**For Patients with Non-Squamous NSCLC**

**E5508 Available Through ECOG-ACRIN**

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 NSCLC

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**Patient Population**
See Section 3.0 for Complete Eligibility Details

**Step 1:**
- Cytological or histological confirmation of NSCLC
- Predominant non-squamous histology (no small cell elements)
- Stage IV disease (includes M1a, M1b or recurrent disease). Patients with T4NX disease (stage IIIb) with nodule in ipsilateral lung lobe are eligible as long as they are not candidates for combined chemotherapy and RT
- No prior systemic chemotherapy for advanced stage lung cancer
- Patients may have had prior adjuvant chemotherapy if at least 12 months have elapsed
- At least two weeks must have passed since completion of prior radiotherapy
- No prior paclitaxel, pemetrexed, or bevacizumab; prior carboplatin is allowed if given as part of adjuvant chemotherapy
- Age ≥ 18 years, ECOG PS 0-1, and adequate lab values
- Patients with brain metastasis must have received local therapy to the brain and have no evidence of progression in the brain for at least 2 weeks from the time of completion of local therapy prior to registration
- No major hemoptysis within four weeks prior to registration
- Patients with uncontrolled intercurrent illness are excluded
- Must have measurable or nonmeasurable disease (RECIST)
- No history of atelectasis or major bleed within 12 months prior to registration
- No major surgery within 6 weeks of registration
- No clinically significant cardiovascular disease
- No history of serious non-healing wounds
- Must not have cavitary lesions in the lungs

**Step 2:**
- Must have an overall response of stable or better after 4 cycles of induction with adequate lab values

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**Treatment Plan**
See Section 5.0 for Complete Treatment Details

**Induction Therapy—Step 1:**
- Paclitaxel 200 mg/m² IV over 3 hours on Day 1
- Carboplatin AUC = 6 IV over 15-30 mins on Day 1
- Bevacizumab 15 mg/kg IV over 30-90 mins on Day 1
- Give four 21-day cycles

**Maintenance Therapy—Step 2:**
For patients that experience complete response, partial response or stable disease.

Patients must be registered to Step 2 within 6 weeks of the last day of chemotherapy administration on Step 1. If there is more than a 6 week delay, the patient must go off study. Patient doses should be recalculated at the start of Step 2 treatment.

**Arm A:**
- Bevacizumab 15 mg/kg IV over 30-90 mins on Day 1
- Give 21-day cycles until progression or unacceptable toxicity

**Arm B:**
- Pemetrexed 500 mg/m² IV over 10 mins on Day 1
- Give 21-day cycles until progression or unacceptable toxicity

**Arm C:**
- Pemetrexed 500 mg/m² IV over 10 mins on Day 1
- Bevacizumab 15 mg/kg IV over 30-90 mins on Day 1
- Give 21-day cycles until progression or unacceptable toxicity

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**Patient Enrollment**
All Sites: Oncology Patient Enrollment Network (OPEN) [https://open.ctsu.org](https://open.ctsu.org)

**Protocol Information**

Please Enroll Your Eligible Patients!
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**Schema**

**Step 1:**
- **Registration**
- Stage IIIb-T4N0-IV M1a/Iv M1b NSCLC
- Recurrent Non-squamous histology
- ECOG PS 0 or 1
- No prior chemotherapy
- Adequate bone marrow, renal and hepatic parameters
- No history of major hemoptysis
- Informed consent

**Cycles 1-4:**
- **Induction**
  - Arm A
  - Paclitaxel 200 mg/m² IV
  - Carboplatin AUC = 6
  - Bevacizumab 15 mg/kg IV
  - Day 1 of every cycle

**Step 2:**
- **Randomization**
- Stratification factors:
  - Gender (male vs. female)
  - Stage (IIb-T4N+/M1a vs. IV/M1b vs. recurrent)
  - Best response to first-line therapy (CR/PR vs. SD)
  - Smoking status (never vs. ever-smokers)

**Cycles 1 and up:**
- **Maintenance**
  - Arm A
  - Bevacizumab 15 mg/kg IV
  - Day 1 of every cycle**

  - Arm B
  - Pemetrexed 500 mg/m² IV
  - Day 1 of every cycle**

  - Arm C
  - Pemetrexed 500 mg/m² IV
  - Bevacizumab 15 mg/kg IV
  - Day 1 of every cycle**

1 cycle = 21 days
Accrual = 1495

- Stage IIIb-T4Nx patients must have a nodule in the ipsilateral lung lobe and must not be candidates for combined chemotherapy and radiation.
- Continue until progression or unacceptable toxicity.