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Study protocol for evaluation of the safety and efficacy of 99mTc-3PRGD2 SPECT/CT for integrin αVβ3-targeted imaging of lung cancer and the lymph node metastases: a prospective, multicenter, self-controlled phase 3 clinical trial

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Disclaimer

Abstract

This is the study protocol for evaluation of the safety and efficacy of ^{99m}Tc-3PRGD2 SPECT/CT for integrin $\alpha_V\beta_3$-targeted imaging of lung cancer and the lymph node metastases: a prospective, multicenter, self-controlled phase 3 clinical trial. This study uses ^{99m}Tc-3PRGD2 as a novel radioactive diagnostic drug for clinical SPECT/CT imaging of lung cancer and the lymph node metastasis. After intravenous injection into the body, ^{99m}Tc-3PRGD2 is expected to be specifically taken up by integrin $\alpha_V\beta_3$-positive tumors. The images can be obtained by SPECT/CT and used for diagnosis and evaluation of the tumors, thereby guiding the individualized treatments as well.

Attachments

The Study Protocol.p...

307KB

Study protocol

1 **Introduction**

1.1 Background

Lung cancer affects 2.5 million new cases and leads to 1.8 million deaths each year around the world, ranking the most frequently diagnosed cancer and also the leading cause of cancer death of all cancers globally. With an increasing number of patients being diagnosed at early stages, the accurate evaluation of lymph node metastasis plays a pivotal role in optimizing the surgical intervention and other precision treatments for lung cancer, especially for non-small cell lung cancer (NSCLC), to improve the cure rate and extend patients' survival time.

The National Comprehensive Cancer Network (NCCN) guidelines recommend X-ray computed tomography (CT) for initial evaluation and 18F-fludeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT for further staging of NSCLC patients. However, the utility of CT in nodal staging of lung cancer has limitation due to its low sensitivity, which relies on variations in tumor's size and structure. Meanwhile, the metabolic imaging via ^{18}F-FDG PET/CT demonstrates low specificity owing to the nonspecific uptake of ^{18}F-FDG in inflammatory lymph nodes, typically necessitating additional invasive mediastinal staging. Therefore, the development of innovative techniques is imperative to improve the accuracy of staging, and thereby to facilitate the optimal decision-making regarding further treatment of lung cancer patients.

1.2 Study rationale

Integrin $\alpha_V\beta_3$-targeted imaging could potentially bridge this existing technical gap. As a member of integrin family, integrin $\alpha_V\beta_3$ plays a crucial role in mediating tumor formation, invasion, metastasis, and angiogenesis. Therefore, integrin αvβ3 is an attractive target for tumor diagnosis and therapy. However, as of today, no drug has been approved for either diagnosis or therapy by targeting integrin $\alpha_V\beta_3$.

A diagnostic drug targeting integrin $\alpha_V\beta_3$, technetium-99m [^{99m}Tc] labeled hydrazinonicotinamide-PEG4-E[PEG4-c(RGDfk)]2 (^{99m}Tc-3PRGD2), has been preliminarily validated for imaging of lung cancer and other tumors via single photon emission computed tomography (SPECT)/CT, which suggested a promising prospect for its clinical application.

This study uses ^{99m}Tc-3PRGD2 as a novel radioactive diagnostic drug for clinical SPECT/CT imaging of lung cancer and the lymph node metastasis. After intravenous injection into the body, ^{99m}Tc-3PRGD2 is expected to be specifically taken up by integrin $\alpha_V\beta_3$-positive tumors. The images can be obtained by SPECT/CT and used for diagnosis and evaluation of the tumors, thereby guiding the individualized treatments as well.

2 **Study Objectives**

2.1 Primary objective:

The primary objective of this study is to evaluate the efficacy of ^{99m}Tc-3PRGD2 SPECT/CT in mapping of lymph node metastasis according to the nodal mapping system released by the International Association for the Study of Lung Cancer in 2009 (IASLC-2009).

2.2 Secondary objectives:

The secondary objectives include:

• To evaluate the efficacy of ^{99m}Tc-3PRGD2 SPECT/CT in diagnosis of lung cancer.

• To evaluate the safety of ^{99m}Tc-3PRGD2 injection in human beings.

3 Study Design

This is a prospective, multicenter, self-controlled phase 3 clinical trial designed to evaluate the safety and efficacy of an integrin $\alpha_V\beta_3$-targeted imaging, ^{99m}Tc-3PRGD2 SPECT/CT, for diagnosis of lung cancer, with mapping the lymph node metastases as the primary objective.

The pathological results will be considered as the gold standard and the conventional metabolic imaging by ^{18}F-FDG PET/CT will be used for a head-to-head comparison.

4 Study Participants

4.1 Inclusion criteria

Participants must meet all of the following inclusion criteria to be eligible for this study:

(1) Voluntarily participate and sign the Informed Consent Form;

(2) Age ≥18 years old;

(3) Diagnostic CT shows that the longest diameter of the tumor occupying the lung is ≥1.5 cm and the shortest diameter is ≥1.0 cm;

(4) ^{18}F-FDG PET/CT examination shows tumor occupancy in the lungs, with positive hilar and/or mediastinal lymph nodes on either enhanced CT or ^{18}F-FDG PET/CT;

(5) Willing and be able to follow scheduled visits, treatment plans, and laboratory tests;

(6) Clinical laboratory examination and other indicators are within the normal range or abnormal but do not affect related examinations and treatments.

4.2 Exclusion criteria

Patients who have any of the followings are not eligible for enrollment:

(1) Female patients who plan of pregnant within 6 months, or in pregnant or lactating;

(2) Allergic to the test drugs, have allergic constitution, or are allergic to multiple drugs;

(3) Contrast-enhanced CT examination shows ground-glass nodules without solid components;

(4) Before injecting ^{18}F-FDG, fasting blood glucose level exceeds 7.0 mmol/L (tested by rapid blood glucose meter);

(5) Body weight exceeds 100 kg;

(6) With claustrophobia;

(7) Cannot tolerate raising their arms and lying on the scanner bed for 15–30 min;

(8) Those the investigator believes not suitable to participate in this clinical trial;

(9) Those who are currently participating in another clinical trial or have participated in other clinical trials within the past 3 month.

5 Sample size estimate

Based on our prior pilot clinical trial, the specificity of ^{99m}Tc-3PRGD2 SPECT/CT in diagnosing lymph node metastasis is estimated to be 90%, and the specificity of ^{18}F-FDG PET/CT in diagnosing lymph node metastasis is to be 80%. There is 90% confidence to

reach the primary outcome about the specificity of ^{99m}Tc-3PRGD2 SPECT/CT superior to that of ^{18}F-FDG PET/CT with an effect size of at least 15% at a test level of 0.05 (double-tailed). Based on these calculations, the proposed study needs at least 270 participants with surgical pathology results for efficacy analysis.

According to calculations, when the ^{99m}Tc-3PRGD2 injection reaching 400 cases, the probability of having 1% general adverse events caused by the administration of of the candidate drug will be greater than 98%. Therefore, the whole study requires at least 400 participants to receive the experimental drug to obtain the safety data.

6 **Trial profile**

This study is designed to enroll more than 400 patients with suspected lung cancer from 11 medical centers. Participants who meet the inclusion and exclusion criteria will be recruited to undergo SPECT/CT planar scan and chest tomography after intravenous injection of ^{99m}Tc-3PRGD2 at a dose of 0.3 mCi/kg. They will also undergo ^{18}F-FDG PET/CT within a week. Among them, the patients who successfully complete safety tests are included into the safety analysis set.

At least 270 participants are expected to undergo lung lobectomy and lymph node station resection within 2 weeks after the ^{99m}Tc-3PRGD2 SPECT/CT. Their pathological results will be collected and used as the gold standard to evaluate the diagnostic efficacy of ^{99m}Tc-3PRGD2 SPECT/CT for diagnosis of lung tumors and lymph node metastases, with a head-to-head comparison with ^{18}F-FDG PET/CT. Thereafter, those patients who undergo ^{18}F-FDG PET/CT within one week and lung surgery and lymph node resection within two weeks after the 99mTc-3PRGD2 SPECT/CT are included into the efficacy analysis set to evaluate the efficacy of the imaging method in diagnosis of lung cancer and mapping the lymph node metastases.

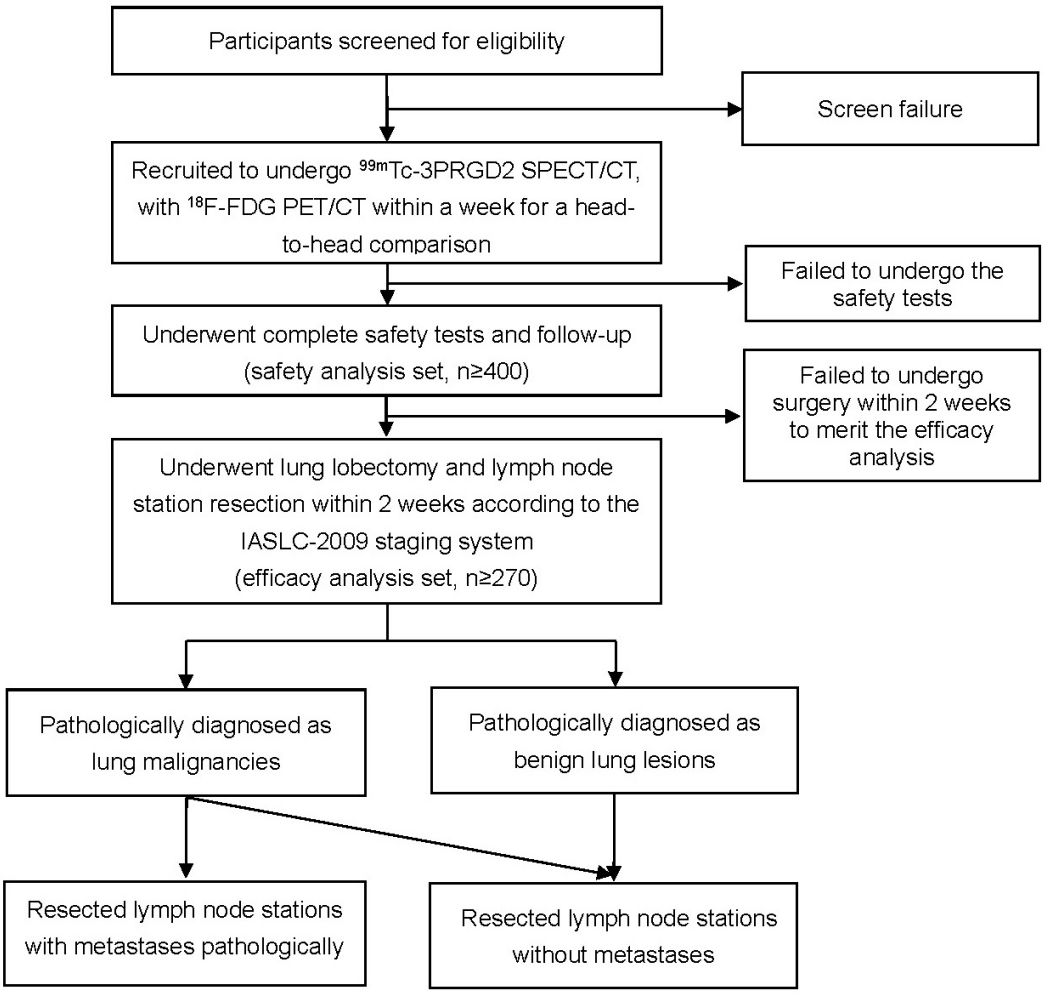

Figure 1. Trail profile

7 ^{99m}Tc-3PRGD2 SPECT/CT and related examinations

7.1 Preparation of the ^{99m}Tc-3PRGD2 injection

The kit is formulated by 40 μg hydrazinonicotinamide-3PRGD2, 3.00 mg trisodium triphenylphosphine-3,3',3"-trisulfonate (TPPTS), 2.00 mg tricine, 29.55 mg succinic acid, and appropriate amount of sodium hydroxide.

For radiolabeling, 1 mL of 740.00–1295.00 MBq (20.00–35.00 mCi) of ^{99m}TcO4- saline solution is added to the kit vial and shake thoroughly to dissolve the solid matter in the vial. Then the vial is water-bathed at 100℃ for 20 min and cooled to room temperature.

The product solution is analyzed by thin-layer chromatography using Gelman Sciences silica-gel paper strips with an eluant of acetone and saline (1:1). The radiochemical purity should exceed 90% before clinical use.

Specification of the ^{99m}Tc-3PRGD2 injection

- Administration method: intravenous injection.

- Dosage: approximate 11.10 MBq (0.30±0.06 mCi) per kilogram body weight.
- Drug kit provider: Foshan Redio Pharmaceutical Co., Ltd.
- Drug kit manufacturer: Beijing Shihong Drug Research and Development Center.
- Drug kit batch number: 20190322, 20190329, and 20210226

7.2 ^{99m}Tc-3PRGD2 SPECT/CT

Whole-body planar scans and chest SPECT/CT imaging are performed 40–50 min after intravenous injection of ^{99m}Tc-3PRGD2. Chest low-dose spiral CT (120 kV, 50 mAs) is used for attenuation correction and anatomical localization. Each patient receives intravenous ^{99m}Tc-3PRGD2 at a dose of 11.10 MBq (0.30 mCi) per kilogram body weight. The ^{99m}Tc-3PRGD2 scans are acquired using the SPECT/CT systems at each center.

7.3 ^{18}F-FDG PET/CT

Patients are fasted for at least 6 hours and the blood glucose level should be measured less than 7.0 mmol/L before intravenous injection of ^{18}F-FDG. The injection dose is approximately 5.55 MBq (0.15 mCi) per kilogram body weight. ^{18}F-FDG PET/CT is performed using the PET/CT systems of each center 1 h after ^{18}F-FDG injection. Low-dose CT (120 kV, 50 mAs) and PET scans (5 to 6 bed positions, 2 min/bed) are carried out sequentially from the middle of the thigh to the base of the skull.

7.4 Enhanced CT

Conventional enhanced CT is performed at each center according to it's routine clinical practice.

7.5 Laboratory tests

Clinical laboratory tests include routine blood tests, blood biochemical tests, routine urine tests, and blood pregnancy test for women in reproductive age for the baseline to each subsequent visit.

The tests are performed during the screening period, on the day right before the drug administration, and in the early morning of the next day after the drug administration.

The blood will be drawn from the subjects on fasting state. If the screening tests is conducted within 3 days before the drug administration, there will be no need to repeat the tests on the day right before the administration.

7.6 Electrocardiogram (ECG) examination

Twelve lead electrocardiogram will be performed during the screening period, on the day right before the drug administration, and in the early morning of the next day after the drug administration.

If the screening tests is conducted within 3 days before the drug administration, there will be no need to repeat the tests on the day right before the administration.

7.7 Vital sign measurement and physical examination

Measures are taken on systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature during the screening period, on the day right before and after the drug administration, and in the early morning of the next day after the drug administration.

Blood pressure and heart rate are measured after the subjects have rested for 5 minutes. For subjects with elevated blood pressure (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), reevaluation and confirmation are conducted after a 10-min

interval. Vital signs are measured twice on the day of administration: once within 30 min before administration and once between 90-120 min after administration.
Physical examination of skin, mucosa, lymph nodes, head, neck, chest, abdomen, spine/limbs and nervous system are performed during the screening period and in the early morning of the next day after the drug administration.

8 **Data collection**

8.1 Data sets

(1) Full analysis set (FAS): A set of participants who have the ^{99m}Tc-3PRGD2 injection at least once. This analysis set should try to follow the intention-to-treat analysis principle (ITT for short). The elimination of participants from this analysis set should be the smallest and in most reasonable way.
(2) Per protocol set (PPS): A set of participants who meet the inclusion criteria, complete all the medication prescribed in the protocol, have good compliance, and undergo surgery to obtain pathological results. It is the case data that fully complies with the trial protocol. PPS is a subset of FAS.
(3) Safety set (SS): A set of participants used for summary during the safety and tolerability evaluation. This data set includes all participants who received at least one dose and had at least one safety evaluation.

8.2 Demographic and medical data collection

This study enrolls more than 400 patients with suspected lung cancer from over 11 medical centers. For each participant, demographic information and medical history will be collected and a specifically designed Case Report Form (CRF) will be filled. The demographic information includes age, sex, nationality, body mass index , smoking history and others. The medical history includes all past medical history, treatment history, allergy history, surgical history, and records of previous and concomitant medications
Previous medications and concomitant medications are summarized based on the SS. Past medication information include any medications discontinued before the first dose date. Concomitant medication includes any medication that starts between the first administration date and the date the participant completes or exits the trial, ends between the first administration date and the date the participant completes or exits the trial, or is still being used on the day the participant completes or exits the trial. Any medication that starts before the first administration date and ends after the participant completes or exits the trial should also be considered as concomitant medication.
Previous medications and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Chinese version on September 1, 2022, or above) coding system and the Anatomical-Therapeutic-Chemical Drug Classification System (ATC). Concomitant medications are summarized according to preferred terms coded by ATC classification and WHO drug dictionary. In a table, each ATC classification and preferred term are summarized in terms of frequency and percentage, using the total number of subjects in the SS as the denominator. ATC classifications and preferred terms will be arranged in descending order by total subject frequency (or in alphabetical order if the frequencies are the same).
All past and combined medication data are listed and filed by study center and subject number.

8.3 ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT

The ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT images are collected and transferred to a workstation for reading and analyzing independently by 3 physicians with more than 10 years of expertise in nuclear medicine and blinded to the patient's history, pathological diagnosis, and other examinations. A lesion-by-lesion analysis is adopted for the diagnosis of lung tumors, while a station-by-station analysis is applied for the diagnosis of lymph node metastasis.

For semi-quantitative analysis, the SPECT and PET images are measured by the same physician using standardized methods as described below: a volume-of-interest (VOI) method is used to obtain the maximum values (gamma counts for SPECT and standard uptake value for PET) of the lung tumors and the most prominent lymph node in each mediastinal station. The lung lesions are compared with the contralateral lung without any lesion, and the lymph nodes are compared with the aortic arch blood pool. The average values of the control VOIs are measured as the background. The tumor-to-background ratios are then calculated by dividing the two values.

The CT results are be recorded and the CT images are reviewed if neccessary.

8.4 Surgical record and pathological results

The surgical record and pathological results are collected and verified to obtain the gold standard for evaluation of diagnostic values of ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT.

Immunohistochemical staining for integrin β3 is performed in selected specimens of lung cancer, metastatic lymph nodes and benign lymph nodes using formalin-fixed, paraffin-embedded tissue sections and the EnVision method with appropriate pretreatment. The representative specimens are selected by a pathologist based on the quality and quantity of embedded tissues. Two experienced pathologists blinded to the imaging results read the integrin β3-stained slides in a consistent manner and rated the staining on a four-point scale: 0=negative; 1=lightly stained; 2=moderately stained; 3=strongly stained. They must reach a consensus if there is a discrepancy.

8.5 Safety data collection

The safety data of all participants who receive the ^{99m}Tc-3PRGD2 injection are collected and analyzed. Any relevant adverse reactions that emerged during and after the examination are futherchecked and recorded in detail.

The safety indicators include vital signs, laboratory examinations, physical examinations, 12-lead ECG, as well as the overall incidence of adverse events (AEs), the incidence of severe adverse events (SAEs), the incidence of AEs related to the trial drug (AERD), etc.

All adverse events are classified based on organ system (SOC) and preferred term (PT) according to the "ICH International Dictionary of Medical Terminology" (MedDRA), and the severity are recorded and graded according to the Common Adverse Event Evaluation Criteria CTCAE version 5.0.

In this clinical trial, adverse events (AEs) that occurred on or after the day when the subject first take the trial drug and before the subject withdrews from the trial are regarded as "treatment adverse events (TEAE)".

All AEs, TEAEs, TEAEs related to the trial drug (defined as AEs that are definitely, probably, or possibly related to the study drug. If the relationship between the AE and the study drug

cannot be assessed, it is assumed that the AE is related to the study drug), TEAEs of CTCAE grade 3 and above, serious adverse events (SAE), SAEs related to the trial drug, TEAEs leading to death, and TEAEs leading to withdrawal from the trial are recorded. The cases, number of cases and incidence rates are summarized.

All TEAEs, SAEs, TEAEs related to the trial drug, SAEs related to the trial drug, TEAEs leading to death, and TEAEs leading to withdrawal from the trial are summarized according to organ system (SOC) and preferred term (PT) lists. In addition, the severity of TEAEs and their association with the investigational drug are also summarized by organ system and preferred term (PT) list.

If multiple identical TEAEs occur with the same subject, the subject level is only counted once in that AE, but the number of events will be counted based on the actual number of occurrences. If multiple identical AEs of different severity or different causality occur in the same subject, the patient is counted once according to the most severe or relevant category, and the number of events are counted according to the actual number of occurrences.

9 **Quality control**

9.1 Equipments

All equipments involved in the clinical trial, including the SPECT/CT, PET/CT, CT, radioactive dosimeter, blood pressure monitor, body weight meter and others, are quality-contriled and documented in file.

9.2 SPECT/CT and PET/CT examinations

The leading clinical center (Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College) develops the Standard Operating Procedures (SOPs) for quality control of the SPECT/CT and PET/CT examinations.

All participating centers refer to the SOPs and implement the SPECT/CT and PET/CT examinations using the same SOPs.

9.3 Surgery and pathological examinations

The resections of lung tumors and lymph nodes are performed according to the IASLC-2009 nodal mapping system.

The leading clinical center (Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College) develops the Standard Operating Procedures (SOPs) for quality control of surgical resection of lung tumor and lymph nodes, and perform the pathological examination as well.

All participating centers l refer to the SOPs and implement surgery and pathological examinations using the same SOPs.

9.4 Independent analysis

An independent imaging evaluation committee of physicians with more than 10 years of expertise in nuclear medicine and radiology are invited to evaluate the images of ^{99m}Tc-3PRGD2 SPECT/CT, ^{18}F-FDG PET/CT, and enhanced CT blinded to the clinical information and pathological results.

10 **Ethical approval**

The study is performed in compliance with the Declaration of Helsinki and in harmonization with the Good Clinical Practice guidelines. The study protocol has been approved by the

Ethics Committee of the leading clinical center (Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College) and then followed by the ethics committees or institutional review boards of the other participating centers. Written informed consents are obtained from all participants before the study. The participants receive compensation as described in the informed consent form.