

PSHCI 08-009 – A Multicenter, Open-Label, Randomized, Phase II Trial of Docetaxel, Carboplatin and Bevacizumab as First-Line Treatment, Followed by Bevacizumab plus Pemetrexed versus Pemetrexed Alone as Second-Line Treatment of Stage IIIB or IV Non-Small Cell Lung Cancer (NSCLC)

Primary Objective: Progression-free survival (PFS) of bevacizumab and pemetrexed compared to pemetrexed monotherapy during second-line treatment of Stage IIIB or IV NSCLC.

Eligibility Criteria:

- Age \geq 18 years
- Histologically or cytologically confirmed stage IIIB with malignant pleural effusion or stage IV NSCLC except squamous-cell carcinoma
- Measurable disease defined by RECIST
- Adequate organ function
 - Absolute neutrophil count \geq $1.5 \times 10^9/L$
 - Hemoglobin \geq 9.0g/dL
 - Platelets \geq $100 \times 10^9/L$
 - Hepatic enzyme levels: AST and ALT and Alkaline Phosphatase must be within range allowing for eligibility.
 - Bilirubin \leq ULN
 - Serum Creatinine \leq 1.5 mg/DL (or creatinine clearance $>$ 60mL/min)
 - Urine protein/creatinine ratio $<$ 1.0 OR urine dipstick proteinuria $<$ 2+ (patients discovered to have \geq 2+ proteinuria on dipstick analysis at baseline should undergo a 24 hour urine collection and must demonstrate \leq 1g of protein in 24 hours to be eligible)
 - INR \leq 1.5
 - PTT \leq ULC
- ECOG Performance Status 0-1
- Estimated survival of \geq 12 weeks
- Provide written informed consent

Exclusion Criteria:

- Prior chemotherapy for advanced NSCLC
- Neoadjuvant or adjuvant treatment within six (6) months of registration
- Prior radiation therapy within three (3) weeks of registration; all side effects must have resolved by registration
- Prior treatment with an investigational or marketed agent that acts by antiangiogenesis mechanisms
- Large ($>$ 4 cm) centrally located lesions or large lesions in close proximity to major blood vessels unless treated with palliative radiation.
- Brain metastases or leptomeningeal disease, except for patients who have had a resection and/or completed a course of cranial irradiation, have no worsening CNS symptoms, and have discontinued all corticosteroids for that indication for at least one (1) month prior to registration
- History of gross hemoptysis (defined as bright red blood of at least $\frac{1}{2}$ teaspoon or 2.5 mL per episode) within three (3) months of registration unless definitively treated with surgery, radiation, arteriographic embolization, or endobronchial interventions at least 4 weeks prior to registration.
- Presence of cavitary lesion
- Presence of squamous histology (mixed tumors will be categorized by the predominant cell type unless small cell elements are present, in which case the patient is ineligible; sputum cytology alone is not acceptable)
- Peripheral neuropathy $>$ grade 1
- Major surgery, open biopsy or significant traumatic injury within four (4) weeks of registration or anticipation of need for major surgical procedure during the course of the study.
- Minor surgical procedures, fine needle aspirations or core biopsies within one (1) week prior to registration
- Current ongoing therapeutic anticoagulation with full-dose warfarin or its equivalent.
- Current or recent (within ten [10] days of the first dose of study treatment) use of aspirin (at least 325 mg/day) or other NSAIDs with anti-platelet activity or treatment with dipyridamole (Persantine), ticlopidine (Ticlid), clopidogrel (Plavix) or cilostazol (Pletal)
- History of prior malignancy within the past three (3) years except for curatively treated basal cell carcinoma of the skin, cervical intra-epithelial neoplasia, or treated localized prostate cancer with a

- current PSA or < 1.0 mg/dL on two successive evaluations, at least three (3) months apart, with the most recent evaluation no more than four (4) weeks prior to registration.
- History of serious systemic disease including:
 - Unstable angina, NYHA \geq Grade II or congestive heart failure
 - Inadequately controlled hypertension (blood pressure >150/100 mmHg while taking antihypertensive medications)
 - Unstable symptomatic arrhythmia requiring medication
 - Myocardial infarction within six (6) months prior to registration
 - Stroke within six (6) months prior to registration
 - Transient ischemic attack within six (6) months prior to registration
 - Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within six (6) months prior to registration
 - Clinically significant peripheral vascular disease or evidence of bleeding, diathesis (prone to bleeding) or coagulopathy
 - Active systemic bacterial, fungal or viral infection, including known HCV and HIV
 - Pregnancy or women who are breast-feeding; women of child-bearing potential and non-vasectomized men must agree to use effective methods of birth control during and three (3) months following treatment period and women of child bearing potential must have a negative pregnancy test.
 - History of severe hypersensitivity reaction to docetaxel or any other drugs formulated with polysorbate 80
 - Any other medical condition, including mental illness or substance abuse, which in the judgement of the investigator, is likely to interfere with a patient's ability to provide informed consent, cooperate, and participate in the study, or to interfere with the interpretation of the results.
 - Use of any investigational agent within four (4) weeks prior to registration

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