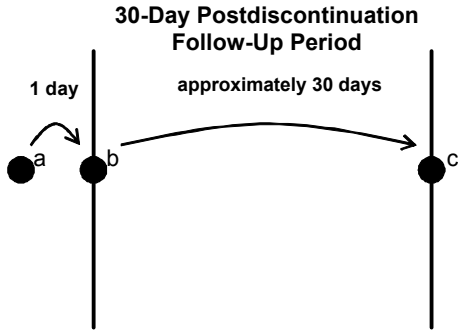
Sites will perform safety evaluations as described in this section and the Study Schedule (Appendix 1) until study completion. During the extension period, investigators remain responsible for performing any procedures and tests needed for the appropriate care of the patient; however, only data regarding study drug administration, AEs, and SAEs will be reported on the CRF.

6.3.1. Adverse Events

After the informed consent document is signed, all AEs related to protocol procedures are reported to Lilly or its designee via ~~case report form (~~CRF~~)~~.

6.3.1.2. Postdiscontinuation Safety Follow-Up Assessments

For all patients, a follow-up visit will occur approximately 30 days after discontinuation from study treatment. The 30-day postdiscontinuation follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. The 30-day postdiscontinuation follow-up visit occurs at or near the end of the 30-day postdiscontinuation follow-up period (see Figure JMHD.~~2~~3).



[a] The date the patient and the investigator agree to discontinue the patient from all study treatment. (Also referred to as the Summary Date.)

[b] Day 1 of the 30-day postdiscontinuation follow-up period.

[c] The 30-day follow-up visit, approximately Day 30 of the 30-day postdiscontinuation follow-up period.

Figure JMHD.~~2~~3. 30-day follow-up period.

For patients who discontinue from study treatment prior to study completion, e~~E~~valuation at the 30-day postdiscontinuation follow-up visit will include:

For patients who discontinue from study treatment during the extension period, postdiscontinuation follow-up procedures will be performed as shown in the Extension Period Schedule (Appendix 10).

6.4. Sample Collection and Testing

Appendix 2 lists the specific tests performed ~~for this study~~until study completion. During the extension period, investigators are responsible for performing any procedures and tests needed for the appropriate care of the patient; however, the results of the procedures and tests will not be reported on the CRF.

~~**8.2.14. Criteria for Study Closure**~~

~~The study will end (study closure) when data collection is stopped. The study is designed to enroll approximately 900 patients and perform a final analysis after 676 deaths have been observed, at which time database lock will occur. Lilly has the right to stop collecting data after the database has been locked; however, after the final analysis, data may continue to be collected on surviving patients.~~

~~At the investigator's discretion, patients receiving maintenance therapy at the time of study closure may continue to receive their assigned maintenance therapy until disease progression or initiation of other therapy. However, if an SAE occurs, Lilly may request additional information (such as local lab results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.~~

Protocol Attachment JMHD.1. Study Schedule

[c] The 30-day postdiscontinuation follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. The 30-day postdiscontinuation follow-up visit occurs at or near the end of the 30-day postdiscontinuation follow-up period (see Figure JMHD.~~2~~3).

Appendix 10. Protocol JMHD Extension Period Schedule of Events

Protocol Appendix JMHD.10. Extension Period Schedule

Data regarding study drug administration, AEs, and SAEs will be collected on the CRF as shown in the Extension Period Schedule. Investigators remain responsible for performing any procedures and tests needed for the appropriate care of the patient.

	Maintenance Therapy 21-Day Cycles	Postdiscontinuation Follow-Up Period
Cycle Number	**All Cycles**	**30-day FU[a]**
Procedure		
ICD (prior to any procedures or tests)	x	
CTCAE grading[b]	x	x
AE collection	x	x
SAE collection	x	x
Study drugs[c]		
Pemetrexed – Arm A[d]	x	
Bevacizumab – Arms A and B[e]	x	

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; FU = follow up; iv = intravenous; ICD = informed consent document; SAE = serious adverse event.

[a] The 30-day postdiscontinuation follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. The 30-day postdiscontinuation follow-up visit occurs at or near the end of the 30-day postdiscontinuation follow-up period (see Figure JMHD.3).

[b] During study therapy, perform before each cycle.

[c] Study drug may be administered ± 3 days from scheduled Day 1 of current cycle (Day 22 from prior cycle) only due to unavoidable scheduling conflicts. Day 1 is the day that the dose is actually administered, and all study drugs should be administered on the same day. Note that Day 1 may be delayed >3 days due to protocol-defined cycle delays to allow for recovery from toxicity (see Sections 5.5.1.2, 5.5.1.3, and 5.5.1.4). If bevacizumab is omitted from a cycle due to toxicity, pemetrexed should be administered on Day 1 ± 3 days (see Section 5.5.1.5).

[d] Pemetrexed – Arm A: 500 mg/m^2 iv administered over 10 minutes on Day 1 of each cycle.

[e] Bevacizumab 15 mg/kg iv over 30 to 90 minutes on Day 1 of each cycle. See Section 5.2.4 for bevacizumab administration guidelines. Arm A: Administer bevacizumab after pemetrexed.

Leo Document ID = f9a15652-2559-440d-9acc-b88261f28453

Approver: Jingyi Liu (AM\C114496)
Approval Date & Time: 07-Aug-2012 20:36:04 GMT
Signature meaning: Approved

Approver: Allen S Melemed (AM\QD92122)
Approval Date & Time: 09-Aug-2012 05:08:05 GMT
Signature meaning: Approved