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Statistics analysis plan 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 statistics analysis plan 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

PDF

Statistical Analysis...

287KB

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 $\alpha_V\beta_3$ 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 **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 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 by the administration of the candidate drug will be greater than 98%. Therefore, the entire study requires at least 400 participants to receive the experimental drug to obtain the safety data.

5 **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 ^{99m}Tc-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.

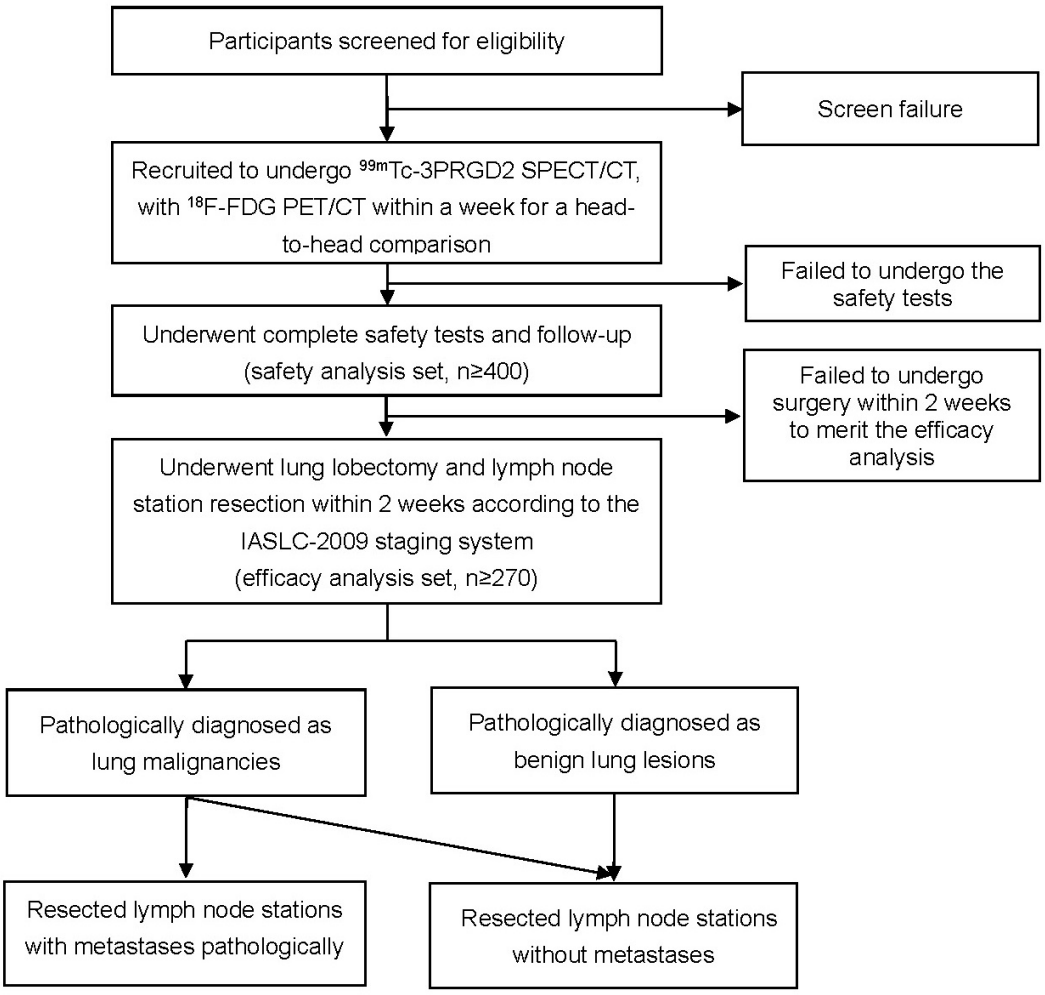

Figure 1. Trail profile

6 Main outcomes

6.1 Primary outcome

The primary endpoint of this study is to determine whether ^{99m}Tc-3PRGD2 SPECT/CT has a significantly higher diagnostic specificity over ^{18}F-FDG PET/CT in assessing lymph-node metastasis of lung cancer.

6.2 Secondary outcomes

The secondary outcomes include:

(1) Defining the diagnostic sensitivity, accuracy, positive predictive value, negative predictive value, and corresponding 95% confidence interval (CI) of ^{99m}Tc-3PRGD2 SPECT/CT in evaluation of the lymph node metastasis of lung cancer, with a head-to-head comparison to ^{18}F-FDG PET/CT.

(2) Defining the diagnostic values and corresponding 95% CI of ^{99m}Tc-3PRGD2 SPECT/CT in differentiation of malignant and benign lung tumors, with a head-to-head comparison to ^{18}F-FDG PET/CT.

(3) Defining the safety of ^{99m}Tc-3PRGD2 injection for SPECT/CT imaging in human beings.

7 **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 receive at least one dose and have at least one safety evaluation.
In this trial, baseline data will be analyzed using FAS analysis. The primary outcome and the secondary outcomes will be analyzed simultaneously with FAS and PPS. When the conclusions obtained by FAS and PPS are consistent, the credibility of the conclusion can be increased. In the safety analysis, SS will be used to analyze the adverse events (AEs) data, vital signs, laboratory indicators and others. Participants who terminate early due to the AEs and/or have various non-trial drug reasons will be recorded in the safety analysis.

8 **Statistical Analysis**

8.1 Descriptive statistical analysis
● Continuous variables will be summarized as mean ± standard deviations, and the median, minimum, and maximum values will be provided.
● Categorical variables will be described as numbers and percentages.
8.2 Efficacy analysis
● Unless otherwise specified, both full analysis set (FAS) and per protocol set (PPS) will be used for efficacy analysis.
● Using the pathological results as the gold standard, the diagnostic values including sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and the corresponding 95% CI of both ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT will be calculated.
● The paired chi-square test (McNemar's test) will be used to compare the difference between the diagnostic values of ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT.
● The Pearson correlation coefficient will be used for data with normal distribution, and the Spearman correlation coefficient will be used for data with skewed distribution.
● For the data with normal distribution, the mean T/B ratios of ^{99m}Tc-3PRGD2 and ^{18}F-FDG from the same patient will be compared using a paired t test (parametric test).
● The unpaired t test will be used to compare the mean T/B ratios of the lymph node stations with and without metastases.
● In semi-quantitative analysis, the diagnostic performances of ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT will be compared using receiver operating characteristic curve analysis and z statistics.

● Subgroup analysis will be performed as needed.
● All tests will be double-tailed, with $P<0.05$ indicating statistically significant.
8.2 Safety analysis
● All safety analyzes will be performed using the safety set (SS).
● All past and combined medication data will be listed and can be sorted by study center and subject number.
● AEs: A checklist for all AEs will be provided, classified, and can be sorted by study center and subject number.
● Physical examinations: A list of all participants' vital signs and other physical examination findings will be provided. Crosstabs of the changes from baseline will be provided.
● Laboratory tests: A checklist of all subject laboratory tests and blood pregnancy tests will be provided. Cross-tabulation of the changes of the laboratory results from baseline to each subsequent visit will be provided, with clinical abnormality assessment about the quantitative measurement and clinical evaluation.
● ECG: A list of all participants' ECT results will be provided. Cross-tabulation of change from baseline ECG to each subsequent visit, with assessment (normal, abnormal without clinical significance, and abnormal with clinical significance).

9 **Time plan for the statistical analysis**

The statistical analysis will only be performed at the end of the study when the safety data of the last participant are collected.

10 **Software used for the statistical analysis**

Prism 5.0 (GraphPad, San Diego, California) and SPSS statistical software (version 21.0, IBM SPSS Inc, IBM, Chicago, IL, USA) will be used for the statistical analysis of the study.