A Randomized Phase III Study of Maintenance Therapy With Bevacizumab, Pemetrexed, or a Combination of Bevacizumab and Pemetrexed Following Carboplatin, Paclitaxel, and Bevacizumab for Advanced Non-squamous Non–Small Cell Lung Cancer (NSCLC)
Overall E5508 Study Objective

To compare maintenance therapy with bevacizumab, pemetrexed, or a combination of both following 4 cycles of carboplatin, paclitaxel, and bevacizumab, with the goal of identifying an optimal maintenance regimen that results in improved survival for patients with advanced-stage, nonsquamous non–small cell lung cancer (NSCLC).

Overview of NSCLC

- In 2008 worldwide, lung cancer was the leading cause of cancer-related deaths (23%) and the most commonly diagnosed cancer in males, representing 17% of new cancer patients. In females, lung cancer is the fourth most common cancer and the second leading cause of cancer-related death.
- Among all cancer patients in 2008, lung cancer accounted for 1.6 million patients (13%) and 1.4 million deaths (18%).
- In the United States, approximately 215,000 new patients are diagnosed with NSCLC each year.
- Lung cancer predominantly consists of NSCLC, with different types characterized by cell size, shape, and growth patterns.
- The most common types of NSCLC include squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.
- Prognostic factors associated with poor outcomes include bulky tumor size (> 3 cm), nonsquamous histology, and metastases to multiple lymph nodes.

Role of Maintenance Therapy in NSCLC

- Standard treatments for patients with advanced-stage NSCLC and good performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1) generally depend on platinum-based combination therapy, which may include paclitaxel, gemcitabine, docetaxel, or vinorelbine.
- An ECOG phase III clinical study showed that the efficacy of various combinations of 2 drugs, including cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, and carboplatin/paclitaxel, resulted in similar efficacy for advanced-stage NSCLC.
- Optimal efficacy with combination chemotherapy is reflected in modest improvements in overall survival (OS) following 4 to 6 cycles of treatment for advanced NSCLC.
Treatment beyond 6 cycles with these initial systemic therapies does not further improve efficacy, whereas it increases side effects.

Exploration of continued therapy, known as maintenance or consolidation treatment, following achievement of a maximal response with frontline combination chemotherapy demonstrates an improvement in survival.

A randomized study of docetaxel maintenance versus second-line treatment (following disease progression) after initial carboplatin/gemcitabine showed a significant improvement in median progression-free survival (PFS; 5.7 vs 2.7 mo; \( P = .0001 \)) and a trend toward improved OS (12.3 vs 9.7 mo; \( P = .085 \)) with maintenance docetaxel. These improvements in survival were shown with earlier use of maintenance docetaxel without negatively impacting tolerability or quality of life.

Possible survival benefits provided by maintenance therapy have been investigated with other chemotherapeutic agents, including gemcitabine, erlotinib, and gefitinib, and provide support for continued evaluation to determine the optimal maintenance therapy options in advanced-stage NSCLC.

Role of Bevacizumab in Maintenance Therapy for NSCLC

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF). It is the first targeted therapy approved by the US Food and Drug Administration (FDA) based on its enhanced activity in combination with chemotherapy for advanced-stage NSCLC.

Inhibition of VEGF by bevacizumab causes a blockage of blood vessel formation and tumor-related angiogenesis that contributes to metastases.

First-line bevacizumab is approved in combination with carboplatin and paclitaxel for advanced, recurrent, or metastatic NSCLC, as well as for metastatic colorectal cancer, renal cell carcinoma, and progressive glioblastoma.

A phase III ECOG clinical study of bevacizumab versus no maintenance following 6 cycles of initial carboplatin/paclitaxel (median 19 mo follow-up) showed that maintenance bevacizumab significantly improved survival (12.3 vs 10.3 mo; \( P = .003 \)), PFS (6.2 vs 4.5 mo; \( P < .001 \)), and overall response rate (35% vs 15%; \( P < .001 \)), compared with patients receiving no maintenance.
• These favorable results were complicated by increased toxicity in patients receiving bevacizumab, including higher incidences of grade 3/4 hypertension, proteinuria, and fatigue\textsuperscript{13}

• Positive results from this phase III study have led to the adoption of carboplatin, paclitaxel, and bevacizumab by ECOG for patients with advanced nonsquamous NSCLC

• A recent report of the AVAiL phase III study examined bevacizumab versus placebo maintenance following cisplatin/gemcitabine induction.\textsuperscript{14} This study confirmed the PFS advantage seen when bevacizumab is added as a maintenance regimen, although OS outcomes were similar among maintenance arms

**Role of Pemetrexed in NSCLC Maintenance Therapy**

• Pemetrexed is a multitargeted antifolate drug approved in the United States for first-line use in combination with cisplatin, as a single agent following chemotherapy, and in the maintenance setting following 4 cycles of first-line platinum-based chemotherapy\textsuperscript{15}

• Main adverse events associated with pemetrexed include myelosuppression, diarrhea, and skin rash, although toxicity may be improved with vitamin B\textsubscript{12} and folic acid\textsuperscript{15}

• A phase III clinical study established the noninferiority (the study’s primary end point) of OS with second-line pemetrexed versus docetaxel following progression with platinum-based chemotherapy\textsuperscript{16}

• In this study, pemetrexed showed lower incidences of neutropenia, hospitalization, and most other toxicities, compared with docetaxel\textsuperscript{16}

• Another study established pemetrexed as first-line therapy in combination with cisplatin, demonstrating its noninferiority to cisplatin/gemcitabine in terms of OS.\textsuperscript{17} In addition, pemetrexed demonstrated superior median survival in a preplanned subset analysis of patients with nonsquamous cell histology (cisplatin 12.6 vs cisplatin/gemcitabine 10.9 mo)

  – This study provided the foundation for the US and European approvals of cisplatin/pemetrexed in nonsquamous (but not squamous cell) NSCLC
In a phase III study of randomized maintenance pemetrexed versus placebo following 4 cycles of platinum-based therapy, patients with advanced NSCLC showed significant improvements with maintenance pemetrexed reflected in a median PFS of 4.3 versus 2.6 months ($P < .0001$) and a trend toward improved OS (13.0 vs 10.2 mo; $P = .06$). Patients with nonsquamous histology showed a significant 5-month improvement in OS (14.4 vs 9.4 mo; $P = .005$).

Pemetrexed appears to be well tolerated, allowing for prolonged use in the maintenance or consolidation settings without cumulative toxicity.

Rationale for Maintenance Therapy

Based on positive clinical data supporting the use of bevacizumab or pemetrexed as maintenance therapy in advanced NSCLC, this phase III study is being conducted to compare the 2 maintenance therapies alone or in combination following 4 cycles of carboplatin/paclitaxel/bevacizumab induction therapy in patients with advanced-stage nonsquamous NSCLC.

Initial phase II clinical data showed that combined carboplatin, pemetrexed, and bevacizumab followed by maintenance pemetrexed and bevacizumab in advanced nonsquamous NSCLC resulted in an overall response rate (ORR) of 55%, median PFS of 7.8 months, and OS of 14.1 months.

Grade 3/4 hematologic toxicities were considered modest, including 6% anemia, 4% neutropenia, and 8% thrombocytopenia. No cases of grade $\geq 3$ hemorrhagic events or hypertension were present.

Clinical trials that support the use of maintenance therapy in advanced-stage NSCLC are presented in Table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>Comparison of Maintenance Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III</td>
<td></td>
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</tbody>
</table>
| Fidias et al, 2009⁷ | 307 | Docetaxel maintenance vs second-line treatment (post progression) after initial carboplatin/gemcitabine | Docetaxel maintenance  
PFS: 5.7 mo  
OS: 12.3 mo  
Second-line docetaxel  
PFS: 2.7 mo  
(P = .0001)  
OS: 9.7 mo  
(P = .085)  |
| ECOG 4599 |     |                                                                            |                                    |
| Sandler et al, 2006¹³ | 878 | Carboplatin/paclitaxel (CP; 6 cycles) ± maintenance bevacizumab in advanced nonsquamous NSCLC | CP + bevacizumab  
Median number of cycles = 7  
OS = 12.3 mo  
PFS = 6.2 mo  
ORR = 35%  
Fewer AEs  
CP + placebo  
Median number of cycles = 5  
OS = 10.3 mo  
(P = .003)  
PFS = 4.5 mo  
(P < .001)  
ORR = 15%  
(P < .001)  |
| AVAiL |     |                                                                            |                                    |
| Phase III |     |                                                                            |                                    |
| Reck et al, 2010¹⁴ | 1043 | Cisplatin/gemcitabine (CG) + maintenance bevacizumab (7.5 or 15 mg/kg) vs placebo | Significant PFS prolongation with bevacizumab  
OS > 13 mo in all groups  
Significant increase in ORR with bevacizumab (35%-38% bevacizumab vs 22% placebo)  
Safety consistent with prior studies  |
| Phase III |     |                                                                            |                                    |
| Ciuleanu et al, 2008¹⁸ | 663 | Pemetrexed vs placebo post platinum-based therapy                          | Pemetrexed  
PFS = 4.3 mo  
OS = 13.0 mo  
CR + PR + SD = 52%  
Nonsquamous PFS = 4.5 mo  
Placebo  
PFS = 2.6 mo  
(P < .001)  
OS = 10.2 mo  
(P = .06)  
CR + PR + SD = 33%  
(P < .001)  
Nonsquamous PFS = 2.6 mo |
| Phase II |     |                                                                            |                                    |
| Patel et al, 2009¹⁹ | 50  | Pemetrexed + bevacizumab maintenance post carboplatin/pemetrexed/bevacizumab | ORR of 55%  
Median PFS = 7.8 mo  
Median OS = 14.1 mo  
No grade ≥ 3 hemorrhagic events or hypertension AEs |

AEs = adverse events; CR = complete response; NSCLC = non–small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease.
Overview of E5508 Protocol

This is a phase III study of patients ≥ 18 years of age with recurrent stage IIIB to IV nonsquamous NSCLC. Patient accrual is ongoing. The study design is outlined in Figure 1.

Figure 1: Study Design

- All eligible patients receive the combination regimen of paclitaxel, carboplatin, and bevacizumab as induction therapy (arm I). After 4 cycles of induction therapy, patients experiencing complete response (CR), partial response (PR), or stable disease (SD) are randomized to 1 of 3 maintenance therapy arms (arm A, B, or C). Patients with progressive disease (PD) are removed from the protocol treatment and are evaluated during long-term follow-up

• **Induction therapy (arm I; step 1, cycles 1-4):** Each cycle consists of 21 days for combination treatment. All therapeutic agents are delivered on day 1 of each cycle
  - Paclitaxel 200 mg/m² IV over 3 hours
  - Carboplatin AUC (area under curve) = 6 mg/mL IV over 15 to 30 minutes, immediately following paclitaxel infusion
    - Dose will be calculated based on a patient’s actual body weight at each treatment visit and the AUC dosing
  - Bevacizumab 15 mg/kg IV infusion over 30 to 90 minutes after completion of carboplatin infusion
    - Dose will be calculated based on a patient’s actual body weight at screening, and may be recalculated if body weight changes > 10% are observed during the study
• Stratification and randomization
  – Patients experiencing CR, PR, or SD are stratified prior to randomization for maintenance therapy based on gender, stage of disease, best response to first-line induction therapy, and smoking status
  – Patients with PD do not receive maintenance therapy, but are monitored for long-term follow-up
  – Patients eligible for step 2 must be registered within 6 weeks of the last day of chemotherapy administration on step 1. If more than 6 weeks have elapsed, then the patient is off the study
  – Patients eligible for step 2 will be randomized to treatment with 1 of the 3 following treatment arms

• Maintenance therapy (arm A, arm B, or arm C; step 2, cycles 1 and up): All therapeutic agents are delivered on day 1 of each 21-day cycle. Patient doses are recalculated at the start of step 2. Maintenance therapy is continued until disease progression, unacceptable toxicity, or withdrawal of patient consent
  – Arm A: bevacizumab 15 mg/kg IV infusion over 30 to 90 minutes
  – Arm B: pemetrexed 500 mg/m² IV over 10 minutes
  – Arm C: pemetrexed is administered prior to bevacizumab
    • Pemetrexed 500 mg/m² IV over 10 minutes
    • Bevacizumab 15 mg/kg IV infusion over 30 to 90 minutes

• Patients are monitored every 3 months for 2 years, then every 6 months for 2 to 5 years
  – Patients may also undergo periodic blood sampling during the study for pharmacokinetic and biomarker analyses
E5508 Study Objectives

**Primary Objective**
- Compare OS associated with maintenance therapy with bevacizumab versus pemetrexed versus combination bevacizumab/pemetrexed in patients with advanced-stage NSCLC

**Secondary Objectives**
- Determine response rate among the 3 maintenance treatment arms
- Evaluate PFS
- Assess safety and potential biomarkers

**Main Inclusion Criteria***
- \( \geq 18 \) years of age with cytologically or histologically confirmed nonsquamous NSCLC
- NSCLC classified as IIIB-T4Nx, IV M1a, or IV M1b stage of disease
- Adequate laboratory values and organ function
- ECOG performance status of 0-1
- Measurable or nonmeasurable disease as defined by RECIST criteria

**Main Exclusion Criteria***
- Prior malignancy within the past 3 years (except superficial melanoma, basal cell carcinoma, or carcinoma in situ)
- Prior systemic chemotherapy for advanced-stage lung cancer
- Prior paclitaxel, pemetrexed, or bevacizumab
- Major hemoptysis within the past 4 weeks
- Pregnancy or breast-feeding
- Progression of brain metastasis within 2 weeks after completion of local therapy, prior to registration
- Uncontrolled hypertension or uncontrolled intercurrent illness (eg, ongoing/active infection, symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmia, or psychiatric illness)
• Arterial thrombotic events or major bleeding within the past 12 months, significant vascular disease within the past 6 months; clinically significant cardiovascular disease
• Major surgery (eg, thoracotomy, laparotomy, craniotomy) or significant traumatic injury 6 weeks prior to registration, history of serious nonhealing wounds
• Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.

**Adverse Events**

• Proactive management of potentially severe toxicities is planned for these study treatments
• Adverse events with a possible relationship (likely, less likely, or rare but serious) to bevacizumab and pemetrexed are outlined in Table 2
<table>
<thead>
<tr>
<th>Likely (&gt; 20%)</th>
<th>Less Likely (≤ 20%)</th>
<th>Rare But Serious (&lt; 3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bevacizumab</strong></td>
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</tr>
<tr>
<td>Neutrophil count decreased, reproductive system and breast disorders—other (ovarian failure), hypertension</td>
<td>Anemia, febrile neutropenia, cardiac disorders (supraventricular arrhythmias), abdominal pain, colitis, constipation, diarrhea, dyspepsia, gastrointestinal hemorrhage, gastrointestinal obstruction, ileus, mucositis oral, nausea, vomiting, fatigue, infusion-related reaction, noncardiac chest pain, pain, allergic reaction, infection, infections and infestations—other (perirectal abscess), wound complication, wound dehiscence, alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, cardiac troponin I increased, platelet count decreased, weight loss, white blood cell count decreased, dehydration, anorexia, arthralgia, musculoskeletal and connective tissue disorder—other (bone metaphyseal dysplasia), myalgia, osteonecrosis of jaw, dizziness, headache, peripheral sensory neuropathy, syncope, hematuria, proteinuria, vaginal hemorrhage, allergic rhinitis, cough, dyspnea, epistaxis, hoarseness, pruritis, rash maculopapular, urticaria, thromboembolic event</td>
<td>Blood and lymphatic system disorders—other (renal thrombotic microangiopathy), acute coronary syndrome, heart failure, left ventricular systolic dysfunction, myocardial infarction, ventricular arrhythmia, ventricular fibrillation, gastrointestinal fistula, gastrointestinal perforation, gastrointestinal ulcer, anaphylaxis, injury, poisoning and procedural complications—other (anastomotic leak), intracranial hemorrhage, ischemia cerebrovascular, reversible posterior leukoencephalopathy syndrome, acute kidney injury, renal and urinary disorders—other (nephrotic syndrome), urinary fistula, vaginal fistula, bronchopleural fistula, bronchopulmonary hemorrhage, respiratory/thoracic/mediastinal disorders—other (nasal-septal perforation or tracheo-esophageal fistula), vascular disorders—other (arterial thromboembolic event)</td>
</tr>
<tr>
<td><strong>Pemetrexed</strong></td>
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<tr>
<td>Neutropenia, anemia, thrombocytopenia, fatigue, nausea, anorexia, dyspnea, rash, peripheral neuropathy</td>
<td>Fever, vomiting, dysphagia, pharyngitis, stomatitis, thromboembolism, dehydration, chills, edema, elevation of liver function, alopecia, depression, anxiety, confusion, chest pain, arrhythmia, skin discoloration, constipation, abdominal pain, weight loss, diarrhea, flatulence, myalgia, back/chest/bone pain, epistaxis, hyperglycemia, eye pain, hypertension, hypotension, blurred vision, headache, dysgeusia</td>
<td>Allergic reaction, pulmonary, cardiac or renal damage, hematuria, hemoptysis</td>
</tr>
</tbody>
</table>
Managing Adverse Events

- All dose reductions are considered permanent, with no re-escalation of dose allowed
- All toxicity should resolve to grade ≤ 1 before initiation of a new treatment cycle, with the exception of anemia, alopecia, neuropathy, proteinuria, and non-treatment-related and clinically insignificant laboratory abnormalities
- Induction phase dose modifications
  - If induction phase treatment is discontinued prior to cycle 3, patient will be removed from treatment; if after cycle 3, patient may be considered for maintenance phase (step 2)
  - A maximum of 2 dose reductions per patient are allowed at each step regardless of cause
  - Hematologic toxicity for paclitaxel and carboplatin
    - Anemia: dose reduction not necessary; treat with erythrocyte growth factor and red blood cell transfusion per institutional guidelines
    - Neutrophils: absolute neutrophil count (ANC) must be ≥ 1500/mm$^3$; delay treatment to allow recovery to required ANC and platelet counts
      - For grade 3/4 febrile neutropenia, reduce dose per Table 3
    - Platelets: must be ≥ 100,000/mm$^3$ on day 1 of each cycle
      - Dose reduction will only be done for grade 4 platelet toxicity (Table 3)

<table>
<thead>
<tr>
<th>Table 3. Dose Reduction Schedule During Induction Phase (Step I)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>First episode</td>
</tr>
<tr>
<td>Second episode</td>
</tr>
<tr>
<td>Third episode</td>
</tr>
</tbody>
</table>

*Only carboplatin is reduced for grade 4 platelet toxicity.
AUC = area under curve; CR = complete response; PR = partial response; SD = stable disease.
Nonhematologic toxicity for paclitaxel and carboplatin

- Gastrointestinal toxicity: control nausea/vomiting with antiemetics
  - Grade 3/4 vomiting or grade 3 nausea (Table 3)
  - Resolve nausea/vomiting to grade ≤ 1 prior to initiating new cycle of therapy; discontinue treatment if no resolution to grade 1 or less in 3 weeks

- If stomatitis occurs on day 1 of any cycle, withhold treatment until resolution to grade ≤ 1; discontinue treatment if no resolution to grade 1 or less in 3 weeks
  - For grade 3/4 acute stomatitis, dose-reduce per Table 3 once stomatitis resolves to grade ≤ 1

- Hepatic toxicity (for paclitaxel)
  - Dose-reduce paclitaxel by 25 mg/m² if aspartate aminotransferase (AST) > 5 x upper limit of normal (ULN) and/or total bilirubin > normal limit, but ≤ 1.5 x ULN
  - Hold carboplatin and paclitaxel, then reduce paclitaxel by 25 mg/m² if total bilirubin > 1.5 x ULN. If a third reduction of paclitaxel is required, discontinue induction treatment
  - Hepatic values must recover to grade ≤ 1 within 3 weeks or induction treatment will be discontinued

- Cardiovascular toxicity (for paclitaxel)
  - Symptomatic arrhythmia: stop paclitaxel infusion and discontinue induction treatment
  - Chest pain and/or symptomatic hypotension < 90/60 mm Hg or requiring fluid replacement: stop paclitaxel infusion and perform ECG
    - Give IV diphenhydramine and dexamethasone if hypersensitivity is considered
    - Consider epinephrine and bronchodilators if chest pain is thought to be not cardiac related
    - Discontinue induction treatment
• Neurologic toxicity (for paclitaxel)
  – Neurologic toxicity grade 2: hold paclitaxel until recovery to grade ≤ 1, then reduce dose 20% to 160 mg/m²
  – Neurologic toxicity grade ≥ 3: hold paclitaxel until recovery to grade ≤ 1, then reduce dose 30% to 140 mg/m²
  – Hold carboplatin if paclitaxel is withheld and administer when paclitaxel is resumed
  – If third reduction, discontinue induction treatment. Recovery to grade ≤ 1 is required within 3 weeks, or induction treatment will be discontinued

• Allergic reactions (for paclitaxel)
  – Moderate symptoms: stop paclitaxel infusion and give IV diphenhydramine
    • Resume paclitaxel at lower rate after symptom recovery
    • Discontinue paclitaxel and induction therapy if symptoms recur
  – Severe life-threatening symptoms: discontinue paclitaxel infusion and give IV diphenhydramine and dexamethasone
    • Add epinephrine or bronchodilators if needed
    • Discontinue induction therapy
  – Other grade 3/4 toxicities related to induction treatment: hold treatment until resolution to grade ≤ 1
    • If recovery to grade ≤ 1 does occur within 3 weeks, resume treatment at reduced doses per Table 3
    • If grade 3/4 toxicities persists > 3 weeks or a third reduction is required, discontinue induction treatment

• Bevacizumab dose modifications during induction therapy (step 1)
  – Paclitaxel and carboplatin dose delays will result in holding bevacizumab therapy; discontinuation will remove patient from the study
  – If bevacizumab is held ≤ 3 weeks, continue scheduled paclitaxel/carboplatin; if ≥ 3 weeks, discontinue all protocol treatment, unless specifically noted otherwise
- **Proteinuria**: urine dipstick must be 0-1+ or urine protein/creatinine (UPC) ratio must be < 3.5 to allow bevacizumab treatment; discontinue all protocol treatment if bevacizumab is held for > 2 months. If patient experiences grade 4 proteinuria or nephrotic syndrome, discontinue all protocol therapy.

- **Hypertension**: control with antihypertensives; no bevacizumab dose reduction.
  - Grade 2 asymptomatic, but diastolic BP < 100 mm Hg: begin antihypertensives and continue bevacizumab.
  - Grade 2/3 symptomatic or diastolic BP > 100 mm Hg: hold bevacizumab until symptoms resolve and BP < 160/90 mm Hg.
  - Grade 4: discontinue bevacizumab.
  - Uncontrolled hypertension for 4 weeks: discontinue treatment.

- **Thromboembolic event**: take caution for patient requiring anticoagulation due to increased risk of bleeding.
  - Grade 3/4 venous thrombosis: may continue bevacizumab during initiation or continuation of therapeutic anticoagulation.

- **Bleeding or hemorrhage**:
  - Grade 1 hemorrhage: hold bevacizumab until bleeding resolves to grade 0; resume bevacizumab at 15 mg/kg once resolved.
    - Discontinue treatment if bleeding elevates to grade ≥ 2 with resumption of bevacizumab.
  - Grade 2/3/4 hemorrhage: discontinue all protocol therapy.

- **Hemoptysis**: if grade > 1, discontinue protocol treatment.
  - Grade 1: evaluate patient for source; if no source found and resolution occurs within 1 week, reinitiate bevacizumab at 15 mg/kg.

- **Arterial thromboembolic events**:
  - Grade 2: if new or worsened since bevacizumab, discontinue all protocol treatments.
  - Grade ≥ 3: discontinue all protocol treatments.
Liver function abnormalities
- Monitor prior to each bevacizumab dose
- Grade ≥ 3 ALT or AST elevation: withhold bevacizumab until grade ≤ 1; if elevation recurs or persists > 3 weeks, discontinue all treatments

Bowel perforation/anastomotic dehiscence: discontinue bevacizumab

Leukoencephalopathy syndrome (including reversible posterior leukoencephalopathy syndrome [RPLS]):
- Hold bevacizumab in patients with symptoms or signs suggestive of RPLS
- Discontinue protocol treatment on positive confirmation by MRI or if treatment delay is > 3 weeks due to toxicity
- Resume protocol treatment if RPLS is mild, and resolves clinically and radiographically within 2 to 4 weeks; resumption of protocol treatment may be considered, after consultation with study chair

Other grade 3/4 toxicities thought to be related to bevacizumab: hold bevacizumab until resolution to grade ≤ 1
- If grade 3/4 toxicity persists > 3 weeks or recurs after resuming therapy, discontinue protocol treatment

Maintenance phase dose modifications
- Note: holding bevacizumab treatment does not alter pemetrexed administration, and vice versa
- Bevacizumab dose modifications
  - Similar to those outlined in the induction phase
  - If discontinued in bevacizumab arm (arm A), patient enters long-term follow-up
- Pemetrexed dose modifications
If toxicity occurs, inquire with patient about compliance with folic acid intake; ensure administration of vitamin $B_{12}$ every 3 cycles.

Hematologic toxicity: delay pemetrexed if the following indices are not met—if delayed > 3 weeks, discontinue all treatment protocol (arm B) or continue on bevacizumab only (arm C).
- ANC must be $\geq 1500/\text{mm}^3$
- Platelets must be $\geq 100,000/\text{mm}^3$
- Grade 3/4 febrile neutropenia (Table 4)
- Consider leucovorin treatment for grade 4 leukopenia and grade 4 neutropenia lasting > 3 days, grade 4 thrombocytopenia, or bleeding associated with grade 3 thrombocytopenia.

### Table 4. Pemetrexed Dose Reduction Schedule During Maintenance Phase (Step 2)

<table>
<thead>
<tr>
<th>Pemetrexed Reduced Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode</td>
</tr>
<tr>
<td>375 mg/m²</td>
</tr>
<tr>
<td>Second episode</td>
</tr>
<tr>
<td>250 mg/m²</td>
</tr>
<tr>
<td>Third episode</td>
</tr>
<tr>
<td>No further therapy; enter long-term follow-up phase</td>
</tr>
</tbody>
</table>

Nonhematologic toxicity related to pemetrexed: delay pemetrexed if grade ≥ 3.
- If > 3 weeks, discontinue treatment (arm B) or continue bevacizumab only (arm C).

Renal toxicity: take caution with NSAIDs in patients with mild to moderate renal insufficiency; avoid NSAIDs 2 days before, on the day of, and 2 days after pemetrexed.

Stomatitis: consider leucovorin for grade 3/4 stomatitis.

Clinically significant effusions: consider draining effusion prior to dosing and discontinue treatment if cytology confirms progression of disease.
- May resume pemetrexed on resolution.
• Grade 3/4 nausea/vomiting: manage with antiemetics
• Grade 3/4 mucositis: resume pemetrexed at 50% of previous level
• Grade 4 transaminase elevation, grade 3/4 diarrhea (or requiring hospitalization): dose-reduce 25%; resume at 75% of previous dose
• Other grade 3/4 nonhematologic toxicities: resume at 75% of previous dose if deemed appropriate by treating physician

For Further Study Information

• For more information about the E5508 study, please contact or see the following:
  – ClinicalTrials.gov registration number: NCT01107626; http://www.clinicaltrials.gov/ct/show/NCT01107626
  – For more information about ECOG-ACRIN, visit http://www.ecog-acrin.org/

References


15. ALIMTA (pemetrexed) prescribing information. Indianapolis, IN: Lilly USA, LLC; 2011.


