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 NSCLC

Study Schema

Study Objectives

Primary Objective

- Compare overall survival 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 progression-free survival
- Assess safety and potential biomarkers
Table 1. E5508 Regimens for Treatment Arms: Induction and Maintenance Therapies

<table>
<thead>
<tr>
<th>Arm</th>
<th>Induction therapy* (step 1; arm I)</th>
<th>Maintenance therapy* (step 2; arms A, B, C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm I</td>
<td>4 cycles of paclitaxel 200 mg/m² IV over 3 h, carboplatin AUC = 6 mg/mL IV over 15-30 min, and bevacizumab 15 mg/kg IV infusion over 30-90 min</td>
<td>Bevacizumab 15 mg/kg IV infusion over 30-90 min</td>
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<tr>
<td></td>
<td></td>
<td>Pemetrexed 500 mg/m² IV over 10 min</td>
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<td></td>
<td></td>
<td>Pemetrexed 500 mg/m² IV over 10 min plus</td>
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<td></td>
<td></td>
<td>bevacizumab 15 mg/kg IV infusion over 30-90 min</td>
</tr>
</tbody>
</table>

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 there is more than a 6-week delay, the patient is off the study.
- Patients eligible for step 2 will be randomized to treatment with 1 of the 3 following treatment arms:

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance therapy* (step 2; arms A, B, C)</td>
<td>Bevacizumab 15 mg/kg IV infusion over 30-90 min</td>
<td>Pemetrexed 500 mg/m² IV over 10 min</td>
</tr>
<tr>
<td></td>
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Long-term monitoring†
- Patients are monitored every 3 months for 2 years, then every 6 months for 2-5 years.
- Patients may also undergo periodic blood sampling during the study for pharmacokinetic and biomarker analyses.

*Doses are based on body weight and to be recalculated at the start of step 2. All therapeutic agents are delivered on day 1 of each cycle (21 d).
†Response and progression are measured using the international Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1; Eur J Cancer. 2009;45:228-247).
AUC = area under curve; CR = complete response; IV = intravenous; PD = progressive disease; PR = partial response; SD = stable disease.

Eligibility Criteria*

Main Inclusion Criteria*
- ≥ 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.

For Further Study Information

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