Eligibility Criteria

1. Patients must have undergone complete resection of their non-small cell lung cancer (NSCLC) [stage IB (≥ 4cm) – IIIA (T2-3N0, T1-3N1, T1-3N2) prior to enrollment. Refer to Appendix X for staging guidelines per AJCC 6th edition. Accepted types of resection will consist of lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy. Resections by segmentectomy or wedge resection will not be accepted. Mediastinal lymph node resection sampling at specific levels is required pre-operatively (mediastinoscopy) or intraoperatively (level 7 and 4 for right sided tumors or level 7 and 5 and/or 6 for left sided tumors). Please refer to Section 5 for specific details on lymph node level sampling requirements and resection criteria.
   1.1 If patient’s tumor is stage IB, it must be ≥ 4 cm in size.
   1.2 If patient’s lymph node stage (N) = N0 or N1, is sampling of at least one lymph node from each of the specified levels documented?
2. Patients must be no less than 6 weeks (42 days) and no more than 12 weeks (84 days) post-thoracotomy at the time of randomization and must be adequately recovered from surgery.
3. Age ≥ 18 years.
4. ECOG performance status 0 or 1.
5. Patients must not have received the following:
   5.1 Prior systemic chemotherapy at any time. Methotrexate (MTX) given in low doses for non-malignant conditions with the last dose at least 2 weeks prior to date of registration will be allowed. Other low dose chemotherapies for non-malignant conditions will be considered but review by the study chair is required.
   5.2 Hormonal cancer therapy or radiation therapy as prior cancer treatment within 5 years of randomization. (Prior surgery, biologic therapy, hormonal therapy or radiation therapy for a malignancy over 5 year prior to enrollment that is now considered cured is acceptable.)
6. Patients must not have any history of cancer within 5 years from randomization, with the exception of in-situ carcinoma of the cervix or completely resected non-melanoma skin cancer.
7. Required laboratory values obtained within two weeks of randomization:
   • ANC ≥ 1500 mm$^3$
   • Platelets ≥ 100,000 / mm$^3$
   • Prothrombin time/INR ≤ 1.5 Or, if patient on therapeutic anticoagulation, prothrombin time/INR ≤ 3.0.
   • PTT ≤ institution upper limit of normal (ULN) or if patient is on therapeutic anticoagulation, PTT must be ≤ 1.5 x ULN
   • Total bilirubin ≤ 1.5 mg/dL
   • SGOT (AST) < 5x upper limit of normal (ULN)
   • SGPT (ALT) < 5x upper limit of normal (ULN)
8. Patients must have adequate renal function as determined by the following tests within two weeks prior to randomization:
   • Serum Creatinine ≤ 1.5 institutional upper limit of normal (ULN)
   • Urine protein should be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For ratio > 0.5, 24-hour urine protein must be obtained and the level must be < 1000 mg for patient enrollment. See Section 3.9 for further detail.
9. Patients with a known history of myocardial infarction or other evidence of arterial thrombotic disease (angina) will be allowed on study only if they have had no evidence of active disease for at least 12 months prior to randomization.
10. Patients with any history of cerebral vascular accident (CVA) or transient ischemic attack (TIA) will not be allowed on trial.
11. Women must not be pregnant or breast-feeding due to the potential harm to the fetus or infant from cytotoxic chemotherapy and the unknown risk from bevacizumab. It is also unknown if the agent are excreted in to the breast milk. All females of childbearing potential must have a blood or urine test within two weeks prior to randomization to rule out pregnancy.

12. Both fertile men and women must agree to use adequate contraceptive measures during study treatment and for at least 6 months after completion of bevacizumab.

13. Patients must not have any clinically significant ongoing, active or serious infection, symptomatic or uncontrolled congestive heart failure, symptomatic or uncontrolled cardiac arrhythmia, or any other medical condition or psychiatric illness/social situation that would limit compliance with study requirements.

14. Patients must have no history of bleeding diathesis or coagulopathy.

15. All patients must have a documented BP with systolic ≤ 150 and diastolic ≤ 90 within 28 days of registration. Patients with known hypertension must by on a stable regimen of anti-hypertensive therapy.

16. Patients receiving daily treatment with aspirin or non-steroidal anti-inflammatory agents (NSAIDS) are eligible. Treatment with dipyridamole (Persantine), ticlopidine (Ticlid), clopidogrel (Plavix) and/or cilostazol (Pletal) is not allowed. Patients must have stopped taking any of these agents at least 7 days prior to randomization.

17. Patients must not have serious non-healing wound, ulcer, bone fracture or have undergone a major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to randomization OR core biopsy within 7 days prior to randomization.

18. Patients must not have a history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days prior to randomization.

19. Patients must not have any anticipated major surgical procedure(s) during the course of the study.

20. Patients must not have known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

21. Patients may be on stable regimen of therapeutic anticoagulation or may be receiving prophylactic anticoagulation of venous access devices, provided that coagulation studies meet entry criteria. Caution must be exercised for patients requiring anticoagulation, including treatment with low dose heparin or low molecular weight heparin for DVT prophylaxis while on study due to an increased of bleeding with bevacizumab.

22. Patients with ongoing post-operative hemoptysis (define as bright red blood of ½ teaspoon or more) are not eligible. Patients with pre-operative hemoptysis that has resolved post-operatively are eligible.

23. All patients must be informed of the investigational nature of this study and give a written informed consent according to institutional and federal guidelines.

**Pemetrexed/Cisplatin Therapy**

Patients who will receive pemetrexed/cisplatin therapy must meet all eligibility criteria listed above and two criteria below:

24. Patients assigned to pemetrexed/Cisplatin therapy must NOT have squamous cell histology.

25. Calculated Creatinine Clearance must be obtained within 2 weeks of randomization and calculated CrCl must be ≥ 45mL/min using the standard Cockcroft and Gault formula (See Appendix XIII), or the measured glomerular filtration rate (GFR) using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA) must be used to calculate CrCl.

**Pre-study parameters**

1. H&P/Performance status
2. Weight/Height/Blood Pressure
3. CBC w/diff, platelets
4. Serum chemistries – sodium, potassium, chloride, BUN, Creatinine, Total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase
5. PT/PTT and INR
6. UPC ratio
7. EKG (required)
8. CXR (required)
9. Radiologic/disease evaluations – Pre-study evaluation should be completed no earlier than 14 days prior to randomization. Patients may be randomized 6-12 weeks post-operatively. Prior to surgical resection patients must have had adequate staging to rule out metastatic disease (CT or equivalent scan or thorax, CT/MRI of brain as clinically indicated), strongly encourage for all patients with stage IIIA disease, CT/US of liver/abdomen as clinically indicated, radionuclide bone scan as clinically indicated, positron emission scanning (PET) as clinically indicated.

10. Pregnancy test – Blood or urine test for women of childbearing potential; within two weeks prior to randomization.

**Stratification Factors**

1. Type of chemotherapy: Regimen 1, 2, 3 or 4
2. Stage: IB vs II vs IIIA-N2 vs IIA-T3N1
3. Histology: Squamous cell vs other histologies
4. Gender

**Treatment Plan – see section 5.1**

Patients are randomized to Arm A or Arm B

**Arm A**

| 1 of 4 chemotherapy regimens¹, no bevacizumab | → | Until disease progression, unacceptable toxicity or a total of 4 – 21 day cycles |

**Arm B**

| 1 of 4 chemotherapy regimens¹, plus bevacizumab² | → | Chemotherapy + bevacizumab will be given until disease progression, unacceptable toxicity or a total of 4 - 21 day cycles
Then, bevacizumab for up to 1 year (measured from the first day of protocol treatment) |

¹Physicians choice of chemotherapy regimens:

**Chemotherapy Regimen 1**
- Vinorelbine 30 mg/m² IV push over 10 minutes, days 1 and 8
- Cisplatin 75 mg/m² IV over 60 minutes day 1, immediately following vinorelbine

**Chemotherapy Regimen 2**
- Docetaxel 75 mg/m² IV over 60 minutes day 1
- Cisplatin 75 mg/m² IV over 60 minutes day 1, immediately following docetaxel

**Chemotherapy Regimen 3**
- Gemcitabine 1200 mg/m² IV over 30 minutes, day 1 and 8
- Cisplatin 75 mg/m² IV over 60 minutes day 1, immediately following Gemcitabine

**Chemotherapy Regimen 4**
- Premetrexed 500 mg/m² IV over 10 minutes, day 1
- Cisplatin 75 mg/m² IV over 60 minutes day 1, immediately following Premetrexed

²Bevacizumab – Arm B only
First four cycles - 15 mg/m² day 1, immediately following chemotherapy
Continue every 3 weeks for up to one year.

For toxicities and dosage modifications, see section 5.2, 5.3, 5.4, or 5.5