THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

A Phase II Evaluation of Avastin® in Combination with Docetaxel and Carboplatin as Chemotherapy in Patients with Metastatic Non-Small Cell Lung Cancer
2005-0224

Core Protocol Information

Full Title:	A Phase II Evaluation of Avastin® in Combination with Docetaxel and Carboplatin as Chemotherapy in Patients with Metastatic Non-Small Cell Lung Cancer
Protocol Phase:	Phase II
Version Status:	Terminated 07/27/2017
Version:	22
Document Status:	Final

Abstract

Objectives:

Primary

The primary endpoint of this trial is to estimate progression-free survival, defined as the time from study enrollment to disease progression or death as an indicator of the activity of the Avastin® regimen.

Secondary

• Assessment of overall survival
• Assessment of disease control rate (complete response + partial response + stable disease)
• Evaluation of the safety and toxicity profile of this triple-agent regimen
• To correlate the above primary and secondary objectives with biomarkers and immunohistochemistry from tissue samples (optional)

Rationale: (Be as concise as possible)

In this Phase II trial, the biologic agent Avastin® is combined with cytotoxic chemotherapy, attacking against the factors that lead to the development of tumor blood supply and tumor cell proliferation in NSCLC. Avastin® directly binds to VEGF and inhibits from binding to endothelial cells and in turn blocks blood vessel growth.

The common 21-day dosing regimen has been studied and is used for docetaxel and carboplatin. Due to

the fact that there are not to be overlapping toxicities or pharmacodynamic interactions with the study drug Avastin as well as secondarily for ease of delivery and monitoring, it will be given along with the other two drugs. The treatments will be repeated every 21 days as another cycle with disease evaluation after every 2 cycles in order to monitor for need for continuation of therapy and endpoints closely.

Eligibility: (List All Criteria)

Inclusion:

1) Men and women, at least 18 years old, with histologically confirmed, advanced stage IIIB or IV NSCLC for whom no curative options exist and for whom docetaxel and carboplatin is a reasonable treatment option;

2) At least 1 target lesion that is unidimensionally measurable as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) and has not been previously irradiated;

3) Eastern Cooperative Oncology Group Performance Status of 0 or 1, (determined within 2 weeks prior to receiving study medication;

4) Ability to understand and adhere to the protocol requirements, and give informed consent

5) Use of effective means of contraception (men and women) in subjects of child-bearing potential. Child-bearing potential is defined as follows: A woman of childbearing potential is a sexually mature woman who has not undergone a hysterectomy or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses at any time in the preceding 12 consecutive months).

Exclusion:

1) Patients who have had docetaxel in nonradiosensitizing therapy

2) Patients who have received prior full dose systemic chemotherapy for NSCLC (ie neoadjuvant, adjuvant, or metastatic) within the last 6 months.

3) ECOG status of 2 or greater

4) Screening clinical laboratory values:*ANC of <1,500/µL *Platelet count of <75,000/µL * INR >/= 1.5 *T bilirubin elevation above normal (MDACC upper normal limit is 1.0 mg/dL) *Serum creatinine of >2.0 mg/dL *Hemoglobin of <9 mg/dL (may be transfused or receive epoetin alfa [e.g., Epogen®] to maintain or exceed this level) *The pt is ineligible if: 1.alk phos>5xULN; 2.AST or ALT >5xULN; 3.alk phos >1xULN but </= 2.5xULN AND AST or ALT >1.5xULN but </=5xULN;4.alk phos >2.5xULN but </=5xULN AND AST or ALT > 1xULN but</= 1.5xULN; 5.alk phos >2.5xULN but</=5xULN AND AST or ALT >1.5xULN but </=5xULN

5) Inability to comply with study and/or follow-up procedures

6) History of other disease, active infection, metabolic dysfunction , physical examination finding, or clinical laboratory finding which is uncontrolled requiring medical intervention giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect the interpretation of the results of the study or render the subject at high risk from treatment complications.

7) Current, recent (within 4 weeks of the first infusion of this study), or planned participation in an experimental drug study other than a bevacizumab cancer study

8) Prior exposure to anti-VEGF therapy

9) Blood pressure of > 140/90 mmHg as documented in two consecutive blood pressure readings

within 4 hours

10) Any prior history of hypertensive crisis or hypertensive encephalopathy

11) New York Heart Association (NYHA) Grade II or greater congestive heart failure

12) History of myocardial infarction or unstable angina within 6 months

13) History of stroke or transient ischemic attack within 6 months

14) Significant vascular disease (e.g., aortic aneurysm, aortic dissection)

15) Evidence of bleeding diathesis or coagulopathy

16) Presence of central nervous system or brain metastases at any time

17) Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 0, anticipation of need for major surgical procedure during the course of the study

18) Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to Day 0

19) Pregnant (positive pregnancy test) or lactating

20) Proteinuria at screening as demonstrated by either: Urine protein:creatinine (UPC) ratio > 1.0 at screening OR Urine dipstick for proteinuria > 2+ (patients discovered to have > 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate < 1g of protein in 24 hours to be eligible).

21) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to Day 0

22) Serious, non-healing wound, ulcer, or bone fracture

23) Lung carcinoma of squamous cell histology or any histology in close proximity to a major vessel, cavitation.

24) History of hemoptysis (bright red blood of 1/2 teaspoon or more)

25) Full dose anitcoagulation, chronic use of Aspirin (>325 mg/day) or NSAIDs

26) Inability to comply with study and/or follow-up procedures

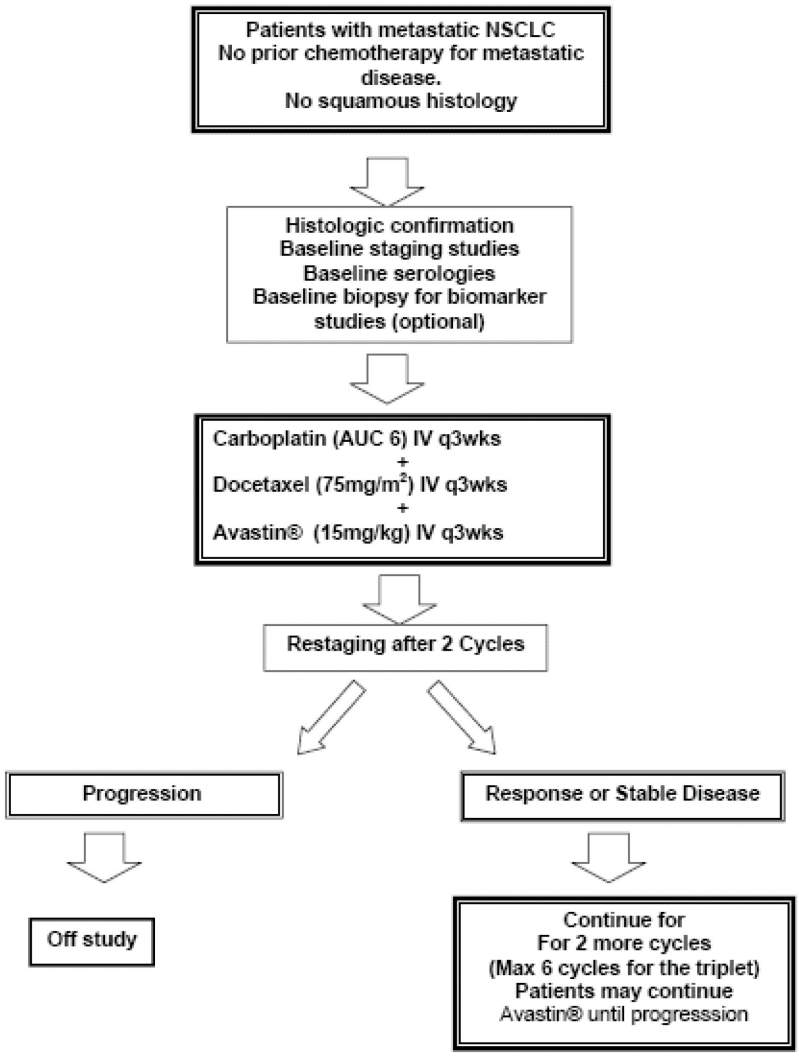
Is there an age limit? Yes

Why? Please explain:
A diagnosis of NSCLC is exceedingly uncommon at ages 18 and below.

Treatment/Study Plan:

This is a single center Phase II open-labeled single-arm nonrandomized study of Avastin® in combination with docetaxel and carboplatin as first line systemic chemotherapy for metastatic non small cell lung cancer. Patients will receive Carboplatin (AUC 6) IV with Docetaxel (75 mg/m^2) IV with Avastin® (15 mg/kg) IV every 3 weeks. (Patients will receive standard premedication with dexamethasone before docetaxel infusion.) After 2 cycles, patients will be restaged. If there is evidence of progression, they will be taken off study. If, however, there is either response or stable disease, they will be continued on the regimen just described for 2 more cycles, followed again by restaging studies to

evaluate for progression versus stable or responsive disease. This will continue the triplet regimen for a maximum of up to 6 cycles. Patients who are stable or still responding may continue Avastin® until progression. If 3 or more patients experience a grade >/= 3 drug-related adverse event, then dose modification will be considered.



Estimated number of patients enrolled will be 50 total. Estimated rate of accrual will be 5 patients per month for a total of 50 patients in 10 months, and each to be followed for 12 months minimum as possible.

Disease Group: Lung

Treatment Agent: Avastin, Carboplatin, Docetaxel

Statistical Considerations:

The primary objective of this single-arm, phase II clinical trial is to evaluate the efficacy of carboplatin, docetaxel, and Avastin® in the treatment of patients with metastatic non-small cell lung cancer who have not received prior systemic chemotherapy. The primary endpoint is progression-free survival. Up to 50 patients will be accrued in approximately 10 months; each patient will be followed for at least 12 months.

Total study duration should be less than 24 months. Assuming a one-sided type I error rate of 10%, we have at least 81% power to detect an increase in median survival from a historical estimate of 4.5 months to 6.3 months.

Planned Efficacy Evaluations, Variables, and Analysis

The primary endpoint of this study is the estimation of progression-free survival, defined as the time from enrollment to disease progression or death. Secondary endpoints include the assessment of overall survival, disease control rate (complete response + partial response + stable disease) and the evaluation of the safety profile of this triple-agent regimen. Survival distributions will be summarized using the method of Kaplan and Meier. Comparisons with historical controls of survival distributions by patient subgroups will be tested using the log rank test. Multivariable models of PFS and OS will be analyzed using the Cox (proportional hazards) regression model.

Continuous variables will be summarized using the mean (s.d.) and median (range). Categorical variables will be summarized in frequency tables. Graphical summaries will be emphasized for describing the distribution of variables. The Pearson correlation, or its non-parametric analogue, the Spearman correlation, will be used to assess linear correlations among variables. Scatter plots and other powerful bi-variate plots will be used to characterize association among variables.

Protocol Monitoring:

Who is monitoring the day-to-day implementation and performance of this study, i.e., Good Clinical Practice?

Data Monitoring Committee:

Is this study randomized or blinded? No

Patient/Participant Evaluation: (Pretreatment and Interim Testing)

Pre-Treatment Evaluations:

Unless otherwise specified, the following evaluations must be performed within four weeks prior to each patient's on-study (initial **Avastin®** treatment) date:

- Pregnancy test (serum or urine) for women of childbearing potential (within 2 weeks of treatment).
- Medical history and documentation of the rationale for treatment of the patient's disease with Avastin
- Physical examination, including vital signs (blood pressure), performance status and tumor assessment.
- Baseline staging exams (i.e. chest x-ray, CT, brain MRI)
- Urine protein:creatinine ratio or urine dipstick (and 24 hour collection if indicated)
- Hematology (within 2 weeks of treatment): complete blood count (CBC) with differential and platelet count.
- Serum Chemistries: sodium, potassium, magnesium, calcium, glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, total protein, albumin, SGOT(AST), and SGPT (ALT).
- PT, PTT, and/or INR (within 2 weeks of treatment)
- (Optional) Tumor biopsy for biomarker analysis

Evaluations During Treatment (See Timetable below)
Blood pressure monitoring every 3 weeks, prior to each Avastin® dose
Urine protein approximately every 2 cycles (with every other dose)

Visit and Evaluation Timetable

	Baseline		Cycle					
Cycle		1	2	3	4	5	6	7+
Study Day		1						
Patient clinic visit [B]	X	X	X	X	X	X	X	X
Physical Examination including vital signs [B]	X	X	X	X	X	X	X	X
ECOG PS [B]	X	X	X	X	X	X	X	X
Disease Assessment (imaging of disease via CT or MRI, CXR) [A]	X		X [D]		X [D]		X [D]	X [D]
Brain MRI	X							
Hematology [B] (CBC,diff,platelet)	X [C]		X	X	X	X	X	X
Coagulation Profile (PT,PTT and/or INR)	X [C]							
Chemistry (Na,K,Ca,Mg,BUN,Cr, AST,ALT,LDH,T Protein, albumin, glucose, uric acid, T bilirubin, alkaline phosphatase) [B]	X		X	X	X	X	X	X
Urine protein [A]	X			X		X		X [A]
Pregnancy Test (serum or urine)	X [C]							
Tumor Biopsy for Biomarker Evaluation (Optional)	X		X [D]		X [D]			
Prior and Concurrent Medications [B]	X	X	X	X	X	X	X	X
Adverse Events [B]		X	X	X	X	X	X	X [B]

[A] every 2 cycles

[B] every cycle

[C] within 2 weeks of treatment

[D] Tests performed at the end of given cycle

Biosafety:

Does this study involve the use of Recombinant DNA Technology?	No
Does this study involve the use of organisms that are infectious to humans?	No
Does this study include any products manufactured or produced at MD Anderson Cancer Center?	No

Radiation Safety:

Does this study involve the use of radioisotopes?	No

Does this protocol include the administration of a radioactive drug to human research subjects intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of the drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e. to carry out a clinical trial)?	No

Where Will Study Be Conducted:

B) MDACC + Community Programs (CCOP/Network)

The study will be conducted at MDACC and its affiliated County Hospital, Lyndon Baines Johnson General Hospital via the Clinical Trials Outreach Program (CTOP) program.

Is this an M. D. Anderson Cancer Therapy Evaluation Program (CTEP) Protocol? No

Estimated Accrual:

Total Accrual at M.D. Anderson Cancer Center:	Total accrual will be 50 participants.
Estimated monthly accrual at M.D. Anderson:	It is estimated that accrual will be 5 participants per month.
Total accrual will be:	50 participants

Basis of Study:

This protocol is performed on an Outpatient basis.

Length of Stay: (What is the length & frequency of hospitalization)

N/A

Return Visits: (How often must participants come to MDACC)

Patients will return to the clinic every 21 days.

Home Care: (Specify what (if any) treatment may be given at home)

N/A

Public Display of Protocol on the Office of Protocol Research Web Site:

The Office of Protocol Research maintains a website (www.clinicaltrials.org) listing protocols actively accruing patients. No information is given about drug dose or	Yes

schedule. Would you like this protocol listed on this website?

If this protocol has a corporate sponsor, we also need to get the sponsor's written approval to post the trial on the website. Shall OPR send a letter requesting this permission to your sponsor?	Yes

Prior protocol at M. D. Anderson:

List the protocol number for the last clinical treatment/behavioral protocol on which you were the Principal Investigator that accrued patients at M. D. Anderson. 2003-0424

Space Requirements for Clinical Trials:

Will implementing this protocol require additional space (clinical, office, departmental)? No

Additional Space will not be made available in the future.

Sponsorship and Support Information:

Does the Study have a Sponsor?	Yes
Name of Sponsor or Supporter:	Genentech, Inc.
Does the Sponsor Provide Funding for the conduct of the study?	Yes
Is this Protocol listed on any Federal Grant or Foundation Funding Application?	No
Grant Number:	N/A
Does the Sponsor supply drug(s) or device(s)?	**N**

Does this protocol require an IND? No

Please check the items below to verify that the following information is correct:

The data will not be provided to the FDA or to an outside source.
The data will not be used to expand the label or change the advertising for the drug.
There will be no substantial change in the dosage, drug, or route of administration or other factor that will significantly increase the risk to the patient.

Does this protocol use a "Combination" of drugs or other therapies (Drug, Radiation or Surgical Therapy) or Diagnostic Procedures that pose a significant risk to the patient?
No

If this protocol includes an FDA Approved Therapy, please list the disease, dose and route of administration:

	Approved Use	**Proposed Use in this Protocol**
Disease:	Avastin: Metastatic Colorectal, Non-small cell lung cancer Docetaxel:Breast Cancer, Head & Neck Cancer, Metastatic Prostate Cancer, Non-small cell lung cancer Carboplatin:Ovarian Cancer	Avastin, Docetaxel, and Carboplatin:Metastatic Non-small cell lung cancer
Dose:	Avastin:15mg/kg IV infusion Docetaxel:75mg/m(2) Carboplatin: AUC of 6	Avastin:15mg/kg IV infusion Docetaxel:75mg/m(2) Carboplatin: AUC of 6
Route of Administration:	Avastin:IV Docetaxel:IV Carboplatin:IV	Avastin:IV Docetaxel:IV Carboplatin:IV

Rationale For Planned Therapy:
In this Phase II trial, the biologic agent Avastin is combined with cytotoxic chemotherapy, attacking against the factors that lead to the development of tumor blood supply and tumor cell proliferation in NSCLC. Avastin directly binds to VEGF and inhibits from binding to endothelial cells and in turn blocks blood vessel growth.

The common 21-day dosing regimen has been studied and is used for docetaxel and carboplatin. Due to the fact that there are not to be overlapping toxicities or pharmacodynamic interactions with the study drug Avastin as well as secondarily for ease of delivery and monitoring, it will be given along with the other two drugs. The treatments will be repeated every 21 days as another cycle with disease evaluation after every 2 cycles in order to monitor for need for continuation of therapy and endpoints closely.

For FDA approved drugs
www.fda.gov/cder/da/da.htm

For the FDA Investigational New Drug (IND) Exemption Rationale
www.access.gpo.gov/nara/cfr/waisidx_03/21cfr312_03.html
Then select 312.2

For FDA approved biological therapies
www.fda.gov/cber/

Device:

Is this protocol testing a new device or a device in a new application? No

For a list of significant/non-significant risk devices
www.fda.gov/oc/ohrt/irbs/devices.html