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Exploring Auger-Enhanced PSMA-Targeted RLT: A First-in-Taiwan Clinical Study of 161Tb-PSMA-I&T in Patients with Metastatic Castration-Resistant Prostate Cancer

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Protocol Synopsis

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I. Protocol title:

Exploring Auger-Enhanced PSMA-Targeted RLT: A First-in-Taiwan Clinical Study of ^{161}Tb-PSMA-I&T in Patients with Metastatic Castration-Resistant Prostate Cancer

II. Objectives:

This study is a small-scale phase I dose escalation clinical trial aims to evaluate ^{161}Tb-PSMA-I&T, a new generation PSMA-targeted radioligand therapy (RLT) using ^{161}Tb to replace ^{177}Lu, its safety, dosimetry, biodistribution, pharmacokinetics, and preliminary efficacy in Taiwanese men with metastatic castration-resistant prostate cancer (mCRPC), and to inform future clinical trials.

III. Test drug:

1. Name: ^{161}Tb-PSMA-I&T
2. Dosage form: Injections
3. Strength: 20-40 mCi/mL (0.74-1.48 GBq/mL) at EOS
4. Dosage and administration: 4.4 GBq (120 mCi), 5.4 GBq (150 mCi), 7.4 GBq (200 mCi) every treatment cycles per dose level, slow intravenous (IV) injection for 5 minutes
5. Mechanism of action (if known): Targeting tumor cells highly expressing PSMA on its surface, PSMA-I&T will specifically binds to PSMA and being internalized into the tumor cell, and transfer radioactive cytotoxicity to the tumor cell through beta particles and Auger electrons emitted by ^{161}Tb.
6. Pharmacological category: Radioactive agent (ATC code: 780000)

IV. Developmental phase: ☑ First in human phase ☐I ☐II ☐III ☐IV ☐Others

V. Study design:

1. ☐Control: ☐placebo

☐active (please specify name and dosage)

☐other

☑Uncontrolled

2. Blinding: ☑open-label ☐evaluator blind ☐single blind ☐double blind

☐double dummy ☐other

3. Randomized: ☐yes ☑no

4. ☑Parallel ☐Cross-over ☐Other

5. Duration of treatment: days 18 weeks months years(with additional 18 weeks of follow-up after treatment completed)

6. Titration: ☑forced ☐optional ☐none

7. ☐Multi-national ☑Multi-center(Taiwan) ☐Single center

VI. Endpoints:

1. Primary: Incidence, nature, and severity of treatment-emergent adverse events (TEAEs) graded by CTCAE v5.0 across the entire treatment and 18-week post-treatment surveillance period

2. Secondary: Quantitative absorbed doses in kidneys, salivary glands, bone marrow, and tumor lesions calculated from serial post-therapy SPECT/CT imaging; PSA change (%) from baseline at 6, 12, 18, 24, and 36 weeks; radiographic response using PSMA PET/CT (e.g., SUVmax reduction) and conventional CT per RECIST 1.1; and changes in exploratory biomarkers (e.g., PSMA PET metrics, circulating tumor DNA levels)

VII. Selection criteria:

1. Main inclusion criteria:

1. Age ≥ 20 years, with ability to provide informed consent, cooperate with all study-related procedures and assessments including blood tests and imaging
2. Histologically confirmed adenocarcinoma of the prostate with evidence of metastatic castration-resistant prostate cancer (mCRPC)
3. Prior surgical orchiectomy or chemical castration maintained on luteinizing hormone-releasing hormone analog, with a serum testosterone level <50 ng/dL (castrate range)
4. Prior treated with at least one line of taxane-based chemotherapy unless medically unsuitable, and at least one line of androgen receptor pathway inhibitor (e.g., abiraterone, enzalutamide, apalutamide, or darolutamide)

5. Prior treated with ^{177}Lu-labeled PSMA RLT unless medically unsuitable or declined by the patient
6. Progressive disease defined according to Prostate Cancer Clinical Trials Working Group 3: Either a PSA progression of more than 2 rising PSA values from baseline with intervals ≥ 1 week, or a soft-tissue progression on images per RECIST 1.1 criteria, or a bone progression on images with more than 2 new lesions
7. Evidence of significant PSMA-avid lesions on ^{68}Ga- or ^{18}F-labeled PSMA PET/CT within 12 weeks prior to screening, which defined as ^{68}Ga-PSMA or ^{18}F-PSMA uptake greater than that of liver or spleen parenchyma (depend on the tracer used) in at least one metastatic lesion of any size in any organ system
8. A life expectancy of ≥ 6 months and Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
9. Adequate bone marrow and organ functions
   (1) Hemoglobin ≥ 10 g/dL without RBC transfusion within 4 weeks
   (2) Absolute neutrophil count ≥ 1.5×10^9/L
   (3) Platelet count ≥ 150×10^9/L
   (3) Creatinine clearance ≥ 50 mL/min (Cockcroft-Gault)
   (4) AST and ALT ≤ 3 × ULN, total bilirubin ≤ 1.5 × ULN
10. Willingness to comply with the use of medically acceptable forms of barrier contraception if sexually active

2. Main exclusion criteria:

1. History of allergic reaction to PSMA-targeted compounds or radiometals
2. Prior radioligand therapy with ^{223}Ra or ^{177}Lu-PSMA within 6 months
3. Prior surgery or radiotherapy within 4 weeks prior to first investigational dose
4. Prior systemic therapies against prostate cancer within 4 weeks, including androgen receptor pathway inhibitor, chemotherapy, targeted therapy such as PARP inhibitors (PARPi)
5. Discordant disease on PET images: FDG-positive disease with minimal PSMA expression
6. Urinary tract obstruction causing hydronephrosis unless appropriately treated beforehand
7. Known symptomatic brain metastases or leptomeningeal disease, symptomatic or impending cord compression unless appropriately treated beforehand
8. Other active malignancy requiring systemic treatment
9. Significant cardiovascular disease (e.g., recent myocardial infarction, unstable angina)
10. Concurrent severe uncontrolled illness that may jeopardize patient safety, including uncontrolled infections

VIII. Study procedures:

1. Pre-treatment screening

1. Eligible patients meeting inclusion criteria signed inform consent form.
2. Eligible patients completed both PSMA and FDG PET to ensure no discordant disease by exclusion criteria.
3. First dose of ^{161}Tb-PSMA-I&T should be given within 12 weeks from PSMA PET.

2. Administration of ^{161}Tb-PSMA-I&T

1. Three fixed prespecified doses of 4.4, 5.4, and 7.4 GBq of ^{161}Tb-PSMA-I&T parted every 6 weeks (three study participants for each dose level, additional 3 participants recruited to dose level observed with dose-limiting toxicity, with a total number of 12 participants).
2. Premedication with steroid and antiemetics following current treatment protocol for ^{177}Lu-PSMA RLT.
3. Introduce pre- and post-injection hydration protocols to mitigate nephrotoxicity.
4. Intravenous delivery of ^{161}Tb-PSMA-I&T via automated syringe-pumping equipment over 5 minutes under physician supervision.
5. Monitoring of blood pressure, pulse rate (by limb leads EKG), respiratory rate, oxygen saturation (SpO2), and body temperature throughout the injection process and until 30 minutes after injection.

3. Pharmacokinetics and organ dosimetry

1. Blood tested at 3, 10, 30, 60 minutes, and 2, 4, 8, 24, 48, and 72 hours post-injection in the first treatment cycle, with a total amount of 20 mL (2 mL each for 10 time-points). No blood tests required during following treatment cycles.
2. Urine tested at multiple time points up to 72 hours post-injection in the first treatment cycle.
3. Post-therapy imaging including whole body planner images of anterior and posterior projections (takes about 20-25 minutes) and SPECT/CT (takes about 40-50 minutes) acquire at 2, 24, 48, 120, and 168 hours post-injection (first cycle), or at 24 hours only (subsequent cycles).

4. Post-treatment monitoring

1. Dose-limiting toxicities (DLTs) assess within 42 days after first dose given
   (1) Non-hematologic adverse events, Grade ≥ 3 except for
   i Gastrointestinal symptoms which resolved to grade ≤ 2 within 5 days after optimal treatment
   ii A flare of local pain which resolved to grade ≤ 2 within 7 days
   iii Fatigue

(2) Hematologic adverse events

i Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia lasting > 7 days

ii Grade 4 or febrile neutropenia lasting > 7 days, or Grade 3 neutropenia with active infection

iii Grade 4 anemia lasting > 7 days

(3) Mean absorbed dose of key organs at risk exceeding dose limits

i Kidneys: >23 Gy

ii Liver: >30 Gy

iii Salivary glands: >25 Gy

iv Red marrow: >2 Gy

v Total body: >0.75 Gy

2. Blood samples including blood cell counts, renal and liver functions, tumor markers, CRP, with a total amount of 95 mL (5 mL each for baseline and 18 follow-ups) evaluate one week after every dose given, bi-weekly during treatment cycles, and tri-weekly during follow-up until 36 weeks after first dose given. Self-reported symptoms and quality of life assessment including pain score.

3. PSMA PET/CT every 12 weeks after first dose given following standard protocol.

5. Discontinuation of study intervention

1. Treatment hold and monitoring strategy: If any of the following conditions are met, the subsequent treatment cycle will be postponed until resolution or recovery to an acceptable level:

(1) Hematologic toxicity:

i Hemoglobin < 9 g/dL

ii Absolute neutrophil count < 1.5×10^9/L

iii Platelet count < 75×10^9/L

iv Grade 3 bone marrow suppression lasting > 2 months

v Grade 4 bone marrow suppression lasting > 1 month

(2) Nephrotoxicity: Grade ≥3 renal toxicity, as defined by CTCAE criteria

(3) Hepatotoxicity: Clinically significant liver enzyme abnormalities, or Grade ≥3 hepatic adverse events

(4) Other non-hematologic toxicity: Any other uncontrolled non-hematologic adverse event of Grade ≥3 that is considered related to the study intervention

2. Permanent discontinuation strategy: Situations that will lead to permanent discontinuation of the study intervention include:

(1) Treatment hold exceeds 4 weeks from the scheduled cycle (i.e., total interval >10

weeks from the prior cycle)

(2) Inadequate radiotracer uptake observed on post-treatment PSMA SPECT imaging, indicating insufficient tumor targeting or therapeutic feasibility (refer to Section 4.2, Justification for Dose)

(3) Development of life-threatening serious unexpected adverse reaction (SUSAR) such as stroke or acute myocardial infarction

(4) Proved severe hypersensitivity to ^{161}Tb-PSMA-I&T

(5) Other new evidence suggests an increased risk outweighted potential benefit to receive the study intervention

IX. Concomitant treatment:

1. Permitted: Androgen deprivative therapy (ADT)

2. Prohibited: Androgen receptor pathway inhibitor (ARPI), chemotherapy, targeted therapy such as PARP inhibitor (PARPi), radiotherapy, other radionuclide therapy such as ^{223}Ra and ^{177}Lu-based PSMA RLT

3. Special precautions to nephrotoxic or myelosuppressive agents

X. Statistics

1. Primary hypothesis: ☐superiority ☐non-inferiority

☐equivalence ☑other: dose excalation safety trial

2. Sample size: 12 enrolled

20 evaluable

3. Efficacy population: ☐ITT ☑PP ☐other

Safety population: ☐ITT ☑PP ☐other

The Safety Analysis Set will include all participants who receive any amount of ^{161}Tb-PSMA-I&T. The Dose-Limiting Toxicity evaluable population will include participants who complete the first 42-day DLT assessment period or who experience a DLT within this period. The Efficacy-Evaluable Set will include participants who receive at least one treatment cycle and have at least one post-baseline PSA or imaging assessment.

4. Statistical method(s) for efficacy/safety evaluations:

This is an early-phase, dose-escalation study primarily designed to evaluate safety, tolerability, pharmacokinetics, and radiation dosimetry of ^{161}Tb-PSMA-I&T. All analyses will be descriptive and exploratory unless otherwise specified. No formal hypothesis testing is planned for the primary safety endpoint.

1. Safety evaluations:

The primary safety analysis will summarize the incidence of DLTs within 42 days after the first administration of ^{161}Tb-PSMA-I&T by dose cohort. Adverse events and serious

adverse events will be coded, tabulated, and graded according to CTCAE v5.0. The number and percentage of participants experiencing any AE, treatment-related AE, Grade ≥3 AE, SAE, DLT, treatment interruption, treatment discontinuation, or death will be summarized by dose cohort and overall.

Laboratory values, including hematologic, renal, and hepatic parameters, will be summarized using descriptive statistics at each scheduled time point and as change from baseline. Clinically significant abnormalities will be listed individually. No inferential comparison between dose cohorts is planned.

Radiation pharmacokinetics, biodistribution, organ absorbed dose, tumor absorbed dose, and whole-body exposure parameters will be summarized using mean, standard deviation, median, interquartile range, minimum, and maximum. These parameters will be presented by dose cohort and treatment cycle, where applicable.

Exploratory correlations between injected activity, tumor burden, pharmacokinetic parameters, and absorbed radiation dose will be assessed using Pearson correlation for approximately normally distributed continuous variables and Spearman rank correlation otherwise. Normality will be assessed using visual inspection of histograms and Q–Q plots; Spearman correlation will be used if normality is not supported or if outliers are present.

2. Efficacy evaluations:

Preliminary antitumor activity will be assessed exploratorily using serum PSA response, imaging response, and disease control. PSA change from baseline will be summarized as absolute and percentage change at each scheduled time point. PSA response will be defined as a ≥50% decline from baseline, unless otherwise specified. PSA responses will be displayed using waterfall plots and PSA trajectories using spider plots.

Radiographic response will be assessed using prespecified imaging criteria, including PERCIST-based metabolic response where applicable. Disease control rate will be summarized as the proportion of participants achieving complete response, partial response, or stable disease. Exact binomial 95% confidence intervals will be provided for response proportions when sample size permits.

Exploratory associations between baseline imaging or molecular biomarkers and response outcomes may be evaluated using logistic regression or non-parametric methods, depending on sample size and event distribution. Given the early-phase design and limited sample size, these analyses will be considered hypothesis-generating only.

3. Multiplicity and model assumptions:

No adjustment for multiplicity will be applied because the primary objective is safety

evaluation and all efficacy and biomarker analyses are exploratory. Findings from multiple exploratory analyses will be interpreted cautiously and reported as hypothesis-generating. For logistic regression analyses, model stability will be assessed by event counts, separation, and width of confidence intervals. If the number of events is insufficient, regression modeling will not be performed, and results will be summarized descriptively. For correlation analyses, linearity and outliers will be assessed visually. Pearson correlation will only be used when approximate linearity and normality assumptions are reasonable; otherwise, Spearman rank correlation will be used.

4. Missing data:

No formal imputation of missing data is planned. Safety analyses will be based on observed data. Missing or unevaluable efficacy assessments will be described, and sensitivity summaries may be provided when clinically relevant.

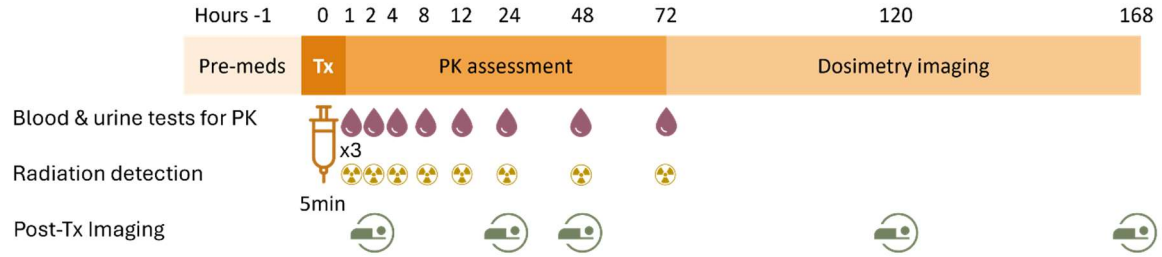
5. Statistical software:

All analyses will be performed using R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

5. Planned interim analysis: ☑yes □no

XI. Please attach flow chart and/or assessment schedule, if available.

1. Every treatment cycle:



2. Entire study workflow: