STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Study Title: An Exploratory Clinical Study Evaluating the Safety, Tolerability, and Preliminary Efficacy of ^{177}Lu-CTR-FAPI in Patients with Metastatic Solid Tumors

Protocol ID: 2024A-1337

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1. STUDY SYNOPSIS

Study Phase: Exploratory (Investigator-Initiated Trial, IIT)

Investigational Product: ^{177}Lu-CTR-FAPI

Indication: FAP-high expressing metastatic solid tumors (focusing on breast cancer, sarcoma, and thyroid cancer)

Methodology: Single-center, non-randomized, single-arm, open-label study

Sample Size: 12 participants

Intervention: Intravenous injection of ^{177}Lu-CTR-FAPI; single standard dose of 200 mCi (7.4 GBq) ±10%, administered every 6±1 weeks for a maximum of 4 cycles.

2. INTRODUCTION AND RATIONALE

Cancer-associated fibroblasts (CAFs) in the tumor microenvironment abundantly express fibroblast activation protein (FAP), making it an ideal target for radionuclide therapy. Covalent targeted radioligands (CTR) can covalently bind to target proteins via specific chemical reactions, thereby substantially prolonging the retention time of radiopharmaceuticals at the tumor site and increasing their uptake. Preliminary data indicate that ^{177}Lu-CTR-FAPI exhibits good targeting capabilities, extended retention time, and an acceptable safety profile in solid tumors. This study aims to further evaluate its safety, radiation dosimetry, and preliminary efficacy in selected advanced solid tumors with high FAP expression.

3. STUDY OBJECTIVES

3.1 Primary Objective

To evaluate the safety and tolerability of ^{177}Lu-CTR-FAPI in patients with metastatic solid tumors.

3.2 Secondary Objectives

1. To evaluate the in vivo biodistribution of ^{177}Lu-CTR-FAPI and calculate the radiation absorbed dose in normal organs and target lesions.
2. To preliminarily evaluate the clinical efficacy of ^{177}Lu-CTR-FAPI in patients with FAP-high expressing metastatic solid tumors.

4. STUDY DESIGN

This is a single-center, non-randomized, single-arm, open-label exploratory clinical trial. Ten eligible patients will receive the investigational drug. Patients will undergo intensive blood sampling and whole-body imaging during the first administration cycle to assess biodistribution and radiation dosimetry, with continuous evaluation of safety and efficacy throughout the treatment and follow-up periods.

5. STUDY POPULATION

5.1 Inclusion Criteria

1. Pathological diagnosis confirmed metastatic solid tumors (breast cancer, sarcoma, and some thyroid cancers, etc.) that failed standard treatment or lacked standard treatment.
2. Age: 75 ≥ age ≥ 18 years.
3. ECOG score: 0 - 2.
4. ^{68}Ga-CTR-FAPI PET/CT confirmed high expression of FAP in the tumor (more than 50% of the lesions with SUVmax ≥ 10).
5. The FAP immunohistochemical score of tumor cells is ≥ 2 (except for thyroid cancer).

6. There is at least one measurable lesion (RECIST 1.1).
7. Organ/marrow functions meet the specified thresholds, and there are no severe electrocardiogram abnormalities (QTcF ≤ 470ms).

5.2 Exclusion Criteria

1. There is brain metastasis or other central nervous system lesions.
2. The expected survival period is less than 6 months.
3. Within 4 weeks before administration, the patient has received chemotherapy, targeted therapy, immunotherapy, or other anti-tumor treatments or investigational drugs.
4. The patient has previously received other systemic radionuclide therapy (excluding ^{131}I treatment for thyroid cancer).
5. There is uncontrolled pleural effusion, ascites, severe cardiovascular or cerebrovascular diseases, or infection.

6. TREATMENT PLAN

Investigational Drug: ^{177}Lu-CTR-FAPI

Route of Administration: Intravenous (IV) infusion via an infusion pump over approximately 20 minutes.

Dosage: A single standard dose of 200 mCi (7.4 GBq) ±10%. Administered every 6±1 weeks, up to a maximum of 4 administrations. If specific toxicities occur (e.g., hematological or hepatic/renal toxicity), the dose may be reduced to 100 mCi (3.7 GBq) based on predefined criteria.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1 Imaging and Dosimetry Assessment

Whole-body planar imaging and localized SPECT/CT quantitative tomographic imaging, combined with blood sample measurements, will be performed at multiple time points from 1 hour up to 7-9 days following the initial injection of ^{177}Lu-CTR-FAPI.

7.2 Efficacy Assessment

1. Tumor imaging evaluations will be conducted every 8 weeks.
2. Objective Response Rate (ORR) and Progression-Free Survival (PFS) will be evaluated according to RECIST 1.1 criteria.

7.3 Safety Assessment

1. Continuous monitoring of vital signs and physical examinations.
2. Regular laboratory tests (including complete blood count, urinalysis, liver function, and renal function tests).
3. 12-lead Electrocardiogram (ECG).
4. Continuous monitoring and recording of Adverse Events (AEs) throughout the entire study period.

8. STATISTICAL ANALYSIS PLAN (SAP)

8.1 General Considerations

As an exploratory trial, no formal sample size calculation based on statistical hypothesis testing is performed. The statistical analysis will be primarily descriptive, utilizing SAS 9.4 software.

8.2 Analysis Sets

Full Analysis Set (FAS): All enrolled participants who receive at least one dose of the study drug.

Safety Set (SS): All participants who receive at least one dose of the study drug

and have subsequent safety evaluation records.

8.3 Biodistribution and Dosimetry Analysis

1. Regions of Interest (ROIs) will be drawn for source organs and target lesions on SPECT/CT images.
2. Time-Activity Curves (TACs) will be generated to calculate cumulative activity.
3. Radiation absorbed doses for normal organs and target lesions will be calculated using OLINDA/EXM software. Results will be reported as means and standard deviations (SD).

8.4 Efficacy Analysis

ORR and PFS will be calculated based on RECIST 1.1 criteria. Continuous and categorical variables will be descriptively presented using mean/SD and frequencies/percentages, respectively.

8.5 Safety Analysis

All adverse events will be medically coded and graded according to CTCAE v5.0. The incidence of safety events will be summarized by system organ class and severity grade based on the Safety Set. Particular attention will be given to tracking changes in hematological and hepatic/renal toxicity parameters.

8.6 Handling of Missing Data

Given the small sample size, missing data will not be imputed. All analyses will be based solely on observed data.

9. ADVERSE EVENT REPORTING

The investigator is fully responsible for patient safety monitoring. Any Serious

Adverse Event (SAE) must be reported to the ethics committee and relevant health administrative departments within 24 hours of awareness.

10. ETHICAL CONSIDERATIONS

This study will be conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines. The study protocol and Informed Consent Form (ICF) must be reviewed and approved by the Institutional Ethics Committee prior to implementation.