# Peking University Shenzhen Hospital

< The Real-World Study of Anlotinib Treatment for Advanced Non-Small Cell Lung Cancer>

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# Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator

Fen Wang

Signed: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_01/01/2020\_\_\_

Fen Wang

Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Dr.

Title: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

# Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

List of Abbreviations

|  |  |
| --- | --- |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation |
| N | Number (typically refers to participants) |
| NCI | National Cancer Institute |
| NMPA | National Medical Products Administration |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| UAP | Unanticipated Problem |

# STUDY SYNOPSIS

|  |  |
| --- | --- |
| Title: The Real-World Study of Anlotinib Treatment for Advanced Non-Small Cell Lung Cancer | |
| SUMMARY | **Anlotinib is a multi-targeted tyrosine kinase inhibitor mainly blocking vascular endothelial growth factor signaling pathway. This study aims to evaluate the efficacy and safety of anlotinib in advanced non-small cell lung cancer (aNSCLC) in the real world. Unresectable stage IIIB to IV NSCLC patients treated with anlotinib will be enrolled in the study. Anlotinib will be administered orally once daily at an initial dose from 10 mg to 12 mg on day 1 to day 14 of a 21-day cycle. Tumour responses will be assessed by both radiologists and oncologists every 6 to 12 weeks or significant progression occurred or necessary. The electronic medical order system (EMS) at Peking University Shenzhen Hospital will be used to collect baseline characteristics data, laboratory data, AEs and outcomes. The primary endpoint is progression-free survival (PFS) and secondary endpoints includes objective response rate (ORR), overall survival (OS), duration of response (DOR), and toxicity. Pearson’s Chi-square test or Fisher’s exact test will be used to compare categorical variables. The survival and 95% confidence interval (CI) will be estimated using the Kaplan-Meier method.** |
| Objectives | **Primary: Progression-free survival (PFS)**  **Secondary: Objective response rate (ORR), overall survival (OS), and toxicity.** |
| Population | **1, Age ≥ 8 years;**  **2, Pathologically confirmed stage IIIB/IV or recurrent NSCLC;**  **3, Have at least one radiologically measurable disease as assessed using RECIST; and they do not receive local treatment such as radiotherapy or interventional therapy for the target lesions during anlotinib treatment;**  **4, Receive anlotinib or anlotinib-containing treatment.**  **The estimated sample size is 200.** |
| Number of sites | **1** |
| Methodology | **Anlotinib is a multi-targeted tyrosine kinase inhibitor mainly blocking vascular endothelial growth factor signaling pathway and has been approved by the National Medical Products Administration of China for ≥3rd line treatment of advanced NSCLC. Here we propose a scientific hypothesis that the front-line or combined use of anlotinib is effective in the treatment of advanced NSCLC. We will collect the data of anlotinib treatment in patients with aNSCLC from the EMR of our hospital and analysis the tumour response and the survival.** |
| Duration of the study | **6 months (01/01/2020-06/30/2020)** |
| Participant Duration | **6 months** |
| Estimated Time to complete enrollment | **4 months** |

# STUDY SCHEMA

Prior to

IIIB/IV or recurrent NSCLC patients who receive anlotinib treatment between 01/06/2018 to 30/09/2020 (N=200

Enrollment

Perform baseline assessments.

(*physical examinations, CT imaging of targeted lesion, blood cell count, blood biochemical index, tumor markers*)

Administer initial study assessments.

Visit 1

First

administration

Of anlotinib

Visit 2

Repeat study assessments.

Every 6 to 12

weeks

**Final Assessments**

Visit X

Progression

or death

# 1. INTRODUCTION

## 1.1 BACKGROUND INFORMATION

Non-small cell lung cancer (NSCLC) is the predominate category of the lung cancer and is more than half presenting distant stage when diagnosed. Anlotinib is a multi-targeted tyrosine kinase inhibitor mainly blocking vascular endothelial growth factor signaling pathway and is approved by the National Medical Products Administration of China for ≥ 3rd line treatment of advanced NSCLC. Yet the lack of evidence of frontline or combination treatment, anlotinib exhibits both anti-tumor and anti-angiogenetic effect. This study aims to investigate the potential efficacy and safety of anlotinib either monotherapy or combined with additional antineoplastic agents in patients with advanced NSCLC in the real world.

## 1.2 RATIONALE FOR THE PROPOSED STUDY

Patients with stage IIIB to IV or recurrent NSCLC who received anlotinib or anlotinib-containing regimens will be enrolled in the study. Anlotinib is administered orally once daily on day 1 to day 14 of a 21-day cycle and is continued until tumor progression, death, or unacceptable toxicity. Tumor responses are assessed by both radiologists and oncologists every 6 to 12 weeks or significant progression occurred or necessary. The electronic medical order system (EMS) at Peking University Shenzhen Hospital will be used to collect baseline characteristics data, laboratory data, AEs and outcomes.

## 1.3 POTENTIAL RISKS AND BENEFITS

The potential risk is that PHI could get released into public view and the benefit is that the results from the study may provide evidence of frontline or combination treatment of anlotinib in advanced NSCLC.

## 1.3.1 Potential Risks

To protect patient information, we will minimize patient identifiers by assigning each participant with a unique code. All data generated in the study will be stored in PKUSZH with the unique code; the list of the unique codes will be maintained on secure servers, accessible to key research personnel only. However, there are no guarantees and there is always a risk that PHI could get released into public view.

## 1.3.2 Potential Benefits

The study may not provide direct benefit to participants, however the result from the study may provide an attractive alternative chemo-free strategy for the 1st-line treatment of the patients with advanced NSCLC, especially of those who are senile, in poor condition, unwilling or unable to receive chemotherapy; and provide additional evidence for the application of 2nd-line anti-angiogenesis combination therapy.

## 1.3.3 Risk-Benefit Ratio

The risks of participating in the study are outweighed by the potential benefits of participating in the study.

**2.** STUDY OBJECTIVES & ENDPOINTS (SPECIFIC AIMS)

## 2.1 OBJECTIVES

The primary objective is progression-free survival (PFS) of each cohort; the second objectives includes objective response rate (ORR), disease control rate (DCR), overall survival (OS), and toxicity.

## 2.1.1 Hypothesis

The study does not have well-defined mechanistic hypotheses due to the observational nature, but rather have a stated goal to obtain data. It will describe the following objectives of anlotinib treatment in advanced NSCLC.

## 2.1.2 Primary Objectives

Progression-free survival (PFS), as defined as the time from the first administration to the documented disease progression or death due to any cause.

## 2.1.3 Secondary Objectives

1. Objective response rate (ORR), as defined as the percentage of patients with at least one confirmed response before any evidence of progression.

2. Disease control rate (DCR), as defined as the percentage of patients with at least one confirmed response plus stable disease before any evidence of progression.

3. Overall survival (OS), as defined as the time from the first administration to death from any cause or last follow-up.

4. Toxicity, as categorized and graded according to the NCI-CTCAE.

## 2.1.4 Exploratory Objectives

The potential biomarkers for anlotinib 1st-line monotherapy.

## 2.2 ENDPOINTS/OUTCOME MEASURES

Not applicable.

## 2.2.1 Primary Endpoints

Not applicable.

## 2.2.2 Secondary Endpoints

Not applicable.

## 2.2.3 Exploratory Endpoints

Not applicable.

# 3. STUDY DESIGN

## 4.1.1 INCLUSION CRITERIA

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

* Any individual >18 years old;
* Pathologically confirmed stage IIIB/IV or recurrent NSCLC;
* Have at least one radiologically measurable disease as assessed using RECIST; and they do not receive local treatment such as radiotherapy or interventional therapy for the target lesions during anlotinib treatment;
* Receive anlotinib or anlotinib-containing treatment.

## 4.1.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

* Other pathological types than NSCLC including small cell lung cancer (including mixed with small cell and non-small cell lung cancer);
* Patients who are diagnosed with malignancies other than NSCLC within the previous 5 years (except those with negligible risk of metastases or death and treated with curative intent, based on primary investigator discretion).

## 4.2. PERMITTED MEDICATIONS/LIFESTYLE CONSIDERATIONS

Not applicable.

## 4.3. STRATEGIES FOR RECRUITMENT AND RETENTION

Potential research subjects will be identified by the investigator or a research team member. Investigators will then screen the patient’s medical records to determine the subject eligibility for study participation. Eligible patients will be screened based on the inclusion/exclusion criteria above.

## 4.4 SCREEN FAILURES/PARTICIPANT DISCONTINUATION/PARTICIPANT WITHDRAWAL

## Reasons for Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study participant’s participation in the study if:

* Any clinical event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
* The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
* Study ends or is terminated.

## 4.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <investigator, funding agency, sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

* Insufficient adherence to protocol requirements.
* Data that is not sufficiently complete and/or evaluable.
* Determination of futility.
* Withdrawal of funding

5. STUDY METHODOLOGY / ADMINISTRATION OF SURVEYS

## 5.1 STUDY PROCEDURES/EVALUATIONS

Anlotinib is administered orally once daily on day 1 to day 14 of a 21-day cycle and is continued until tumor progression, death, or unacceptable toxicity. Tumor responses are assessed by both radiologists and oncologists every 6 to 12 weeks or significant progression occurred or necessary. The EMS at Peking University Shenzhen Hospital will be used to collect the patients’ data including medical history, medications history) and physical examination, radiographic assessments, laboratory data, AEs at baseline and every visit point.

## 5.2 LABORATORY PROCEDURES (if applicable)

### **Special Assays or Procedures**

Not applicable.

## 5.2.1 SPECIMEN PREPARATION, HANDLING, AND STORAGE (if applicable)

Not applicable.

## 5.2.2 SPECIMEN SHIPMENT/ANALYSIS PLAN (if applicable)

Not applicable.

# 6. STUDY SCHEDULE OF ACTIVITIES:

## 6.1 SCREENING

* Review medical/dental history to determine eligibility based on inclusion/exclusion criteria.
* Review medications history to determine eligibility based on inclusion/exclusion criteria.

## 6.2 ON STUDY PERIOD

* Collect the information from EMS of eligible patients.

## 6.3 END OF STUDY PROCEDURES

* Collect the information from EMS of eligible patients.

# 7. STATISTICAL CONSIDERATIONS

## 7.1 STUDY HYPOTHESES

Null hypotheses due to the nature of the study.

## 7.2 ANALYSIS PLANS

Patients’ baseline characteristics will be reported with descriptive statistics as proportions for categorical variables and medians (range) for continuous variables. Pearson’s Chi-square test or Fisher’s exact test will be used to compare categorical variables and tumor responses between groups. The median follow-up period will be computed based on the reverse Kaplan-Meier method. The median PFS, OS and 95% confidence interval (CI) will be estimated using the Kaplan-Meier method, with differences between groups being evaluated using the Log-rank test. All statistical analyses will be performed using the statistical package for the social sciences (SPSS) software version 23 (SPSS Inc., Chicago, IL, USA).

## 7.3 SAMPLE SIZE CONSIDERATIONS

Not applicable.

### **Accrual Estimates**

3 months.

## 7.4 EXPLORATORY ANALYSIS

The potential biomarkers for anlotinib 1st-line monotherapy will be analysis using Cox proportional hazards regression.

## 7.5 HANDLING SCREEN FAILURE/SUBJECT DISCONTINUATION

Patients, who prematurely withdraw before the end of the study, will be replaced by new patients to ensure an adequate number of patients completing the study, unless the reason for discontinuation is progression of disease.

# 8. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

## 8.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45CFR Part 46 and/or the ICH-E6.

## 8.2 INSTITUTIONAL REVIEW BOARD

The protocol, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both, the protocol must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

## 8.3 INFORMED CONSENT PROCESS

Not applicable.

## 8.4 EXCLUSION OF WOMEN, MINORITIES, AND CHILDREN (SPECIAL POPULATIONS)

Not applicable.

## 8.5 PARTICIPANT CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the investigators and study staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the investigators.

The study monitor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

# 9. DATA HANDLING AND RECORD KEEPING

Source data must be contained in designated source documents folders. Source data includes (but not limited to) all information, observations, questionnaires, surveys, interview notes, original records of findings - hospital records, clinical and office charts, lab results, and, x-rays, scans for the study.

All entries should be printed legibly in black ink. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents must be completed in a neat, legible manner to ensure accurate interpretation of data.

All missing data must be explained. If any entry error has been made, to correct such as error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or white out errors.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the regulatory bodies (eg. FDA), and University compliance and quality assurance groups of all study related documents (eg. Source documents, regulatory documents, data collection instruments, study data etc). The investigator will ensure the capability for inspections of applicable study-related facilities (eg. Pharmacy, diagnostic lab, etc).

The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

## 9.1 DATA MANAGEMENT RESPONSIBILITIES

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. The investigator or designee must review unanticipated problems and deviations.

## 9.2 DATA CAPTURE METHODS

Not applicable.

## 9.3 TYPES OF DATA

In order to contact patients and caregivers by telephone for the particular session activity purposes, it will be necessary to collect participants’ names, addresses, and telephone numbers. Sites must complete Contact order form and send via secure Office Automation System of PKUSZH or hand it to the research study personnel. The contact will be stored at a secure locked location accessible to key research personnel only and will be destroyed upon completion of the study.

## 9.4 STUDY RECORDS RETENTION

Study records will be maintained for at least three years from the date that the grant is submitted to the IRB.

# 10. INVESTIGATOR OVERSIGHT

It is the responsibility of the Principal Investigator to oversee the entire study; this oversight includes safety and study integrity. This oversight includes careful assessment and appropriate reporting of the study data.

# 11. COMPLIANCE WITH THE STUDY

## 11.1 PROTOCOL DEVIATION AND UNANTICIPATED PROBLEMS

## UNANTICIPATED PROBLEMS

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

* unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
* UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

## PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the protocol, International Conference on Harmonization (ICH), Good Clinical Practice (GCP) and protocol-specific guidelines. The deviation (any activity conducted outside the parameters established by the protocol) may be either on the part of the participant, the investigator, or the study site staff and may or may not pose a risk to participants or others or may affect the integrity of the data obtained from the study.

The risk posed by the deviation, to the study or the study participant gives rise to an Unanticipated problem (UAP). It is crucial to document the deviation/unanticipated problem in the protocol deviation log (Appendix D) and submitted to the IRB as per the sites regulations. As a result of deviations, corrective actions are to be developed and implemented promptly.

UAPs and protocol deviations that pose risk to participants or others, and that are not AEs, or that affect study integrity will be submitted to the IRB via the <eazUP system> within 5 working days of the investigator becoming aware of the event.

UAPs and protocol deviations that do not pose risk to participants or others and do or do not affect study integrity must be entered in the deviation log (Appendix D) and submitted to the IRB at the next continuing review.

# 12. STUDY FINANCES

## FUNDING SOURCE

The study is financed through a grant from Wu Jieping Medical Foundation, Shenzhen Sanming Project, and Shenzhen Science and Technology Innovation Commission Project.

## CONFLICT OF INTEREST

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study.

# 13. FUTURE USE OF STORED SPECIMEN/DATA

Not applicable.

# 14. PUBLICATION AND DATA SHARING POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical studys registration policy as a condition for publication. The ICMJE defines a clinical study as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical studys be registered in a public studys registry such as [*ClinicalStudys.gov*](http://www.clinicaltrials.gov), which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

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