A Randomized Double-Blind Placebo-Controlled Trial of Neoadjuvant Pazopanib for Stage I/II Non-Small Cell Lung Carcinoma

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A) Study Background and Rationale

Lung cancer is the leading cause of cancer deaths in both men and women worldwide.[1] The vast majority of patients diagnosed with lung cancer are found to have non-small cell lung carcinoma (NSCLC).[2] Upwards of 80% of these people present with locally advanced or metastatic disease.[3] The minority that is found to have stage I and II disease can be potentially cured with surgery, and have the best 5-year survival rates that are on average 52%.[4] However, even those with resectable disease have a high rate of recurrence, with 29-38% relapsing within 2 years of surgery.[5]

Adjuvant chemotherapy has been shown in several randomized trials to provide statistically significant survival benefits in patients with resected stage II/IIIA disease, but the difference is modest at best.[6] Most recently, a large study analyzing all data in the National Cancer Database on patients diagnosed with and definitively treated for locally advanced (stage IIIA-N2) NSCLC between 1998 and 2004, demonstrated that neoadjuvant therapy significantly prolonged progression-free survival (PFS) and overall survival (OS).[7]

Several theories exist as to why cancer recurs after curative surgery (complete resection with negative margins). The most commonly cited is that stray residual cancer cells remain in the vicinity of the original tumor or at a distal site, which overtime propagate and develop into a new tumor. Another theory is that some types of perioperative anesthesia induce HIF-1a transcription factor, which stimulates protumerogenic behavior in residual cells.[8] Finally, it is thought that surgery itself can induce angiogenesis, a process of new vessel formation, thereby enhancing residual cells' ability to feed their growth into new tumors and to metastasize to other parts of the body.[9,10] It was therefore proposed that pre-treatment with agents that inhibit angiogenesis could potentially address this effect of surgery. There is, however, no current evidence for efficacy of this approach.

VEGF inhibitors are a class of drugs that target the process of angiogenesis, and are some of the most commonly used anti-tumor agents today. Bevacizumab, a first in the class of VEGF inhibitors to be used in cancer therapy, is currently FDA approved in combination with chemotherapy for colon, advanced NSCLC, breast, and RCC, and as a single agent for glioblastoma.[11] It is a monoclonal antibody against VEGF-A, and is the only one in the class of antiangiogenesis agents. Others, such as sunitinib and Sorafinib, used for the treatment of RCC and unresectable HCC, respectively, are tyrosine kinase small molecule inhibitors of multiple proangiogenic growth factor receptors. In contrast to monoclonal antibodies, these small molecule non-specific

TKIs are often successful as single agents and are thought to be capable of superior blockade of tumor growth and metastasis.[12,13]

In light of recent success of bevacizumab in combination with chemotherapy for late stage NSCLC[14,15] and evidence of substantial benefits of neoadjuvant therapy on prolonging survival,[7] there has been growing interest in using VEGF-targeting agents early in preoperative course for patients with resectable disease. Some early efforts have been made with a drug called pazopanib, an oral antiangiogenesis TKI, which targets VEGFR, PDGFR, and c-Kit, and has been shown to be quite effective as monotherapy for the treatment of RCC, ovarian cancer and sarcoma.[16,17,18] A recent phase I study of pazopanib in patients with advanced stage cancer of various solid tumor types, demonstrated that it has significant anti-tumor activity and is relatively well tolerated.[19] In 2010, a phase II, window-of-opportunity study, in patients with resectable Stage I/II NSCLC, neoadjuvant pazopanib monotherapy was shown to be generally well tolerated and effective in reducing tumor volume.[20] It is yet to be determined, however, whether there are long-term benefits to neoadjuvant pazopanib.

Thus, the purpose of this study is to determine the effects of neoadjuvant pazopanib on recurrence rate (RR) and on 5-year overall survival (OS) in patients with stage I/II resectable NSCLC.

B) Study Design

This will be a prospective, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of neoadjuvant pazopanib in patients with stage I/II resectable NSCLC. The results of this study will allow the investigators to determine whether chemotherapy with Pazopanib prior to tumor resection decreases the rate of disease recurrence (RR) and improves 5-year overall survival (OS), as compared to surgery alone, which is the current standard of care. To ensure sufficient power, participants will consist of patients who present to New York Presbysterian/Columbia University Medical Center, as well as several other medical centers, for initial evaluation or as referrals from other physicians. Enrollment will be continued until significance is demonstrated or the number of patients has reached the estimated number required to do so, as determined by the chi square power calculation. The study will undergo IRB review and approval at all participating institutions. Written consent will be obtained from all participants prior to study enrollment.

Patients will be evaluated by a multi-disciplinary team, including Clinical Oncologists, Thoracic Surgeons, Radiologist, and Radiation Oncologists, prior to enrollment in the trial, to determine appropriateness for the study and to establish a primary care team. Patients will then be randomized either to a control group (placebo + surgery) or to the treatment group (pazopanib + surgery). Only the dispensing Pharmacist will be aware of who is receiving placebo or pazopanib prior to the first 24 months of the trial. Randomization will be stratified according to Stage of disease in order to ensure similar distribution between the two groups.

The primary outcome will be tumor recurrence (RR), with or without metastasis, 24 months after initiation of first dose of either placebo or pazopanib, as determined by presence of clinical and radiologic evidence of disease recurrence. The secondary outcome will be overall survival 5 years after initiation of placebo or pazopanib.

Patients in either arm of the study, who are found to have disease recurrence at any point during the study, will be offered further treatment at the discretion of their physician/primary care team.

The trial will be stopped if investigators discover significant benefits in the treatment group, in order to ensure that any new patients presenting with resectable Stage I/II disease will receive pazopanib prior to their scheduled surgeries. Conversely, if neodjuvant treatment significantly worsens the outcomes, it will no longer be offered to patients, and study will be terminated.

Statistical Analysis:

Estimates of RR and OS, stratified by the stage of disease, will be calculated using Kaplan-Meier survival analysis.

Using multivariate Cox proportional hazards models, we will look for variables that significantly correlate with reduced RR and/or improved OS, including age, sex, race/ethnicity, tumor volume, nodal involvement, location of tumor (central vs peripheral), extent of surgical resection of lung tissue, and adjuvant chemotherapy.

The determination of sample size is based on the average RR of 35% at 24 months after surgery, for stage I and II resected NSCLC.

Assuming an effect size of 10%, and in order to achieve 80% power with a 5% Type I error rate, a sample size of 664 patients (332 in each arm) was calculated using a chi square test.

C) Study Procedure

Patients in the treatment group will receive 800 mg of pazopanib PO once daily for 2 weeks, starting within 7-14 days of the initial diagnostic biopsy. Patients in the placebo group will receive placebo pills in place of pazopanib. Tumor resections will be performed after a minimum wash-out period of 1 week after the last dose of placebo or pazopanib has been given. After surgery, those patients in each group with stage II disease, will undergo platinum-based adjuvant chemotherapy, as per the standard of care. Also, those with positive surgical margins may undergo radiation at the discretion of their physician/care team.

All patients will be seen weekly in Oncology clinic during pre-operative period, while on neoadjuvant regimen (placebo or pazopanib), to monitor for development of significant side effects. After surgery, all patients will be evaluated in Oncology

clinic every 3 months for the first 2 years, and then every 6 months up to 5 years. A chest X-ray will be obtained every 6 months and a CT scan of the chest will be obtained at 2 years. If recurrence is detected, patients may undergo further treatment, which will be determined by their physician/ care team.

D) Study Drugs

Pazopanib: Pazopanib is a small molecule tyrosine kinase inhibitor of VEGFR, PDGFR, and c-Kit. The following side effect profile is based on adverse events reported in patients treated with pazopanib for other primary malignancies at maximum tolerated dose.

Cardiovascular: Hypertension, peripheral edema

Central nervous system: Fatigue, headache, dizziness

Dermatologic: Hair color change, rash, alopecia, palmar-plantar erythrodysesthesia, skin depigmentation

Endocrine & metabolic: Hyperglycemia, hypophosphatemia, hyponatremia, thyroid-stimulating hormone (TSH) increased, hypomagnesemia, hypoglycemia, hyperkalemia

Gastrointestinal: Diarrhea, nausea, weight loss, anorexia, vomiting, taste alteration, lipase increased, abdominal pain, mucositis, stomatitis

Hematologic: Leukopenia, lymphocytopenia, thrombocytopenia, neutropenia

Hepatic: Trasaminitis, hyperbilirubinemia, decreased albumin, elevated alkaline phosphatase

Neuromuscular & skeletal: Musculoskeletal pain, myalgia, weakness

Respiratory: Dyspnea, cough

Miscellaneous: Tumor pain

E) Medical Devices

N/A

F) Study Questionnaires

N/A

G) Study Subjects: Selection criteria as described in Altorki et al.

Inclusion criteria:

Age ≥ 21 years

Patients with histologically or cytologically confirmed clinical stage I/II NSCLC

Eastern Cooperative Oncology Group performance status ≤ 1

Adequate hematologic (ANC ≥ 1500; Hb ≥ 9; platelets ≥ 100), hepatic (albumin ≥ 2.5; total bilirubin ≤ 1.5 x upper limit of normal; transaminase levels ≤ 2x upper limit of normal), and renal function (eGFR ≥ 30 or serum Cr ≤1.5).

Exclusion criteria:

Second active malignancy at time of presentation

Received antiangiogenic, cytotoxic, or other experimental therapy in the previous 6 months

History of hemoptysis

Known bleeding or clotting disorder

Cardiovascular disease (angioplasty or stenting, MI, unstable angina, NYHA class II or greater CHF, poorly controlled HTN, or symptomatic PVD)

Pregnancy in female patients

Major surgical procedure or significant traumatic injury within the past month

Patients requiring anticoagulation (warfarin or heparin) while in study

Any GI condition predisposing to perforation

H) Recruitment of Subjects

Patients will be recruited from New York-Presbyterian Hospital / Columbia University Medical Center, as well as several other medical centers. Oncologists and Thoracic Surgeons at these centers will be informed of the study protocol and encouraged to consider appropriateness of their patients for the study.

I) Confidentiality of Study Data

All data will be de-identified and stored securely.

J) Potential Conflict of Interest

There are no potential conflicts of interest to disclose if study is funded by government organizations. However, there is a possibility that this study will be funded by GlaxoSmithKline, the company manufacturing Pazopanib.

K) Location of Study

This study will be conducted in the outpatient Oncology clinics at New York-Presbyterian Hospital / Columbia University Medical Center, as well as at the outpatient Oncology clinics of the participating institutions. It will be done in close collaboration with the departments of Radiology, Thoracic Surgery and Radiation Oncology.

L) Potential Risks

The risks associated with the study are related to the potential side effects of pazopanib, as described in section D of the proposal. Risks of surgery will be explained to patients by their Thoracic Surgeons, and are not altered by administration of neoadjuvant pazopanib. For patients with Stage II disease, who will be receiving platinum-based adjuvant chemotherapy after surgery, the risks, which are not expected to be altered by prior receipt of pazopanib, will be explained by the primary Oncologist.

M) Potential Benefits

The potential benefits of this study include reduced recurrence of cancer and prolonged 5-year survival.

N) Alternative Therapies

Placebo group is the standard of care for early stage NSCLC, which includes surgical resection as per the American College of Chest Physicians guidelines, followed by platinum-based adjuvant chemotherapy for patients with Stage II disease, and/or radiation, if bronchial margin is positive on resection.

Patients may opt out of surgery, but will not be eligible for the current study, and can instead undergo combination chemotherapy and radiation.

Patients may also elect not to undergo treatment, but are strongly discouraged to do so, given a very high success rate in treating early stage NSCLC.

O) Compensation to Subjects

Participants will not be compensated for participation in this study.

P) Costs to Subjects

Participants will not incur costs associated with participation in this study.

Q) Minors as Research Subjects

N/A

R) Radiation or Radioactive Substances

Patients with positive bronchial margin (R1 resection) may be recommended to undergo radiation therapy directed at the site of concern.

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