STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Study Title: An Exploratory Clinical Study Evaluating the Safety, Biodistribution, and Therapeutic Response of [177Lu]Lu-TEFAPI-06 in Patients with Metastatic Solid Tumors

Protocol ID: [2023A-371]

Date: [July 27, 2023]

1. STUDY SYNOPSIS

Study Phase: Exploratory (Phase 0/I)

Investigational Product:[177Lu]Lu-TEFAPI-06

Indication: fibroblast activation protein (FAP)-high expressing metastatic solid tumors

Methodology: Open-label, single-center, single-arm study

Sample Size: 5 participants

Intervention:Single intravenous injection of approx. 20 MBq/kg [177Lu]Lu-TEFAPI-06.

2. INTRODUCTION AND RATIONALE

FAP is highly expressed in the cancer-associated fibroblasts (CAFs) of the tumor microenvironment in various solid tumors, making it a promising target for radionuclide therapy. [177Lu]Lu-TEFAPI-06 is a novel radiopharmaceutical designed to target FAP. This study is initiated to evaluate its safety profile, biodistribution characteristics, and preliminary therapeutic potential in humans.

3. STUDY OBJECTIVES

3.1 Primary Objectives

1. To evaluate the safety and tolerability of [177Lu]Lu-TEFAPI-06 in patients with metastatic solid tumors.

2. To determine the biodistribution and calculate the radiation absorbed dose in normal organs and tumor lesions.

3.2 Secondary Objective

1.To preliminarily assess the therapeutic response of [177Lu]Lu-TEFAPI-06 in patients with FAP-high expressing tumors.

4. STUDY DESIGN

This is a prospective, single-center, open-label, exploratory clinical trial. 5 eligible patients will receive a single dose of the investigational drug. Patients will undergo serial whole-body imaging to assess biodistribution and will be followed up for 1 month to assess safety and efficacy.

5. STUDY POPULATION

5.1 Inclusion Criteria

1. Diagnosed with metastatic solid tumors via pathology.

2.Confirmed high FAP expression in tumor lesions via [18F]-FAPI PET/CT screening (Tumor uptake significantly higher than background).

3. Expected survival time＞3 months.

4. Voluntarily signed the informed consent form.

5.2 Exclusion Criteria

1. Pregnancy or lactation.

2.Severe hepatic or renal dysfunction (e.g., Creatinine > 1.5x ULN; ALT/AST > 3x ULN).

3. Severe hematological suppression (e.g., WBC < 3.0×10^9/L, Platelets < 75×10^9/L).

4. Known severe allergy to the drug or its components.

5.Any other condition that the investigator deems unsuitable for participation.

6. TREATMENT PLAN

Drug:[177Lu]Lu-TEFAPI-06

Route of Administration: Intravenous (IV) injection.

Dosage:A single dose of approximately 20 MBq/kg.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1 Imaging Schedule

Following the injection of [177Lu]Lu-TEFAPI-06, whole-body planar imaging and SPECT/CT tomography will be performed at the following time points:0.5 hours, 2 hours, 24 hours, 48 hours, 72 hours, and 120 hours post-injection.

7.2 Efficacy Assessment (Follow-up)

Timeline:Baseline (pre-treatment) and 1 month post-treatment.

Modality:[18F]-FAPI PET/CT.

Biological Markers:Tumor-specific serum markers will be measured at baseline and follow-up.

7.3 Safety Assessment

Vital signs and physical examination.

Laboratory tests: Complete blood count (CBC), Urinalysis, Liver function tests (LFTs), Renal function tests.

12-lead Electrocardiogram (ECG).

Adverse Event (AE) monitoring throughout the study.

8. STATISTICAL ANALYSIS PLAN (SAP)

8.1 General Considerations

This is a small-sample exploratory study (N=5). The statistical analysis will be primarily descriptive. No formal sample size calculation based on power analysis was performed due to the pilot nature of the study.

8.2 Analysis Sets

Full Analysis Set (FAS):All participants who received the study drug and have at least one post-baseline efficacy evaluation.

Safety Set (SS):All participants who received the study drug.

8.3 Biodistribution and Dosimetry Analysis

Data Processing:Regions of Interest (ROIs) will be drawn on whole-body SPECT/CT images for source organs (heart, lung, liver, kidney, spleen, brain) and tumor lesions.

Calculations:

1.Radioactive counts in ROIs will be converted to activity using system calibration factors.

2. Time-Activity Curves (TACs) will be generated for each organ.

3. Cumulative activity (residence time) will be calculated by integrating the TACs (using mono-exponential or bi-exponential fitting as appropriate).

4.Software:OLINDA/EXM software will be used to calculate the mean

absorbed dose (mGy/MBq) for organs and the effective dose (mSv/MBq) for the whole body.

Statistical Output:Mean and Standard Deviation (SD) of absorbed doses per organ will be reported.

8.4 Efficacy Analysis

Primary Endpoint (Imaging):Comparison of Standardized Uptake Values (SUVmax and SUVmean) of the primary tumor and representative metastatic lesions between baseline and 1-month post-treatment [18F]-FAPI PET/CT scans.

Background Reference: Mean SUV of normal liver tissue.

Secondary Endpoint (Biomarkers):Comparison of serum tumor marker levels pre- and post-treatment.

Statistical Test:Continuous variables (SUV, biomarker levels) will be tested for significant changes using the Paired t-test (if normally distributed) or Wilcoxon signed-rank test (if non-normally distributed).

A P-value < 0.05 will be considered statistically significant.

Data will be presented as Mean ± SD or Median (Range).

8.5 Safety Analysis

Adverse Events (AEs):All AEs will be coded and graded according to CTCAE v5.0(Common Terminology Criteria for Adverse Events).

Tabulation:The number and percentage of patients experiencing AEs will be summarized by system organ class and severity grade.

Laboratory Data:Descriptive statistics will be used to summarize changes in hematology and chemistry values from baseline to post-treatment. Particular attention will be given to renal toxicity and myelosuppression (Grade 3/4 toxicity).

8.6 Handling of Missing Data

Given the small sample size, missing data will not be imputed. Analyses will be performed on observed data only.

9. ADVERSE EVENT REPORTING

The investigator is responsible for monitoring the safety of patients. Any Serious Adverse Event (SAE) must be reported to the Ethics Committee within 24 hours of awareness.

10. ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. The protocol and informed consent form (ICF) have been reviewed and approved by the Institutional Ethics Committee.